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**EDITORIAL**

- 1 Stress and quality of life in dermatological patients: Are out-patients' needs different?
Manolache L

REVIEW

- 4 Propranolol for infantile hemangioma: Current state of affairs
Moyakine AV, van der Vleuten CJM
- 17 Psoriasis treatment: Unconventional and non-standard modalities in the era of biologics
Mahajan VK

MINIREVIEWS

- 52 Treatment of mycosis fungoides, in the era of stem cell transplantation
Patir P, Vural F

SYSTEMATIC REVIEWS

- 57 Clinical pharmacokinetics profile of ivermectin 1% cream after dermal applications on the face
Benkali K, Rony F, Graeber M, Jacovella J, Chappuis JP, Peirone MH, Poncet M, Delage S, Bouer R, Wagner N

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Stress and quality of life in dermatological patients: Are out-patients' needs different?

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Abstract

The debut, progression and maintenance of skin disease are related to stress (acne, alopecia areata, atopic dermatitis, lichen planus, psoriasis, urticaria, vitiligo, herpes, hyperhidrosis, pemphigus, rosacea or seborrheic dermatitis). Environmental, socio-professional, life events are representing external factors. Personality, previous experiences, traits of anxiety are individual

factors influencing the state of stress. Perceived stress could be more harmful especially in "high reactors" to stress. Coping abilities to stress could be increased in social programs. There was a recent interest in measuring the quality of life in the last years. There are dermatology and disease specific questionnaires that could help. Out-patients have less time to wait for very sophisticated procedures. They expect faster results. For simple, acute diseases it is important to have a good communication and good understanding of the instructions to get results as soon as possible. For chronic diseases a strong long-term alliance is needed, so the patients should revisit for his benefit and not for giving up. Small questions regarding potential stressful events, impact on the quality of life, stigmatization, the level of symptoms (pruritus), psychiatric comorbidities (anxiety, depression), short questionnaires for quality of life give us a better picture, personalize the doctor-patient relationship and could influence the choice of treatment. Many skin disorders could be seen from a psychosomatic point of view and the final goal, especially for the chronic diseases, is to improve through our treatments the impact on the quality of patient's life.

Key words: Stress; Perceived stress; Quality of life; Out-patients; Dermatology life quality index; Children dermatology life index

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Core tip: The debut, progression and maintenance of skin disease are related to stress. Besides external factors, individual factors could influence the state of stress. Perceived stress, high reactors to stress, coping abilities, quality of life questionnaires are some directions to discuss. Out-patients have different needs and expectations than in-patients. Good communication, empathy, personalized questions, short questionnaires could make a strong, long-term doctor-patient relationship with better results and satisfaction for both sides.

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The interest for stress involvement in dermatological conditions and also for the impact of cutaneous diseases on the quality of patient's life increased in the last years. I have made an extended review^[1] reporting that stressful events could induce, aggravate or maintain different skin diseases such as: Acne, alopecia areata, atopic dermatitis, lichen planus, psoriasis, urticaria, vitiligo. There were described such connections even with herpes, hyperhidrosis, pemphigus, rosacea or seborrheic dermatitis.

Other aspect is represented by the secondary stress induced by the skin disease itself, influencing the quality of life.

The impact of a stressful situation on patient's life (perceived stress) could induce more harm than the situation itself. There are patients "high reactors" to stress. For them it is a risk of developing psychosomatic diseases after some minor life situations perceived as stressful.

The state of stress could be influenced by external and individual factors. Environmental, socio-professional factors or different life situations are some of external factors. Major life events that appear in the list of Holmes and Rahe provoke important reactions to people. Serious illness of the patient or of beloved ones, death of family members or friends, separations or divorces are expected to induce anxious-depressive states with different psychosomatic appearances. Personal needs or previous experiences, personality and attitude facing different situations, family models represent individual factors that can also change the state of stress. For example reactions to exams, to quarrels, to changes of jobs, environment could be very different from a person to another. The psychological vulnerability of the person (ex high trait of anxiety) could change the appearance, the development and the progress of the psychosomatic disease.

There is a study^[2] on out-patients with dermatoses that describes women having higher perceived stress. The perceived stress was higher in patients with psoriasis and acne than in tumors and was correlated to mental quality of life.

The reaction of the individual is an attempt to restore the balance and depends on the coping abilities. Social programs including stress management and psychological support are important in the achievement of coping abilities^[3].

Persons with high stress resistance are characterized by a control on the events and life situations, acceptance of the responsibility of the facts that are happening. They are involved in everything they are doing and they accept the changes as natural.

More than 3000 of papers are studying the impact of skin diseases on the patient's quality of life and more than half have been published during the last 5 years, showing an increasing interest on this subject. For the measurement^[4] there are generic instruments and also specific instruments (dermatology and disease specific). There are scales for adults, children, teen-agers, families, infants, etc., in the need for more specific data.

After 15 years of working only with out-patients (more than 100000 consultations) in Romania, I think there are different needs for them. I know that there are different aspects regarding cultural habits, but people have general needs of care. I work with National Insurance System and patients have facile access to ambulatory after a reference from the general practitioner. In our country from Eastern Europe, people want and need to talk and to be listened. There is no intrusion in their intimacy if you ask personal aspects or if you try to personalize the doctor-patient relationship. Usually, there is a close relationship, because the patients are coming back for controls or for other acute episodes. Through years, if there is a good and trustful relationship, the doctors get to know the entire family.

Out-patients have less time to wait for results and other expectations than in-patients. Usually, in the ambulatory they are coming for common skin conditions and the alliance is very important. For simple diseases it is important to get results as soon as possible (ex: Impetigo, different kinds of superficial mycoses, contact eczemas, scabies aso), so, good communication and good understanding of the instructions will have the best benefit. They need detailed information and they should ask questions. For chronic diseases such as acne, psoriasis, atopic dermatitis, onychomycosis, chronic urticaria, warts, etc., the alliance will represent the key point for the patient to return and not to give up with the long-term therapy.

In an era of fast movements and expectations, I consider that it will be very helpful for both doctor and patient to keep in mind small questions regarding potential stressful events, impact on the quality of life, stigmatization, the level of symptoms (pruritus), psychiatric comorbidities (anxiety, depression). Even they seem to be time-consuming this kind of questions will increase the trust and the satisfaction of the patient and will give us additional information and a more complete picture that could influence the choice of the treatment. Deeper, personalized questions will show to the patient the care and the empathy. For example, I use dermatology life quality index^[5] and children's dermatology life quality index^[6] for almost every patient with acne. There are 10 questions and it takes a few minutes to be filled in. The results of the questionnaires could give me information about the necessity of more aggressive lines of therapy in case of high impact on the quality of life and complex approach (for example, together with endocrinologist, psychologist or psychiatrist). On the other hand, if the impact on the quality of life is very low, even the lesions are important,

that could be a predictor that the patient is not ready for a long-time commitment in therapy.

Questionnaires are usually used in clinic for different types of studies. They are very complex and it takes a long time to be completed. In hospitals, where there are teams that work together they could be done by residents and there are not time-restricted.

But, a consultation for out-patient is short and short questionnaires are more convenient. They have to be very simple (a few questions), easy to be filled in by patients. Some of actual questionnaires have been already translated and used also for outpatients, but maybe it could be interesting to design some new ones especially for a facile use in ambulatories.

Many skin disorders could be seen from a psychosomatic point of view and the final goal, especially for the chronic diseases, is to improve through our treatments the impact on the quality of patient's life.

Questionnaires are not only for the clinics, doctors in ambulatories should be open to use them in daily practice as good instruments for measuring the severity and impact or the needs of patients. The short questions could point sensitive areas that could need deeper approach. Translations, validations and a wide use of questionnaires could give us new perspectives.

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Propranolol for infantile hemangioma: Current state of affairs

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Abstract

Infantile hemangioma (IH) is the most common benign

tumor seen in infancy. This review provides up-to-date information on the pathophysiology, variations in clinical presentation, and natural history of IH, elaborating on associated anomalies, such as PHACE(S) syndrome and LUMBAR syndrome. Because of the benign and self-limiting characteristics seen in more than 90% of cases of IH, a conservative approach is usually chosen. However, some circumstances, such as ulceration, vision loss, breathing difficulties, or potential disfigurement, will require treatment during the proliferative phase. For decades, treatment of IH has primarily consisted of corticosteroids or surgery. Since 2008, propranolol has become the treatment of first choice. In this article, we bring to light the crucial changes in the treatment of IH over the past years. To date, there is still a lack of data on the possible long-term effects of propranolol treatment in young infants. A theoretical probability of the central nervous system being affected (that is, impairment of short- and long-term memory, psychomotor function, sleep quality, and mood) has recently been suggested. This review highlights research topics concerning these long-term adverse effects. Finally, information is provided on the potential instruments to measure IH severity and activity in clinical trials and/or in clinical practice and the recently developed and first-validated IH-specific quality-of-life questionnaire.

Key words: Infantile hemangioma; Propranolol; Beta-blocker; Adverse effect; Development

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Core tip: The discovery that propranolol is efficacious in the treatment of infantile hemangioma (IH) has led to an upsurge in publications, increasing our knowledge of this subject. In this review, we provide the most up-to-date information on the pathophysiology, variations in clinical presentation, and natural history of IH. We look at possible working mechanisms of several treatments and the current concerns regarding the treatment of

first choice, propranolol. Finally, we provide an overview of instruments, measuring IH severity and/or activity and IH-related quality of life.

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INTRODUCTION

Infantile hemangioma (IH) is a benign vascular tumor caused by endothelial cell proliferation. With a prevalence of about 4%-10% in the first year of life, it is the most common benign tumor of infancy^[1-4]. IHs may be located in any region of the body, including the internal organs, but are mostly (60%) located in the skin of the head and neck region^[5,6]. The liver is the most common extracutaneous site of IHs. Hepatic IHs, which can be focal, multifocal, or diffuse, are the most common benign liver tumors of infancy^[7]. IHs are seen 3-5 times more often in females than in males. Other risk factors for developing an IH [including their crude odds ratios (OR)] are: Caucasian race, low birth weight (OR = 1.8), prematurity (OR = 1.8), family history of IH (OR = 2.5), and being born from a multiple birth (OR = 2.2)^[8-10]. Because of their benign and self-limiting character, no intervention is needed in more than 90% of cases. However, there are circumstances that will require treatment during the proliferative phase. These concern infants with IHs with a substantial morbidity, such as ulceration, vision loss, breathing difficulties, or potential disfigurement because of the tumor location. Until 2008, the treatment of IHs consisted of systemic or intralesional corticosteroids or surgery^[11,12]. In 2008, treatment of IH with propranolol was reported for the first time^[13]. After that, multiple publications followed, and the approach to IHs dramatically changed. This shift in the management of cutaneous IHs has also influenced the treatment of hepatic IHs^[7,14,15]. Propranolol is currently considered to be the treatment of first choice for IHs.

Propranolol has been used for several decades to treat cardiovascular diseases, such as hypertension, ischemic heart disease, and arrhythmias in adults and children. Although there is an abundance of experience with propranolol in infants, responses to propranolol have been far better studied in adults than in children^[16]. Propranolol has its side effects, although these are mild compared with previous IH treatments. The short-term side effects consist of hypotension, bradycardia, respiratory symptoms, hypoglycemia, gastrointestinal complaints, and cold extremities. The lipophilic nature of propranolol facilitates the crossing of the blood-brain barrier, causing adverse effects such as a sleepy and drowsy feeling during the day and restlessness

at night^[17]. Based on studies in adult volunteers and animals, it has been postulated that there may be long-term side effects of this drug, affecting the developing central nervous system, when given to infants^[18].

Our review summarizes the discoveries that have been made since 2008 regarding the treatment of IHs with propranolol. It also highlights the most important areas that still remain unknown.

PATHOPHYSIOLOGY

Despite its high incidence, the pathophysiology of IH is still unclear. There is no universally accepted theory, and no single hypothesis is sufficient to describe and explain all of its features. The three most common hypotheses that partially explain development of IH are listed below.

Placental embolization theory

IH endothelial cells share immunohistochemical markers with the placental microvasculature. Both possess glucose transporter protein type 1 (GLUT-1), Lewis Y antigen, merosin, laminin, chemokine receptor 6, CD15, insulin-like growth factor 2 (IGF-2), and indoleamine 2,3-dioxygenase. This immunohistochemical profile differentiates IHs from other vascular birthmarks or tumors^[19-22]. In addition, there is a high level of genetic similarity between the placenta and IH^[23]. Therefore, it was hypothesized that embolization of placental endothelial cells to the fetus could play a role in the pathogenesis of IH. This hypothesis was strengthened by findings that transcervical chorionic villus sampling is associated with a threefold increased incidence of IH and that placental abnormalities, such as abnormal placentation, are associated with a higher incidence of IH^[24-27]. However, the latter may also be explained by the hypoxia hypothesis. In contrast to the placental embolization theory are the failed attempts to detect the presence of maternal-fetal chimerism in IH tissue^[28].

Angio- and vasculogenesis theory

Both angiogenesis (growth of new blood vessels from pre-existing vessels) and vasculogenesis (*de novo* formation of blood vessels from stem cells) are hypothesized to contribute to IH formation. IHs may result from somatic mutations in a gene mediating endothelial cell proliferation (growth regulatory pathways)^[29]. Such mutations may alternate the vascular endothelial growth factor (VEGF) signaling pathway by reducing the expression of VEGF receptor 1 (VEGFR-1), which causes hyperactivity of VEGFR-2 and may induce IH formation through angiogenesis^[30]. IGF-2 and basic fibroblast growth factor also stimulate angiogenesis and are upregulated in proliferating IHs^[31,32]. Endothelial progenitor cells (EPCs), stem cells of vascular origin that are capable of differentiating into endothelial cells, seem to play a role in the development of IH through vasculogenesis^[33]. EPCs possess the surface markers (CD34⁺ and CD133⁺) that are also found in endothelial cells of growing IHs, suggesting that these bone-

marrow-derived progenitor cells may play a key role in the pathogenesis of IHs by inducing postnatal formation of vascular tissue^[34,35]. In 2008, Khan *et al.*^[36] injected immune-deficient mice with CD133⁺ EPCs, which resulted in the development of GLUT-1-positive vascular tumors in these mice. These findings greatly supported the angiogenesis theory.

Tissue hypoxia theory

Hypoxia, either local or systemic, seems to be the most influential inducer of IH development. Hypoxia stimulates the proliferation of EPCs^[24,37-41]. Transcription factor hypoxia-inducible factor 1 α (HIF-1 α) plays a key role in the tissue hypoxia theory. A hypoxic environment triggers the production of HIF-1 α . HIF-1 α in turn stimulates transcription of target genes, such as GLUT-1, VEGF and IGF-2^[42-45]. These stimulations may take place either directly by HIF-1 α signaling or by hypoxia-induced regulation of mammalian target of rapamycin (mTOR) complex 1 signaling. Deregulation of the mTOR pathway may lead to disorganized growth^[46,47]. Overexpression of VEGF may also take place via the activation of the HIF-2 α pathway as a response to the pathologic signal of a "dangerous hypoxic situation"^[48]. It has also been demonstrated that the combination of hypoxia and an estrogenic environment has a synergic effect on IH endothelial cell proliferation, which may explain the greater incidence of IHs in girls^[48].

As stated above, none of these three theories explains the pathogenesis of IH completely. Given the great variability of clinical presentations of IH, the uneven distribution of IHs over the body, the increased prevalence of IHs in Caucasians, and its familial occurrence, it is most likely that IH pathogenesis is not restricted to one factor, but to a combination of genetic predisposition and various environmental factors^[48,49].

CLINICAL PRESENTATION

IHs develop in the first days, weeks, or months of life. They are not to be confused with congenital hemangiomas, which are fully developed at birth and either rapidly involute during the first year of life (rapidly involuting congenital hemangiomas) or do not involute at all (non-involuting congenital hemangiomas)^[50,51]. Many children who develop an IH are born with a visible precursor lesion, such as a pale macule with telangiectasia or mottled vascular stain, at the future IH location^[52]. Fully developed, an IH feels elastic and frequently warm. The tumor is not pulsating and is painless, except in the case of ulceration^[48]. There is a great variation in size, but in most cases (80%), IHs are not greater than 3 cm in diameter^[8]. Recognized risk factors for developing an IH include female sex, prematurity, multiple gestation, and low birth weight. Caucasians are at greater risk of developing an IH compared with individuals of Hispanic or African origin^[5,6,53].



Figure 1 Superficial focal infantile hemangioma.

In the classification of the International Society for the Study of Vascular Anomalies (ISSVA), four different patterns of IH are described^[54]. According to their pattern, IHs can be grouped into focal, multifocal, segmental (plaque-like, covering an embryologic segment), and intermediate/indeterminate^[48,50]. Intermediate/indeterminate IHs show characteristics of both focal and segmental IHs. They do not entirely encompass an accepted embryologic segment nor do they arise from a single focus^[48,51]. Segmental IHs have a higher complication rate and are associated abnormalities^[55]. Apart from the pattern, the ISSVA classification makes a distinction between four different types of IHs, according to their clinical appearance: (1) superficial (50%-60%); (2) deep (15%); (3) mixed (25%-35%), which are distinguished by the layer(s) of the skin affected^[55]; and (4) reticular/abortive/minimal growth, which is distinguished by its typical growth pattern^[56,57].

Superficial IH

Superficial IHs are the most common type of IHs. They involve the papillary dermis and appear as bright red "strawberry" lesions in the case of a localized superficial IH (Figure 1) or as a plaque-like red lesion in the case of a segmental superficial IH (Figure 2). Segmental IHs are more often associated with complications, such as ulceration and associated anomalies, and more often require therapy^[8,48].

Deep IH

Deep IHs involve the deep, reticular dermis and subcutis, resulting in a tumor with a bluish shine or (when deeper) normal skin color (Figure 3). Because of these characteristics, deep IHs may easily be misdiagnosed at first^[55]. Deep IHs appear later than superficial IHs; typically around the age of 2 mo, and may have a



Figure 2 Superficial segmental infantile hemangioma.

longer proliferative phase compared with the superficial types^[17,51,52].

Mixed IH

Mixed IHs have both superficial and deep components (Figure 4). The proliferative phase of the deep component in mixed IHs also stops later than in superficial IHs^[17,48].

Reticular/abortive/minimal growth IH

A minority of IHs have arrested or minimal growth beyond the stage resembling the precursor lesions. Although their natural course is different from that of the other three types, these lesions do express GLUT-1 proteins and have similar other immunohistochemical characteristics (Figure 5)^[56,57]. Several terms have been used to describe these in the literature. The most commonly used terms are reticular, abortive, or minimal growth IH. IHs of this type seem to have a predilection for the lower body^[57]. The exact incidence of this type of IH is unknown, but it is believed to be relatively rare. However, a recent study by Munden *et al.*^[27] in which 578 pregnant women were prospectively enrolled and their infants followed up for 9 mo after birth, reports that of the infants with an IH, 20% had a reticular, abortive, or minimal growth IH.

Despite several hypotheses, the pathogenesis of segmental vs focal and superficial vs deep IHs remains unclear^[19].

NATURAL HISTORY

IHs have a unique pattern of evolution. As stated above, IHs are not fully developed at birth, but start to grow shortly after birth (usually within a few days or weeks) from normal appearing skin or a precursor lesion^[51]. This typical delay serves as a diagnostic

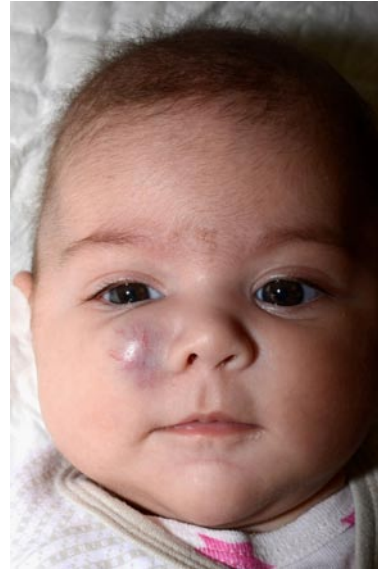


Figure 3 Deep infantile hemangioma.

tool, especially in deep IHs where the skin color may be bluish or even normal^[48]. After a relatively short proliferative phase in the first 3-9 mo of life, the slow involution phase takes place between the median age of 2-4 years^[8,48,58,59]. However, the proliferative phase may extend until 12 mo after birth, and in some cases, up to 24 mo after birth^[48,60]. Approximately 25%-69% patients with IH may develop a residual lesion after complete involution of the IH. Residual lesions may consist of skin atrophy, skin surplus, telangiectasias, pigmentation, scarification after ulceration and/or fibrofatty tissue^[3,58,61]. Epidermal invasion of an IH in combination with a deep component in the IH is most prone to residual lesions^[58]. The difference in reported incidence of residual lesions in several studies may be explained by usage of different populations (*e.g.*, secondary/tertiary referral vs primary referral).

IH AND RISK OF ASSOCIATED ANOMALIES

There are two types of IHs that may be predictive of an underlying anomaly. These are (1) large, flat, segmental IHs of the face, which are associated with PHACE(S) syndrome and (2) IHs in the lumbosacral or perineal region, which may be predictive of LUMBAR syndrome [also known as Perineal hemangioma, External genitalia malformations, Lipomyelomeningocele, Vesicorenal abnormalities, Imperforate anus, and Skin tag (PELVIS) or Spinal dysraphism, Anogenital, Cutaneous, Renal and urologic anomalies, associated with an Angioma of Lumbosacral localization (SACRAL) syndrome].

PHACE(S) syndrome

The term PHACE was introduced in 1996 by Frieden *et al.*^[62], describing a combination of five anomalies: (1) posterior fossa abnormalities; (2) hemangioma of



Figure 4 Mixed type infantile hemangioma.



Figure 5 Minimal growth type infantile hemangioma.

the face (segmental); (3) arterial abnormalities (intra- and extracranial); (4) cardiac and aortic defects; and (5) eye anomalies. A sixth anomaly: Sternal cleft or supraumbilical raphe was added later^[48]. PHACES syndrome is a spectrum of anomalies, because most affected children (70%) have only one extracutaneous manifestation^[63]. The so-called "Dandy-Walker syndrome" is the most common brain involvement, followed by cerebellar hypoplasia or dysgenesis as a result of posterior fossa abnormalities^[48,63]. Until 2009, a diagnosis of PHACES syndrome required the presence of a segmental, flat IH of the face in addition to one or more of the five anomalies described above^[62,64]. In 2009, a consensus was reached defining PHACES as the presence of a characteristic segmental hemangioma or hemangioma greater than 5 cm in diameter of the face or scalp plus one major criterion or two minor criteria^[65]. The exact incidence of PHACES is unknown. It has been postulated that in 20%-31% of children with segmental facial IHs, there is an association with PHACES^[64,66]. A full workup for PHACES syndrome is suggested in every infant with a large (> 5 cm), segmental, facial hemangioma. This includes a complete physical examination as well as careful cardiac (including echocardiogram), ophthalmologic and neurologic (including MRI of the head and MRA of the entire head and neck area) assessments^[67].

LUMBAR syndrome

IHs in the lumbosacral area or perineum are also associated with underlying structural anomalies. These IHs are also most commonly, but not exclusively, segmental^[68]. A tethered cord in the context of spina bifida occulta should be considered, although more extensive associated morbidity may be the case. For these conditions, different acronyms have been suggested, such as SACRAL^[69] and PELVIS^[70]. The most recently proposed acronym, LUMBAR is preferred; it refers to the association of lower body hemangioma and other cutaneous defects, urogenital anomalies, ulceration, myelopathy, bony deformities, anorectal malformations, arterial anomalies, and renal anomalies^[68]. There is no diagnostic consensus for LUMBAR, SACRAL, or PELVIS,

such as for PHACES. Screening with ultrasound scanning of the spine, abdomen, and pelvis is suggested for all patients with a segmental IH greater than 2.5 cm in diameter of any lumbosacral or perineal region who are younger than 3 mo. For children older than 3 mo, MRI is indicated^[68,71].

MANAGEMENT (PAST, PRESENT AND FUTURE)

The management of IHs has been changed drastically since the discovery of the efficacy of propranolol treatment for this indication in 2008^[13]. Although there are no uniform international guidelines available for the treatment of IHs, propranolol is now considered to be the treatment of first choice. Before that, a whole range of treatments had been applied. Some of these treatments are rarely or no longer used (e.g., X-irradiation therapy) because of their side effects and/or low efficacy.

Past

X-irradiation: Although there was already evidence that IHs involute spontaneously, X-irradiation has been widely used for two decades between 1930 and 1950, resulting in (unnecessary) radiation exposure and post-radiation skin atrophy, pigmentation, telangiectasia, contractures, and risk of skin cancer^[72-74].

Vincristine: Vincristine is a vinca alkaloid that is widely used in cancer chemotherapy. Treatment of IHs with vincristine was first described in 1993^[75]. This chemotherapeutic drug inhibits microtubule formation, causing arrest of mitosis and subsequent apoptosis^[76]. Additionally, vincristine seems to affect angiogenesis^[77]. Nowadays, it may only be indicated for severe IHs that are resistant to other therapies. The use of vincristine requires a central venous catheter for chronic administration. Furthermore, it has potential severe side effects, such as peripheral mixed sensorimotor neurotoxicity^[78]. Other, less severe, side effects include rash, alopecia, and local reactions, such as phlebitis and necrosis^[74].

Interferon: The use of subcutaneous interferon α -2a and -2b for the treatment of IHs was first described in 1989^[79]. Its therapeutic effectiveness has been attributed to its anti-angiogenic properties. Interferon α induces apoptosis of endothelial cells, which might also explain the clinically and histologically observed involution without any sign of inflammation or necrosis^[80]. Despite its high success rates, the use of interferon in the treatment of complicated IHs has been abandoned, because of its major side effects, such as spastic diplegia and blood abnormalities^[81,82].

Topical corticosteroids: Potent topical steroids have been described for small, superficial, localized IHs^[83]. Side effects include acne, perioral dermatitis, hypertrichosis, cutaneous atrophy, striae, hypopigmentation, and subcutaneous fat atrophy. Since the availability of topical β -blockers, with fewer side effects, topical steroids are less often prescribed in current practice^[76].

Topical imiquimod: Imiquimod is an immune modulator. In 2002, the potential of imiquimod to shorten the involution phase of IH was first reported^[84]. Due to its anti-angiogenic and apoptotic effects, imiquimod contributes to the regression of IH^[85,86]. Its efficacy is equivalent to the efficacy of the topical β -blocker timolol (0.5% ophthalmic solution), which was first described a few years after the discovery of propranolol treatment for IHs^[87,88]. However, timolol is more effective than imiquimod in terms of color involution and onset time^[89]. Furthermore, imiquimod has a less favorable adverse-reaction profile and has never really become a very common treatment for IHs that are suitable for topical therapy^[88].

Present

Watchful waiting: Knowing IH's natural history, it is justified to be restrictive in actively treating this self-limiting condition. Starting in the 1950s, physicians began to prefer this approach over the invasive X-irradiation and/or surgical removal^[73]. At the present time, watchful waiting is still considered to be the best approach for the vast majority of patients with IH.

Systemic propranolol (first choice): In 2008, after the report of the very successful therapeutic effect of propranolol, IH treatment changed drastically^[13]. Currently, propranolol has become the treatment of first choice for IHs. It seems that propranolol stops growth and induces an IH regression that is much better and safer than previous therapies^[90]. Recently, Léauté-Labrèze *et al.*^[91], published a large-scale randomized placebo-controlled trial showing that propranolol is effective at a dose of 3 mg/kg per day for 6 mo in the treatment of IHs. This treatment resulted in a significantly higher success rate compared with placebo (60% vs 4%). These outcomes are in line with the results of the RCT conducted by Hogeling *et al.*^[92] in 2011. Earlier, Malik *et al.*^[93] had shown in their RCT

that propranolol had a consistent, rapid therapeutic effect with a lower number of complications compared with prednisolone. They also demonstrated that a combination of both propranolol and prednisolone was not superior to propranolol alone^[93]. An RCT carried out by Zaher *et al.*^[94] proved the superiority of oral admission of propranolol compared with topical and intralesional application. While the general mechanism of action of propranolol is well established as an antagonist of both β_1 - and β_2 -adrenergic receptors, the precise mechanism of action on IHs remains uncertain^[19]. It is known that propranolol is effective in IH through vasoconstriction, inhibition of angiogenesis, induction of apoptosis, or dysregulation of the renin-angiotensin system (RAS)^[95,96].

The most common serious adverse effects of propranolol are bradycardia, hypoglycemia, and hypotension. Other reported adverse side effects in adults and children include bronchospasms, congestive heart failure, hypothermia, somnolence, sleep disturbance, nightmares, depression, nausea, vomiting, diarrhea, hyperkalemia, gastro-esophageal reflux, psoriatic drug rash, and respiratory symptoms^[92]. Because of the lipophilic nature of propranolol and the potential to penetrate the blood-brain barrier, the probability of affecting the developing central nervous system of infants with IH was postulated in a report in 2013^[97]. This information was further elaborated by Langley *et al.*^[18] in 2015. In 2014, Gonski *et al.*^[98] showed no gross motor development problems in propranolol-treated children with IH. Recently, our group confirmed these findings. We not only looked for problems with gross motor development, but also included the fine motor/adaptation/personal social functioning and communication in our study^[99-101], using the "van Wiechen scheme", a Dutch screening instrument based on the developmental model of an American developmental psychologist and pediatrician (A. Gesell). No signs of psychomotor developmental problems were found^[101]. Despite these promising findings, it is still unclear what effects, either subtle or not, propranolol has on the developing brain. Future prospective studies on later age, using universal screening tools or more advanced neuropsychologic tests are needed to support these findings. Until then, propranolol should only be prescribed for children with IHs with current or impending complications.

Topical β -blockers (first choice): As an alternative to oral β -blockers, topical β -blockers have been used for superficial IHs. There are different forms of topical β -blockers, but timolol (0.5% ophthalmic solution or 0.1% gel), a non-selective β -blocker, is most widely used^[76]. In 2013, a double-blind placebo-controlled RCT was published, comparing topical timolol 0.5% solution with placebo for superficial IHs. Timolol was shown to be safe and effective^[102]. Recently, timolol 0.5% ophthalmic solution was compared with laser treatment, where timolol proved to be a safe, effective,

and painless alternative to lasers for the treatment of superficial IHs. In mixed IHs, laser treatment provided better results than timolol, because of its deeper penetration^[103]. Comparison between timolol 0.5% ophthalmic solution and 5% imiquimod cream in 54 patients with IH (half of the IH was treated with timolol and other half with imiquimod) showed similar efficacy, but fewer side effects were seen in the timolol group^[89].

Systemic corticosteroids (second choice): In the 1960s, systemic corticosteroids were found to be an effective treatment for IHs^[104,105]. The mechanism of action is still not completely understood, but the main theory is that corticosteroids suppress the VEGF-A expression and therefore inhibit angiogenesis and/or vasculogenesis^[106]. The usually recommended dose is 2-3 mg/kg per day, which is most effective in the early proliferating phase^[107,108]. With a treatment response of 84%-90% and an overall rebound rate of 36%, this therapy became the first-choice therapy for severe IHs, requiring intervention^[73,107,109]. The most common side effects of systemic corticosteroids are cushingoid facies (71%), personality changes (29%), gastric irritation (21%), fungal infection (6%), and diminished weight gain (42%) and height (35%)^[110]. Other possible side effects were systemic infection, hypertension, increased appetite, aseptic necrosis of bones and cardiomyopathy^[20]. Currently, systemic corticosteroids have become a little-used second-line option, because of the lower efficacy and less favorable side-effect profile compared with propranolol^[76].

Intralesional corticosteroids (in specified indications): Intralesional corticosteroids (mostly triamcinolone 10 mg/mL) offer an alternative to systemic therapy for small IHs^[76]. This therapy was initially used by ophthalmologists for periorbital IHs. Because of the risk of retinal artery damage and blindness, intralesional corticosteroids are no longer used for periorbital IHs^[111-113]. The common side effects may include subcutaneous atrophy and hypopigmentation^[76].

Surgery (in specified indications): Surgical treatment of IH is suitable in some specific cases. It is indicated in well-circumscribed, pedunculated, or ulcerated lesions that have failed to respond to medical treatment, grow rapidly, or cause significant deformity^[114]. Although propranolol treatment has been a breakthrough in the management of IHs, many children still require plastic surgery after the involution phase. At the present time, most surgical interventions in IHs are used to treat those involuted IHs that have left residual lesions, such as skin surplus, scarification after ulceration and/or fibrofatty tissue^[115,116].

Laser therapy (in specified indications): Pulsed dye laser (PDL) is the most commonly used laser treatment for superficial and ulcerating IHs and for residual

lesions. The literature on the effectiveness of PDL in IHs is somewhat controversial. Some earlier studies suggest that early treatment of IHs with PDL prevents further growth, induces tumor regression, and improves cosmetic outcome, while a randomized controlled trial of 121 infants showed no significant difference in complete clearance or minimum residual signs between the PDL-treated group and the observational group^[117-120]. Conventional PDL is ineffective in the treatment of deep IHs. Its penetration depth is limited due to the optical absorption and scattering in the epidermis and dermis^[121]. Introduction of a long-pulse PDL in combination with an epidermal cooling system made a greater depth of vascular injury possible^[120,122]. Additionally, the use of long-pulse PDL with an epidermal cooling system decreases the risk of scarring and induction of ulceration^[122]. These types of laser treatment are not painless and may require anesthesia in infants.

The larger, deep IHs may also be effectively treated using the neodymium-doped yttrium aluminum garnet (Nd:YAG) laser. However, due to greater risk of scarring or hypo- or hyperpigmentation, this therapy should be preserved for difficult, recalcitrant cases^[121,123,124].

Therapy with the fractionated CO₂ laser is reserved for involuted IHs with residual fibrofatty tissue, atrophic plaques, or other textural changes^[125].

Future

Other systemic β -blockers: Propranolol is a non-selective, lipophilic, β -adrenergic receptor antagonist, which binds to β_1 - and β_2 -adrenergic receptors^[126]. The potential side effects of propranolol made physicians and researchers search for an alternative β -blocker that is as effective as propranolol, but with fewer side effects. It was suggested that a hydrophilic, selective β_1 -blocker, atenolol, which occurs at lower concentrations in the brain, may have these characteristics^[127,128]. A small randomized controlled trial showed no significant difference in effectiveness between atenolol and propranolol. However, no difference in adverse effects was demonstrated either^[129]. In 2009, oral nadolol, a non-selective β -blocker, which is significantly less lipophilic than propranolol, was found to have a significant effect on IH growth, with a rapid reduction in size^[130,131]. Recently, a small retrospective study of 48 participants showed effects of nadolol similar to those of propranolol. Although serious adverse effects were rare, side effects such as sleep disturbance, behavior problems, gastrointestinal symptoms, and cold extremities were still frequently seen^[132]. In 2010, a case report suggested the use of acebutolol for the treatment of infantile subglottic hemangioma, because of fewer side effects on resting heart rate than propranolol, metoprolol, and atenolol^[133].

In general, β -blocker lipophilicity and/or selectivity are factors that determine the efficacy and side-effect profile. It is unclear whether a degree of lipophilicity

may be required for tissue penetration and efficacy of IH treatment. It is also unclear whether β_1 - or β_2 -blockade or a combination of the two is needed to achieve a therapeutic effect. In conclusion, the search for a β -blocker with the best effectiveness and the most favorable side-effects profile, is still ongoing.

Rapamycin: Rapamycin, also known as sirolimus, is a bacterial macrolide that also has antifungal effects. Since rapamycin is an mTOR inhibitor, it inhibits mTOR signaling, an important regulator of growth and proliferation. By inhibiting the mTOR signaling pathway, rapamycin decreases the elevated VEGF and HIF-1 levels produced by endothelial cells, and reduces IH proliferation^[134-136]. Rapamycin not only negatively affects cell proliferation, but also metabolism, as well as angiogenesis. Additionally, rapamycin seems to limit stem cell replicative capabilities, affecting vasculogenesis^[137]. At this time, rapamycin treatment use is restricted to clinical trials until better safety data are available^[20,76].

Angiotensin-converting enzyme inhibitors: With the expanding knowledge on IH pathogenesis as a result of the discovery of the efficacy of β -blockers for this indication, the regulation of hemogenic endothelium regulated by the RAS in IHs became a point of interest with possible therapeutic consequences^[138]. A year later, expression of components of the RAS by the endothelium of proliferating IHs was shown^[139]. The role of the RAS in IH is supported by the clinical observation of a higher incidence of IHs in premature infants, females, and Caucasians, since these groups have a higher renin level or activity than full-term infants, males, and black infants, respectively^[139-142]. In connection with these findings, a clinical trial of eight patients with IH conducted in 2012 reported promising results for captopril treatment^[143]. Shortly after that, it was contradicted by a small retrospective review from Australia, assessing patients with IH who had to discontinue treatment with prednisolone because of steroid-induced hypertension. Of the patients who received captopril after discontinuing prednisolone, 33% demonstrated no changes in IH and 58% demonstrated a worsening^[144]. More prospective randomized studies are needed to confirm or disprove these findings.

Oral itraconazole: Recently, efficacy of oral itraconazole was reported in six infants with IH. An obvious clinical improvement was noted in all cases during a 3-mo period, with an improvement of 80%-100%. Side effects were mild and limited^[145]. The exact mechanism of itraconazole effectiveness is not yet fully understood, but it seems that itraconazole has an anti-angiogenic effect by inhibiting the VEGFR-2^[146]. The future will teach us what itraconazole adds to the therapeutic arsenal for IHs.

ASSESSMENT OF IH SEVERITY AND ACTIVITY

The number of prospective studies of IH and its treatment has increased rapidly. Especially since the discovery of propranolol for this indication, the need for validated and reliable instruments to measure IH severity and activity in clinical trials has become an important issue. In 2011, the Hemangioma Activity Score (HAS) was developed, which provided a total activity score by measuring the swelling, color, and ulceration of IH. HAS seems to be suitable for evaluating IH activity and response to treatment over time^[147,148]. In 2012, the Hemangioma Investigator Group Research Core developed another scoring system, the Hemangioma Severity Scale (HSS)^[149]. The HSS not only takes the objective items, such as size, location, and complications into account, but it also assesses the subjective items, such as pain and risk of disfigurement^[149]. Recently, a group of Bulgarian dermatologists presented the Hemangioma Activity and Severity Index^[150].

Time will tell which scoring system has the best qualities to be implemented in clinical practice and used for research purposes.

IMPACT OF IH ON QUALITY OF LIFE

It is well known that visible abnormalities, such as IH, may affect the quality of life (QoL) of children or their parents/caregivers. Several studies have tried to measure the impact of IH on children and their parents. Until recently, either validated non-IH-specific or non-validated but IH-specific questionnaires have been used, providing controversial information^[151-153]. This controversy may be explained by the absence of attention to impact of IH-specific factors (*e.g.*, localization, size, and complications) in non-IH-specific questionnaires or by use of non-validated IH-specific questionnaires. Most of them measure the overall psychosocial well-being instead of measuring a specific IH-related psychosocial impact^[151]. In February 2015, Chamlin *et al.*^[154] presented a validated IH-specific QoL questionnaire. It is only matter of time before the first reports of the impact of IHs on the QoL of children and their parents will appear using this validated, IH-specific questionnaire, giving more reliable information. These reports will be followed by studies on the effects of different treatments on QoL. This information will provide us with the tools to optimally deploy the therapeutic arsenal for IHs.

CONCLUSION

The discovery that propranolol is efficacious in the treatment of IH has led to an upsurge in publications, increasing our knowledge of this subject. In this review, we provided the most up-to-date information about the

pathophysiology, variations in clinical presentation, and natural history of IHs. We looked at possible working mechanisms of several treatments and current worries regarding the treatment of first choice, propranolol. Finally, we provided an overview of the instruments measuring IH severity and/or activity and IH-related QoL.

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Psoriasis treatment: Unconventional and non-standard modalities in the era of biologics

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Abstract

Psoriasis is a potentially debilitating inflammatory dermatosis affecting 0.2%-4.8% of the population worldwide causing a significant occupational, personal or psychosocial morbidity to these patients for life. The basic aim of psoriasis therapy is to control the disease to maximum possible extent and improve the

patient's quality of life. Management of triggers for flare-ups, lifestyle modifications, and dietary supplements are often recommended. Intermittent or rotational therapy with frequent alterations in treatment options is usually needed to reduce toxicity of anti-psoriatic drugs in the absence of safer alternatives. Currently, several biological agents categorized as either T-cell targeted (*e.g.*, Alefacept, Efalizumab) or cytokine modulating (*e.g.*, Adalimumab, Infliximab, Etanercept) are available for treating severe psoriasis. However, their high cost is often precluding for most patients. The usefulness of systemic (methotrexate, cyclosporine, acitretin or several other therapeutic agents) or topical (tar, anthralin, corticosteroids or calcipotriol ointments, phototherapy with or without psoralens) therapies has been well established for the management of psoriasis. The literature is also replete with benefits of less used non-standard and unconventional treatment modalities (hydroxycarbamide, azathioprine, leflunomide, mycophenolate mofetil, isotretinoin, fumarates, topical calcineurin inhibitors, peroxisome proliferator-activated receptors agonists, statins, sulfasalazine, pentoxifylline, colchicine, grenz ray therapy, excimer laser, climato-therapy and balneophototherapy, peritoneal dialysis, tonsillectomy, ichthyotherapy, *etc.*). These can be used alternatively to treat psoriasis patients who have mild/minimal lesions, are intolerant to conventional drugs, have developed side effects or achieved recommended cumulative dose, where comorbidities pose unusual therapeutic challenges, or may be as intermittent, rotational or combination treatment alternatives.

Key words: Acetretin; Azathioprine; Balneophototherapy; Calcineurin inhibitors; Calcipotriol; Calcium dobesilate; Climatotherapy; Colchicine; Cyclosporine; Dapsone; Excimer laser; Fumarates; Grenz ray therapy; Hydroxycarbamide; Ichthyotherapy; Isotretinoin; Leflunamide; Methotrexate; Mycophenolate mofetil; Pentoxifylline; Peritoneal dialysis; Phototherapy; Plaque psoriasis; Peroxisome proliferator-activated receptors agonists; Statins; Sulfasalazine; Tonsillectomy

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Core tip: The clinicians must be aware of all available antipsoriasis therapies in view of variable therapeutic outcome(s) that may test one's ingenuity in managing some "difficult to treat" psoriasis patients. The non-standard and off-label therapies will remain an important alternative to more widely used measures in rotational/intermittent treatment(s) or until a therapy that is affordable, safe, effective, and more importantly, remittiv becomes available.

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INTRODUCTION

Psoriasis is a potentially debilitating inflammatory dermatosis affecting 0.2%-4.8% of the population worldwide and with an estimated prevalence of 2.2% to 2.63% in the United States with approximately 150000 newly diagnosed cases per year^[1]. All its clinical forms may eventually evolve into chronic plaque psoriasis characterized clinically by well demarcated, erythematous, scaly plaques. Guttate psoriasis is often self limiting, lasting for 12 to 16 wk, without treatment. However, 1/3rd-2/3rd of these patients may later develop chronic plaque psoriasis. Spontaneous remissions in chronic plaque psoriasis, lasting for variable periods of 1 year to several decades, may occur in up to 50% patients. Erythrodermic and generalized pustular psoriasis tend to be severe and persistent. There is no evidence that the disease is anyway different in either gender. There is no known prevention for psoriasis and in most cases, it remains a life long disease manifesting at unpredictable intervals with weekly, monthly or occasional recurrences. Although not life threatening, psoriasis can significantly impair quality of life with as many as 79% of patients with severe disease reporting a negative impact on their lives, and nearly 5% of them had contemplated suicide in a survey by National Psoriasis Foundation^[2].

A plethora of anti-psoriatic treatments, both topical and systemic, is available for the management of psoriasis (Table 1). During the past four decades or so systemic methotrexate has been used effectively to treat all forms of psoriasis, including erythrodermic pustular and chronic plaque psoriasis. Despite a major concern for hepatotoxicity associated with its long-term use, it is even indicated for long-term management of severe forms of psoriasis. Currently, several biological agents are being used or evaluated for treating severe psoriasis. The Food and Drug Administration (FDA)

Table 1 Therapeutic options for psoriasis

Topical agents	Systemic agents	Phototherapy
Emollients	Methorexate	Natural
Tar and anthralin	Retinoids	Dead Sea Therapy
Dithranol	Cyclosporine A	and PUVA-Sol
Corticosteroids	Hydroxyurea	Artificial
Vitamin D analogs	Tacrolimus	PUVA, Bath PUVA,
Tazarotene	Mycophenolate mofetil	UVB and NB-UVB
Salicylic acid	Sulfasalazine	Newer
Tacrolimus/ pimecrolimus	6-thioguanine	Excimer laser, NB- UVB light enhanced
5-fluorouracil	Calcitriol	Photodynamic
Ascomycin derivatives	Colchicine	therapy
	Dapsone	
	Azathioprine	
	Fumaric acid esters	
	Biologics: Etanercept,	
	Alefacept, Infliximab,	
	Efalizumab,	
	Adalimumab	

UV: Ultraviolet light; PUVA: Psoralene ultraviolet A; Sol: Solar; NB-UVB: Narrow band UV.

approved ones are broadly categorized as either T-cell targeted (e.g., Alefacept, Efalizumab) or cytokine modulating (e.g., Adalimumab, Infliximab, Etanercept). Except for being prohibitory expensive, these apparently have an advantage over current systemic therapies, as systemic adverse effects do not mar their efficacy.

The voluminous literature on treatment of psoriasis is itself indicative of limitations of any therapy. It is often confusing while selecting a treatment regimen as most treatment schedules are aimed to decrease disease severity and extent that it no longer interferes with occupation, personal or psychosocial well-being of the patient. However, the patient's own assessment for their current therapy may remain unsatisfactory. For instance, in two separate surveys 40%-42% of patients felt frustrated with the ineffectiveness of their treatments while 32% reported that treatment was not aggressive enough^[2,3]. As psoriasis is a chronic life long disease, safety of a treatment during long-term use too is of major concern. To date there is no absolutely safe, simple and inexpensive treatment for psoriasis and the selection of various strategies has to be individualized. The basic aim of psoriasis therapy is to control the disease to maximum possible extent and improve the patient's quality of life. Although reduction of psoriasis area severity index (PASI) score to 50% is currently considered adequate, there is no clear association among illness impact, subjective well-being, and the disease severity^[4]. The patients may also assess their psoriasis as more severe than physicians do necessitating the need for more patient centric therapies^[5]. Intermittent or rotational therapy with frequent alterations in treatment options is employed to reduce toxicity of anti-psoriatic drugs while search for safer alternatives continues. This paper focuses and reviews the less used and unconventional treatment modalities which can be useful alternatives to treat psoriasis patients who have mild/minimal lesions, are intolerant to

conventional drugs, have developed side effects or achieved their recommended cumulative dose, where comorbidities pose unusual challenges, or may be as intermittent, rotational or combination treatment alternatives. As management of triggers for flare-ups, lifestyle modifications, and dietary supplements are recommended frequently, it will be prudent to briefly review them along with few first line therapies.

MANAGING TRIGGERS

Despite the knowledge accumulated during past few decades that psoriasis is an immune mediated, regeneration-like reaction of the skin in genetically predisposed individuals wherein various cells including keratinocytes, antigen presenting cells, and T-cells play a dominant role at different stages, the exogenous factors which trigger psoriasis or induce flare-ups are poorly understood. A variety of environmental factors such as physical trauma (scratching, insect bites, surgery, sunburn) causing damage to keratinocytes (Koebner's phenomenon), drugs (antimalarial, clopidogrel, beta blockers, angiotensin-converting enzyme inhibitors, lithium, gemfibrozyl, imiquimod, interferon (IFN)- α , IFN- γ , withdrawal of corticosteroids or cyclosporin), infections (bacterial, viral, and yeast), or metabolic disorders such as hypocalcemia (primary or secondary) are implicated triggers for exacerbations^[6]. Exacerbation and persistence of psoriasis has been attributed to increased hyper-reactivity to superantigens that are usually viral or bacterial proteins^[7]. Bacterial (*Staphylococcus aureus*, *Streptococcus* sp.) endotoxins act as superantigens and activate T-cells, macrophages, Langerhans cells and keratinocyte. Superantigens bind to class II major histocompatibility complex (MHC) molecules and V β segments of the T cell receptor resulting in its activation and cytokine release. Balci *et al*^[8] found a high prevalence of colonization of skin lesions and nares of psoriasis patients by toxigenic strains of *Staphylococcus aureus* as compared to healthy controls. They also observed a significant relationship between PASI scores and toxin production and suggested association between psoriasis and non-classical superantigens such as *mecA*, *etb* and *see*. Although they did not elucidate on therapeutic implications of their findings, antimicrobial therapy may have some role in psoriasis treatment. Other suggested association between *Candida albicans*, *Borrelia burgdorferi*, and *Pityrosporum ovale* remains unsubstantiated^[9-11]. HIV-associated psoriasis usually develop in non-terminal stages of AIDS that is frequently severe, recalcitrant to therapy and has associated arthritis six times more often^[12]. Although zidovudine has not been found effective for psoriasis in HIV-negative patients, it reportedly improves HIV-associated psoriasis^[13,14]. However, exacerbations in HIV-associated psoriasis were treated more effectively with triple antiretroviral therapy (stavudine 30 mg, lamivudine 150 mg, nevirapine 200 mg; all twice daily)^[15].

The role of human papillomavirus type 5, demonstrated in scrapping of lesional skin in nearly 90% of a large series of psoriasis patients, in the etiology of the disease remains to be determined^[16].

The association of psoriasis, pustular psoriasis in particular, with hypocalcemia, mostly from hypoparathyroidism (both idiopathic and familial), that resolved after treatment with calcium has been described by several workers^[17-20]. Similarly, experimental and clinical demonstration of association between vitamin D deficiency and psoriasis has been further supported by the effectiveness of vitamin D analog (calcitriol) in the treatment of psoriasis^[20].

MANAGING LIFESTYLE

Factors such as obesity, smoking and alcohol consumption, diet, and stressful life events have been suggested to affect the course of psoriasis. Although their exact role in the etiology of psoriasis remains unclear, being modifiable they may be important adjunct to the therapeutic management of psoriasis. Psoriasis patients have been observed to present more frequently with obesity than the general population and severe psoriasis, *i.e.*, PASI > 10 and > 20% body surface area involvement^[21-23]. Duarte *et al*^[21] considered obesity a risk factor for severe psoriasis by observing a strong correlation between PASI > 10 and all obesity parameters; waist circumference, waist hip ratio, and body mass index (BMI). Setty *et al*^[22] examined data linking weight gain and incident psoriasis in 78626 women and observed that the relative risk of psoriasis increased with the rise in BMI during the study period of 14 years. The authors attribute this to the production of inflammatory cytokines by adipositis as a possible explanation. There are reports of improved psoriasis in patients who lost weight and after gastric bypass surgery^[24-26]. Nevertheless, obesity does not appear to play a role in the new onset of psoriasis or affect the efficacy of adalimumab in the treatment of psoriasis^[27,28]. However, prospective data is lacking specifically to evaluate the role of weight loss in psoriasis.

Smoking and alcohol consumption

Recent studies suggest that cigarette smoking increases oxidative damage, promotes inflammatory changes, and enhances expression of genes associated with psoriasis^[29]. Several studies across countries have linked current and past smoking habits to the increased severity or new onset psoriasis^[30-36]. Smoking > 20 cigarettes daily has been associated with more than two fold increased risk of severe psoriasis, whereas the association between smoking and psoriasis seems to be stronger in women^[35,36]. Smoking can worsen severity of psoriasis and makes patients less responsive to therapy^[33,35,37]. While non-smokers experience more frequent remissions than smokers, cessation of smoking leads to decreased severity and the excess risk of psoriasis also declines^[33,36,38].

There is extensive published literature on excessive alcohol consumption among psoriasis patients in a recent systematic review^[39]. Alcohol consumption appears to trigger, exacerbate and influence the severity and the progression of psoriasis and psoriatic arthritis^[30,40-42]. The amount consumed and the type of alcohol seems to trigger development and/or exacerbation of plaque psoriasis. Qureshi *et al*^[41] in a recent prospective study followed 82869 women for 14 years and showed that consumption of more than 2.3 alcoholic beverages weekly was an important risk factor for new onset psoriasis. They also deduced that consuming non-light beer is an independent risk factor for developing psoriasis in females. Similarly, alcohol consumption at levels higher than 100 g/d appears to be a risk factor for the development and exacerbation of psoriasis in males^[40,43]. The exact pathomechanisms by which alcohol triggers or exacerbates psoriasis remain poorly understood. Immune dysfunction/immunosuppression and increased susceptibility for infections, excessive production of inflammatory cytokines, and epidermal hyperproliferation by cycle activators such as cyclin D1 and keratinocyte growth factor have been implicated^[44,45]. Not the least, alcohol abuse in psoriasis patients too is associated with decreased response to treatment and has implications for interaction with antipsoriatic medication^[43,46,47].

Diet and dietary supplements

Diet rich in gluten, polyunsaturated fatty acids, and alcohol has been implicated in the severity of psoriasis in a significant number of patients^[48]. An increased incidence of psoriasis in patients with celiac disease has been suggested^[49-51]. A gluten-free diet is also suggested to improve psoriasis severity in celiac disease and even in patients with no celiac disease but with immunoglobulin A and/or immunoglobulin G (IgG) antigliadin antibodies^[50,51]. However, the link between psoriasis and gluten-intolerance remains poorly understood due to inconsistent data. Nonetheless, all psoriasis patients with celiac disease or gluten-intolerance should have a gluten-free diet for overall wellbeing. Polyunsaturated fatty acids, through overproduction of arachidonic acid derived eicosanoids, influence several inflammatory disorders including psoriasis. The outcome from studies on effect of diet rich in omega-3 polyunsaturated fatty acids remains inconsistent. However, intake of fish rich in omega-3 and vegetarian diets may benefit psoriasis patients, as there is decreased intake of arachidonic acid and consequent reduction in inflammatory eicosanoid formation. Omega-3 fatty acids, especially eicosapentaenoic acid and docosahexanoic acid, compete with arachidonic acid as substrates for cyclooxygenase and lipoxygenase, which thereby reduces downstream proinflammatory cytokines in psoriasis plaques. Most studies performed to evaluate their efficacy or fish oil rich in omega-3 fatty acids as dietary supplements in psoriasis report improvement in mean PASI scores^[52-57]. However,

there is no agreement concerning the dose of oral supplementation to be effective and the outcomes of randomized controlled trials are less effective^[55,56]. Parenteral infusions of omega-3 fatty acids has been reported beneficial in patients with acute psoriasis^[57]. Systematic reviews also advocates omega-3 fatty as adjuvant treatment of chronic plaque psoriasis in evidence-based clinical guidelines^[58,59].

Although caffeine consumption has been observed to decrease the therapeutic benefit of methotrexate in rheumatoid arthritis^[60], it does not appear to effect psoriasis or inhibit anti-inflammatory effect or therapeutic benefits of methotrexate in patients with psoriasis or psoriatic arthritis^[61]. Low calorie diet in a study showed a significant improvement after 4 wk as compared to controls and oral vitamin D supplementation can be recommended in psoriasis patients who are not on topical treatment with vitamin D analogues. The reported beneficial role of probiotics in psoriasis needs evaluation^[62,63]. Similarly, curcumin [1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione], has been shown to resolve psoriasis by lowering phosphorylase kinase levels in psoriatic epidermis and decreasing Ki-67 cells, which are capable of division^[64-66]. Psoriasis patients treated with topical steroid plus oral curcumin 2 g/d achieved best PASI 50, PASI 75, PASI 90 and PASI 100 than patients treated with topical steroids plus placebo in a recent controlled trial and perhaps best used as an adjuvant to other therapies^[65]. This phytochemical is one of the curcuminoid extracted from turmeric (*curcuma longa*), others being demethoxy-curcumin and bisdemethoxycurcumin. It exerts anti-inflammatory activity by inhibition of cyclooxygenase, 5-lipoxygenase and glutathione S-transferase and a number of other molecules but lacks clinical data to support its recommendation as a part of psoriasis treatment. In general, there is no sufficient scientific evidence that any special psoriasis diet is beneficial and the influence of diet on the course of psoriasis remains controversial. Nevertheless, avoiding foods suspected of causing inflammation or flare-ups, and eating low energy diet, will reduce risk for psoriasis comorbidities including obesity, diabetes, and cardiovascular diseases.

Infections and antimicrobial agents

Streptococcal infection and onset of guttate psoriasis and exacerbation of chronic plaque psoriasis have been repeatedly linked so much so that some workers routinely treat exacerbations with antimicrobial agents^[67-71]. Saxena *et al*^[72] noted significant improvement in PASI score in 30 patients with chronic plaque psoriasis at 12 wk and excellent improvement at 2 years from treatment with intramuscular benzathine penicillin (1.2 million units) fortnightly for 24 wk initially and then given once a week for a 2-year study period. Later, in a single blind randomized case-control study they used oral azithromycin for 48 wk as a single 500 mg/d for 4 d with a gap of 10 d (total 24 such courses) and achieved PASI 75 in 80% patients in the treatment group^[73]. No

significant change was noted in control group. However, 20% of treated patients experienced recurrence at the end of one-year study period. Polat *et al*^[74] used erythromycin 1000 mg/d and topical corticosteroids in 36 psoriasis patients and only topical corticosteroids in 24 controls for 4 wk. They noted statistically significant difference between the mean PASI of the two groups at the end of the treatment. The treatment used for the study group was also more effective against pruritus. However, these effects were attributed to inhibition of the production of many proinflammatory cytokines, including interleukin-6 (IL-6), IL-8 and TNF- α , perhaps by suppressing NF- κ B or activator protein-1, and reduced neutrophil activity by macrolides rather than to their antibacterial properties. It has therefore been suggested that macrolides might be candidates for adjunctive treatment of psoriasis^[74,75]. It is always prudent to treat appropriately any suspected coinfection to reduce overall morbidity, although, intervention by antibiotics is not considered of significant benefit by some researchers^[76,77].

ANTIMETABOLITES AND OTHER IMMUNOSUPPRESSIVES

The drugs like methotrexate and cyclosporine with their proven efficacy in psoriasis remain well-established therapies of first choice for moderate to severe psoriasis. Methotrexate (0.2-0.4 mg/kg, 7.5 mg to maximum of 30 mg/wk), alone or in combination with other drugs, is highly effective for the treatment of all forms of psoriasis. Its efficacy almost equals that of cyclosporine A or fumarates but is superior to that of hydroxycarbamide or mycophenolate mofetil (MMF)^[78-83]. The efficacy and safety of combination of methotrexate and biologic therapy using adalimumab, etanercept, infliximab, or briakinumab too has been demonstrated in several uncontrolled studies and case series involving patients with psoriatic arthritis as well, and even in patients without previous methotrexate therapy^[84-93]. However, methotrexate induced hepatotoxicity ranging from an asymptomatic transaminasemia to hepatic fibrosis and cirrhosis remains the most important concern in addition to vast potential for drug interactions (Tables 2 and 3). Therapeutic guidelines and recommendations have been available from time to time for monitoring methotrexate induced hepatotoxicity (Tables 4 and 5)^[94-96]. Unfortunately, the potential efficacy of a topical methotrexate preparation in palmoplantar or plaque psoriasis remains unexploited^[97-99]. Drugs like hydroxycarbamide, azathioprine, leflunomide, 5-fluorouracil, paclitaxel, and MMF too have been used infrequently in spite of limited therapeutic benefit vs methotrexate.

Hydroxycarbamide

Hydroxycarbamide (hydroxyurea), an antimetabolite, inhibits DNA synthesis by interfering with catalytic

activity of the enzyme ribonucleoside diphosphatase reductase during the S-phase of the cell cycle. It was reported to be effective in refractory psoriasis for the first time by Yarbo in 1969. Since then many reports have shown favorable but variable results^[100-108]. However, it is probably difficult to evaluate efficacy of hydroxycarbamide from these studies as various workers have used different doses for varying periods of time and evaluated their patients by different criteria. For instance, Layton *et al*^[102] in their study of 86 patient with extensive chronic plaque psoriasis treated with hydroxycarbamide (0.5-1.5 g/d given for 3-96 mo), observed satisfactory remission in 61% patients while other 39% patients had inadequate response or significant relapse during treatment. While Sharma *et al*^[101] obtained 76% reduction in the mean PASI score with hydroxyurea (1-1.5 g/d) given for 12 wk. Moschella *et al*^[103] administered intermittent courses of hydroxycarbamide over a period of 18 mo to treat 60 patients with severe or incapacitating psoriasis and noted good to excellent response in 63% patients in first 6 wk and in 50% patients in 18 mo respectively. Boyd *et al*^[104] in their review summarized therapeutic experience with hydroxycarbamide as excellent in 18%-38% and poor in 15%-20% patients. Weekly doses of hydroxycarbamide too have been tried with variable success^[109]. Hydroxycarbamide, 3.0 or 4.5 gm administered in weekly doses, was found effective in small number of patients and devoid of serious side effects as compared to its reported safety profile of daily therapy in a comparative study^[81]. Eight (53%) patients did not show adequate response (< 25% reduction in PASI) at the end of 4 wk and 8 (53%) patients had mild to moderate improvement (25%-75% reduction in PASI) at 8 wk of treatment. However, at the end of 12-wk study period only 2 (13%) patients achieved marked improvement (> 75% reduction in PASI), 11 (73%) patients had mild to moderate improvement (25%-75% reduction in PASI) and 2 (13%) patients did not respond at all. The mean percentage reduction in PASI score was 48.47% \pm 26.53% at the end of 12 wk. However, methotrexate (15-20 mg/wk) was faster in clearing the lesions and associated with higher adverse effects than hydroxycarbamide. Cutaneous or nail pigmentation, diffuse reversible alopecia, gastrointestinal symptoms, hematological and liver function abnormalities are usual side effects reported in 33% and 43% patients while hematologic side effects comprised 21% and 35% after prolonged hydroxycarbamide therapy in two separate studies^[102,103]. Kumar *et al*^[110] reported side effects in their 65.5% patients, pigmentation of nails, skin or mucosa being the commonest one seen in 58.6% patients. Sharma *et al*^[101] also observed post-inflammatory lesional and nail hyperpigmentation in all their 34 patients apart from hematological adverse effects and skin infections in 23.53% patients. More uncommon and severe adverse reactions necessitating discontinuation of therapy include "flu-like" syndrome, cutaneous

Table 2 Adverse effects of methotrexate therapy

System involved	Adverse effects
General	Fatigue, headaches, chills and fever, dizziness
Skin	Pruritus, pain and burning, urticaria, mild reversible alopecia, ecchymosis, acute ulcerations of psoriatic lesions, reactivation of phototoxic responses
Blood	Bone marrow depression, leukopenia leading to decreased resistance to infection, anemia, thrombocytopenia, bleeding, and megaloblastic anemia, Pancytopenia
Gastrointestinal system	Nausea and anorexia, diarrhea, vomiting, ulcerative stomatitis, pharyngitis, enteritis
Urinary system	Azotemia, microscopic hematuria, cystitis, nephropathy
Respiratory system	Acute pneumonitis, pulmonary fibrosis
Nervous system	Headaches, dizziness, drowsiness, blurred vision, acute depression
Reproductive system	Teratogenesis, defective oogenesis, menstrual dysfunction, reversible oligospermia, defective spermatogenesis
Uncommon side effects	Anaphylaxis, acral erythema, epidermal necrosis, vasculitis, osteopathy, lymphoma

Table 3 Methotrexate drug interactions of significance

Interacting drug	Mechanism/comments
Drugs that increase methotrexate drug levels and toxicity	
Salicylates	Decrease renal excretion, displacement from plasma proteins
NSAIDs	Decrease renal excretion, displacement from plasma proteins
Sulfonamides	Decrease renal excretion, displacement from plasma proteins
Dipyridamole	Increased intracellular accumulation of methotrexate
Probenecid	Increased intracellular accumulation of methotrexate, decreased renal tubular function
Chloramphenicol	Displacement from plasma proteins
Phenothiazines	Displacement from plasma proteins
Phenytoin	Displacement from plasma proteins
Tetracyclines	Displacement from plasma proteins
Drugs that simultaneously inhibit folate metabolic pathway-increase hematologic toxicity	
Trimethoprim	Inhibition of dihydrofolate reductase
Sulfonamides	Inhibition of dihydropteroate synthetase
Dapsone	Inhibition of dihydropteroate synthetase
Drugs that may synergistically increase hepatotoxicity-common target organ	
Systemic retinoids	Common target organ for toxicity-liver
Alcohol	Common target organ for toxicity-liver

NSAID: Nonsteroidal anti-inflammatory drug.

Table 4 Guidelines for monitoring psoriasis patients receiving methotrexate by utilizing PIIINP levels

Indications for considering withdrawal of methotrexate	Elevation of PIIINP above 10.0 µg/L in at least 3 samples in one 12-mo period
Indications for considering liver biopsy	Elevation of pretreatment PIIINP above 8.0 µg/L Elevation of PIIINP above 8.0 µg/L in 2 consecutive samples Elevation of PIIINP above the normal range (1.7-4.2 µg/L) in at least 3 samples over a 12 mo period
Remarks: Serum for PIIINP measurement should be collected prior to starting methotrexate and should subsequently be measured every 2-3 mo during continued treatment	

Table 5 Grading of Liver biopsy as per Roenigk scale and recommendations for further methotrexate therapy

Biopsy grade	Liver histopathologic findings	Recommendation
I	Normal; fatty infiltration, nuclear variability and portal inflammation- mild	May continue methotrexate
II	Fatty infiltration, nuclear variability, portal tract expansion, inflammation and necrosis- moderate to severe	
IIIA	Fibrosis-mild	May use methotrexate with caution and repeat biopsy at 6 mo
IIIB	Fibrosis-moderate to severe	Should not be given except in exceptional circumstances
IV	Cirrhosis	

vasculitis, leukopenia, thrombocytopenia, and fixed drug eruption^[103,104]. Side effects like lesional erythema and tenderness, lesional and nail hyperpigmentation,

arthralgia, dryness of mouth, periorbital swelling and diarrhea 3 d after the weekly dose of hydroxycarbamide not warranting discontinuation of treatment were

observed by Ranjan *et al*^[81]. This low incidence of side effects and particularly absence of serious ones like hematologic toxicity was attributed to less number of doses used for short period of 1 to 2 d in a week. It is also observed that some variants of psoriasis may respond better to hydroxycarbamide than others. A good clearance in pustular psoriasis patients treated with 1-2 g/d hydroxycarbamide has been observed in 45%-63% of psoriasis patients treated^[105,107]. The response is slow in erythrodermic or guttate psoriasis and palmoplantar pustulosis^[103,105,107,108]. Hydroxycarbamide and infliximab combination was more effective in treating a case of recalcitrant psoriasis who had failed therapy with acitretin, bath Psoralen ultraviolet-A (PUVA), narrow band ultraviolet B (UVB), topical tar ointment, diathranol, vitamin D analogs and steroids^[111]. However, its use in combination with other psoriasis treatment remains understudied. Despite slow response, hydroxycarbamide appears a reasonable alternative to methotrexate in patients who either develop gastrointestinal or hepatotoxic side effects due to methotrexate, or have achieved its recommended cumulative dose.

Azathioprine and 6-thioguanine

Azathioprine, an analogue of physiologic purines (adenine, hypoxanthine, guanine), is approved for use in rheumatoid arthritis and renal transplant recipients for its immunosuppressive activity. It is also used in dermatology for the treatment of blistering disorders, parthenium dermatitis, atopic dermatitis or other inflammatory dermatoses. It is rapidly absorbed after oral ingestion and nearly 30% is protein bound. After absorption, azathioprine is converted *in vivo* to 6-mercaptopurine and then its active metabolite, the nucleotide thioinosinic acid. Its maximum effect is on rapidly dividing cells and it may block the active enzyme and antigenic sites due to its alkylating effect on sulfhydryl amino groups. It inhibits mitosis, B-cell proliferation, suppresses T lymphocyte function, and antibody formation. It requires at least 6-8 wk for its onset of action. The recommended dose of azathioprine is 100-150 mg/d (1.5-3 mg/kg per day). Sufficient perspective data from randomized trials is lacking but reports have shown its efficacy in severe psoriasis. DuVivier *et al*^[112] observed 75%-100% clearance of psoriasis in 13 psoriasis patients among 19 of 29 patients who had benefited from treatment with azathioprine. It was found effective in another 5 of 10 treatment-resistant psoriasis patients with $\geq 25\%$ improvement^[113]. Hacker *et al*^[114] used azathioprine in a psoriasis patient who had failed conventional psoriasis therapy (methotrexate, etretinate, corticosteroids) because of inadequate response or adverse effects. Azathioprine was as effective as other drugs in the treatment of psoriatic arthritis as well in a long-term study^[115]. Remissions for > 5 years have been reported in 10 psoriasis patients following treatment with azathioprine pulse therapy in a recent study^[116]. The

researcher used azathioprine "intermittent high dose" (500 mg on 3 consecutive days) repeated every month along with "continuous low dose" (100 mg daily) during the intervening period comprising "one azathioprine pulse" of treatment. The patients were treated in Phase-1 until clearance that occurred after 1-5 pulses (average 3.7 pulses). The responders were shifted to Phase-2 and received same pulse dosing for another 9 mo followed by Phase-3 of "continuous low dose therapy" for one year. The patients were followed up without any treatment (Phase-4). Additionally, patients were treated with oral methotrexate (15 mg weekly), topical tar ointment before starting azathioprine pulse therapy for faster clearance. However, gastrointestinal intolerance, and bone marrow and liver toxicity at high dose remain a major concern. Azathioprine has been used effectively to treat patients with concurrent psoriasis and bullous pemphigoid and seems to be a good choice for such patients during corticosteroid weaning^[117-119].

The major adverse effects of azathioprine include myelosuppression (anemia, leukopenia, thrombocytopenia, pancytopenia) that is more common among population having inherited deficiency of thiopurine S-methyltransferase (TPMT) activity. Liver toxicity (elevation of bilirubin, transaminases and alkaline phosphatase), and gastrointestinal side effects (nausea, vomiting, diarrhoea, oral ulcers, esophagitis, steatorrhea) are less common in recommended doses. Nevertheless, patients should be monitored weekly for 1 mo, then every 2 weekly for 2 mo, and monthly or more frequently for hematologic or hepatic toxicity when dose alteration or other therapy changes are made/planned. Measurement of thiopurine methyltransferase levels can be used for guiding dosing pattern^[120].

Six-thioguanine is the active form of azathioprine that works by inhibition of purine synthesis. It seems suitable alternative therapy for patients of who are failures or excluded for methotrexate, retinoids, or PUVA therapy. It is as effective or perhaps more effective in treating psoriasis than its parent drug. Zackheim *et al*^[121] treated 48 patients having extensive plaque psoriasis with 6-thioguanine. They observed > 75% improvement as an initial response in 79%, > 50% improvement in 8% (including two patients with palmoplantar pustular psoriasis) while 13% had < 50% improvement. Almost 50% improvement continued in 65% patients during follow-up of 21 years (median 13 mo). The therapy was more effective, and better tolerated than methotrexate in majority of the patients who had changed from methotrexate due to inadequate response or side effects. Zackheim *et al*^[122] made similar observations in their retrospective study of 81 patients with plaque psoriasis and five of palmoplantar pustular psoriasis. A pulse-dosing schedule of 2 or 3 times per week showed marked improvement in 10 (71%) of 14 patients studied and maintenance dose varied from 120 mg twice a week to 160 mg 3 times a week^[123]. Pulse dosing schedule

of 6-thioguanine is recommended to minimize its more serious adverse effects like myelosuppression, pancytopenia, and acute hepatitis but requires regular clinical and laboratory follow up^[124]. Nausea, headache and fatigue occur less frequently.

Leflunomide

Leflunomide is an immunosuppressive disease-modifying antirheumatic drug. It is a prodrug and 70% of the drug administered converts into its active metabolite teriflunomide that inhibits mitochondrial enzyme dihydro orotate dehydrogenase (an enzyme involved in de novo pyrimidine synthesis). It is primarily indicated for treating rheumatoid arthritis and is found beneficial for the treatment of psoriasis with concurrent psoriatic arthritis. Kaltwasser *et al*^[124] in a double blind, randomized placebo controlled study comprising 182 patients with psoriasis and psoriatic arthritis achieved a PASI 75 response at 24 wk in 17% patients in leflunomide group. While only 8% patients in placebo group had similar response. Similarly, psoriatic arthritis responded in 59% patients in leflunomide and systemic corticosteroids group vs 30% patients in placebo group.

Gastrointestinal irritation, elevated liver enzymes, leukopenia, drug eruption, headache, increased risk of infections, anaphylaxis, angioedema, anaemia, agranulocytosis, eosinophilia, leucopenia, pancytopenia, vasculitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, oral ulcers, cutaneous lupus erythematosus, severe infection, interstitial lung disease, cirrhosis and liver failure, and teratogenicity are usual adverse effects^[125]. Adequate contraception is recommended during leflunomide and additionally for 3 mo in males and 2 years in females after stopping the drug. Although combination of methotrexate and leflunomide is apparently more effective than either drug used alone (in rheumatoid arthritis), care should also be taken for concomitant use of methotrexate as combination may lead to severe or fatal hepatotoxicity^[126]. Similarly, concurrent vaccination with live vaccines (like haemophilus influenzae type b vaccine and yellow fever vaccines) should be avoided due to the potential of severe infection because of immunosuppression from leflunomide.

Fluorouracil

Fluorouracil (5FU), an antimetabolite, acts principally by inhibiting thymidylate synthase leading to inhibition of pyrimidine thymidine synthesis. This nucleoside is important for deoxyribonucleic acid (DNA) replication. Thymidylate synthase catalyses methylation of deoxyuridine monophosphate to form thymidine monophosphate that is inhibited by 5FU therapy leading to cell death of rapidly dividing tumor cells and decreases epidermal proliferation^[127]. Systemic fluorouracil is used for breast, anal, colorectal esophageal, pancreatic, gastric, and head and neck cancers. It is available as

a solution, cream or a sustained-release preparation in various concentrations (0.5%, 1%, and 5%) for topical/intralesional use in actinic keratoses and Bowen's disease.

Due to its inhibitory effect on epidermal cell proliferation 5FU has been used topically, intralesionally or orally for treating plaque psoriasis^[128-134]. As early as 1972, Tsuji *et al*^[128] treated 13 patients with psoriasis using topical fluorouracil 5% ointment under occlusion. The treated lesions became necrotic followed by re-epithelization after stopping the ointment and complete clearance. Pearlman *et al*^[129,130] used intralesional 1 mL fluorouracil (50 mg/mL) for 1-3 injections at 1- to 2-wk intervals (average 2 injections/patient) in 11 patients with psoriasis. The lesions improved in 2 wk and cleared completely in 4 wk. Subsequently, long remissions were observed in both the studies without significant systemic toxicity. Combining it with epinephrine for intralesional treatment showed improved response requiring single-dose treatment in 53 patients^[132,133]. The combination was superior in improvement of psoriatic plaques than pulsed dye laser or betamethasone in a comparative study^[133]. In a recent open-randomized-controlled study, 40 patients were treated with intralesional 5FU (0.1 mL/cm²) weekly for three injections^[134]. Total or near total clearance of lesions occurred in 35 patients at 12 wk. It was also effective for treating acrodermatitis continua of Hallopeau^[135]. Gastrointestinal upsets, persistent hiccups, mucositis, headache, myelosuppression, photosensitivity, cardio toxicity, and mood alterations are common adverse effects of oral 5FU while pain, necrosis, and hyperpigmentation occurs from intralesional therapy.

Paclitaxel

Paclitaxel, a complex diterpene, is synthetic or derived from the bark of the Pacific yew tree (*Taxus baccata*). This chemotherapeutic agent demonstrates substantial anti-tumor effect in carcinoma of the breast, ovary, and lung, head and neck, bladder, testes, esophagus and endometrium. It has modest effect in Kaposi's sarcoma, lymphoma and carcinoma of the stomach and cervix. It has shown antiproliferative, antiangiogenic, and anti-inflammatory properties prompting a phase II pilot study for its efficacy in 12 patients with severe psoriasis^[136]. A dose-dependent decrease in PASI scores varying from 15% to 80% in different patients was observed. Higher dose (75 mg/m² every 4 wk for 6 doses) produced more significant results than lower dose at more frequent intervals; 37.5 mg/m² every 2 wk for 3 doses and 50 mg/m² for additional 6 doses. No patient had myelosuppression (usual with doses > 100 mg/m² every 3 wk), but hypersensitivity reactions occurred in two patients and another patient had flare up of Crohn's disease. A new oral formulation, nanoemulsion of paclitaxel, has increased bioavailability in experimental animal models but needs evaluation for its clinical efficacy and safety among psoriasis patients^[137].

MMF

MMF is an immunosuppressive drug used extensively in organ transplant recipients to prevent graft rejection prior to its usage for treating autoimmune blistering dermatoses (bullous pemphigoid, pemphigus vulgaris). It metabolizes to mycophenolic acid that inhibits de novo purine synthesis in B and T cells by inhibition of inosine monophosphate dehydrogenase enzyme for selective lymphocyte immunosuppressive effect. Haufs *et al*^[138] reported first use of MMF for psoriasis leading to several case reports and uncontrolled studies demonstrating variable and beneficial effect of MMF for treating psoriasis^[139-145]. Subsequent studies found MMF less effective as compared to methotrexate or cyclosporine but reported less nausea than methotrexate and renal toxicity than cyclosporine^[82,146]. Beissert *et al*^[146] observed a superior efficacy of cyclosporine as compared to that of MMF in a prospective, multicenter, randomized trial to treat chronic plaque-type psoriasis. However, there was no difference in time to relapse, side effects, and psoriasis disability index. As monotherapy, its overall PASI 75 achievement rate is less than 20% and PASI 50 is nearly 50%^[144-146]. MMF also appears a reasonable alternative for patients with cyclosporine induced nephrotoxicity. Although PASI score increased in each patient treated with MMF after a 2-4 wk washout period of cyclosporine, the cyclosporine induced deranged renal function was significantly improved in a study evaluating switching from cyclosporine to MMF^[147]. Regression of erythema, induration and scaling of psoriasis plaques has been reported from topical MMF but further evaluation is needed^[148].

MMF has been also used successfully with cyclosporine minimizing toxicity of both drugs. Ameen *et al*^[149] reported moderate to good improvement with cyclosporin (2.5 mg/kg per day) and MMF (3 g/d) in 3-11 mo among 78% patients with severe recalcitrant psoriasis. It also appear good choice in psoriasis patients having concurrent immunobullous disorders or HIV infection^[150,151].

Severe gastrointestinal side effects (nausea, diarrhoea) and reversible hematologic toxicity are common. Hematologic malignancies, progressive multifocal leukoencephalopathy and serious infections have been reported in transplant recipients receiving MMF but are uncommon in psoriasis patients treated with MMF^[152,153]. Nevertheless, all patients under treatment with MMF will routinely require evaluation for therapy-related complications by complete blood counts, hepatorenal function tests, and electrolyte estimation, and serious infections or neoplasia as per guidelines^[142]. Despite unavailability of high-quality clinical trials, MMF in recommended doses of 1-1.5 g twice daily (maximum dose 3 g/d) appears a good alternative for the treatment of psoriasis in patients who are unable to take other drugs due to contraindication or toxicity or for maintaining disease control achieved from other therapies.

RETINOIDS AND RETINOID ACID METABOLISM BLOCKING AGENTS

Retinoids are synthetic and natural compounds that have biologic activity like that of vitamin A. Tretinoin and isotretinoin are the first generation retinoids while etretinate and acitretin are the second generation retinoids which are aromatic retinoids and supposed to be more effective in psoriasis and other keratinization disorders than first generation retinoids. Bexarotene and alitretinoin belong to third generation. The systemic retinoids, alone or in combination with other systemic (methotrexate, cyclosporine, hydroxyurea, PUVA) or topical agents (calcipotriene, coal tar ointment, steroids), or in rotational and sequential therapy constitute an important form of therapy in severe and resistant psoriasis. Retinoids are effective even as monotherapy particularly in exfoliative erythrodermic psoriasis and pustular psoriasis^[154]. However, clinical data suggest that retinoid monotherapy may be less effective than other systemic agents in short term treatment of chronic plaque and guttate psoriasis. The advantage lies in their being not associated with immunosuppression or limitation of cumulative dose, and having no significant hepatic or renal toxicity. Therefore, they can be used alone or in combination with conventional therapies for psoriasis or biologic agents for treatment and maintenance therapy as well as in HIV affected patients with psoriasis. The exact mechanism of action of retinoids in psoriasis is not understood comprehensively. There are two families of retinoid receptors, a retinoic acid receptor (RAR) family and retinoid X receptor (RXR) family, each having three isoforms: α , β and γ . They perhaps exert their therapeutic effect by modulating three major pathogenic features of psoriasis, abnormal keratinocyte differentiation, keratinocyte hyperproliferation and tissue infiltration by inflammatory cells thus decreasing scaling, erythema and thickness of the plaques. They induce hypergranulosis and decrease number of tonofilaments and desmosomes, and widening of intracellular space causing a keratolytic effect. They inhibit neutrophil migration, alter cytokine production by T lymphocyte, interfere with keratinocyte responsiveness to cytokines or abolish resistance of keratinocytes to apoptosis^[155]. However, isotretinoin has no clearly identified affinity for any retinoid acid receptor. Acitretin, an active metabolite of etretinate, is the most frequently used oral retinoid to treat psoriasis despite its lower efficacy as monotherapy vs methotrexate or cyclosporine. Its combination with UVB (reUVB) or PUVA (rePUVA) increases the responses of both modalities reducing the number and duration of therapy sessions needed to achieve clearance and decrease the cumulative adverse effects of ultraviolet (UV) radiation^[156]. It can also be combined with other systemic agents like methotrexate, cyclosporine and hydroxyurea, biological therapies or with topical agents like calcipotriene and steroids in rotational and sequential therapy^[157]. The efficacy of retinoids in

combination with biological therapies has been reported in several uncontrolled studies and case reports^[158-167]. On the other hand, other retinoids remain under evaluated for treating psoriasis.

Isotretinoin

Isotretinoin up to 2 mg/kg per day has been used in treating psoriasis^[168]. Isotretinoin was first used in the treatment of psoriasis in 1973. Hotard *et al*^[169] analyzed the medication prescribed to patients with a primary and only diagnosis of psoriasis spanning a period of 5 years. Out of 8.5 million visits, only 39% of the patients receiving systemic treatments were women. With respect to retinoids, it was observed that women received less etretinate (35% women among 100 patients on etretinate) than men but more isotretinoin (100% women) than men were, as all 9 patients who received isotretinoin were young females. Isotretinoin is considered more effective in pustular psoriasis than in chronic plaque psoriasis^[170-173]. Moy *et al*^[171] successfully treated 10 of 11 patients with pustular psoriasis using isotretinoin. Pustulation ceased after 3 to 5 d of treatment with daily dose of 1.5-2 mg/kg per day but recurrences were frequent on reduction of the dose. The pustulation subsided when the dose was increased again or most patients required additional agents to control their disease. Similarly, Al-Shobaili *et al*^[174] found excellent outcome in a 16-year-old girl treated with isotretinoin for pustular psoriasis. Isotretinoin can be administered safely in patients who have developed adverse effects to etretinate. Marhold *et al*^[175] reported a case of 29 years old female patient suffering from severe pustular psoriasis and had increased liver enzymes while on etretinate. Liver biopsy revealed changes of drug induced hepatitis. After normalization of the liver parameters following withdrawal of etretinate, isotretinoin was administered during a severe relapse. Contrarily, isotretinoin was well tolerated and resulted in a good therapeutic response. Vahlquist *et al*^[176] also used isotretinoin in a patient of pustular psoriasis of palms and soles, who developed hepatitis after treatment with etretinate. However, they found it only marginally effective. Patients with plaque psoriasis can be treated with isotretinoin in a dose up to 1.5-2 mg/kg per day. Increasing small doses of isotretinoin are recommended initially while treating erythrodermic psoriasis in order not to provoke the disease^[177,178]. Etretinate and acitretin has been shown to control chronic plaque psoriasis more effectively than isotretinoin when used as a single agent. Moy *et al*^[171] compared isotretinoin with etretinate in chronic plaque psoriasis. Ten patients who had psoriasis affecting 20%-50% of their body surface area were treated with isotretinoin 1.5 mg/kg per day for at least 8 wk, and other 19 patients who had psoriasis affecting 40%-90% of their body surface area were treated with etretinate 0.75 mg/kg per day for the same period. Eighteen out of 19 patients treated with etretinate had either a

complete or a moderate response, while only 4 of 10 patients treated with isotretinoin were moderate or complete responders. It showed a significant difference in efficacy in favour of etretinate. However, isotretinoin has shown equal efficacy to other retinoids when combined with psoralen photochemotherapy^[179,180]. Combination of isotretinoin with PUVA was clinically more effective in clearing lesions of chronic plaque psoriasis and improved quality of life than PUVA alone in a recent study^[180]. The mean percentage reduction in PASI score at the end of 12 wk was 51.92 ± 23.83 and 3 (27.27%) patients achieved marked to complete remission in a recent study comparing it with methotrexate^[181]. Isotretinoin appeared less effective than methotrexate and only 4 (36.36%) patients had either mild improvement or were non responder in the first 8 wk.

Adverse effects of retinoids

Diffuse interstitial skeleton hyperostosis, premature epiphyseal closure, pseudotumour cerebri, severe headache and hepatotoxicity are potential important adverse effects. Musculoskeletal (arthralgia, myalgia, fatigue, muscle weakness, tendonitis), neuropsychiatric (mild depression, headache) and gastrointestinal (nausea, vomiting, abdominal pain) abnormalities may also occur. The retinoid teratogenicity remains the major concern and limitation for their use. When taken in the first trimester, they cause severe embryonic abnormalities in up to 50% and spontaneous abortion in up to one third of pregnancies. Malformations occur even with short periods of use, therefore no systemic dose of retinoids is considered safe during pregnancy. The most frequently described congenital malformation from isotretinoin is "the isotretinoin dysmorphic syndrome". It includes facial malformations (rudimentary external ears, absent or imperforate auditory canals, triangular microcephalic skull with large occiput and narrowing of the frontal bone, cleft palate, microphthalmia, depressed mid face), central nervous system anomalies (hydrocephalus, cranial nerve dysfunction), and cardiac malformations (overriding aorta, interrupted or hypoplastic aortic arch, atrioventricular septal defects, abnormal origin of the subclavian arteries). Limb reduction defects and thymic aplasia too have been described^[182]. Hersh *et al*^[183] reported that 10% of live birth records examined showed malformations of pregnancies occurring within 30 d after isotretinoin discontinuation. However, women who conceive one cycle after discontinuing isotretinoin are advised that their teratogenic risk is not higher than baseline^[184]. The risk of retinoid embryopathy in fetuses fathered by men taking isotretinoin is minimal, if any.

Retinoids also adversely affect the skin (xerosis, palmoplantar and digital desquamation, retinoid dermatitis, photosensitivity, pyogenic granuloma, staphylococcus infections), the hair and nails (telogen effluvium, abnormal hair texture, dryness, fragility,

paronychia, onycholysis), the eye (dry eyes with visual blurring, blephroconjunctivitis, photophobia), and mucous membranes (cheilitis, dry mouth, sore mouth and tongue, nasal mucosa dryness, epistaxis). The majority of case control and other epidemiological studies have shown no association between mood change, depression, psychosis and suicide ideation, and isotretinoin use. Nevertheless, individual idiosyncratic psychological adverse response to the drug cannot be excluded^[185]. Similarly, the current evidence is insufficient to establish a causal association between isotretinoin and inflammatory bowel disease^[186].

New generation retinoids

Because of high selectivity for the β and γ subtypes of RARs the new generation retinoids have targeted action on psoriatic keratinocytes with minimum risk of adverse effects. They have better pharmacokinetics, and half-life of active metabolite of tazarotene (tazarotenic acid) is only 7-12 h. This imparts the advantage of contraception just being necessary for a few days after the last dose. The efficacy, safety and tolerability of tazarotene for psoriasis patients have been reported in phase III trials^[187]. It has been used safely for up to 52 wk without any significant increase in retinoid toxicities like hypertriglyceridemia, hypercholesterolemia, altered liver function tests, alopecia or conjunctival dryness. Several studies have also examined the safety and tolerability of topical tazarotene (0.1% and 0.05% gels), alone or in combination with topical corticosteroids (clobetasole, mometasone, flucinonide), calcipotriene or phototherapy for treating psoriasis^[188-193]. Tazarotene 0.1% is generally more effective than the 0.05% cream. Tazarotene gel is non-sensitizer, non-phototoxic or non-photosensitizing, and treatment-related adverse effects like mild-to-moderate local skin irritation occur mainly from tazarotene 0.1% but systemic adverse effects do not occur.

Bexarotene, a synthetic RXR-selective retinoid, is an available treatment for cutaneous T-cell lymphoma. Antipsoriatic effect of oral bexarotene in doses up to 3.0 mg/kg per day during 12 wk of treatment has been evaluated on proliferation, differentiation, and inflammation parameters^[194,195]. Smit *et al*^[194] observed > 50% improvement in modified PASI, plaque elevation, and physician's global assessment in 22%, 52%, and 36% of patients, respectively, in a phase II multicentric trial. No serious treatment related adverse events occurred. However, studies for the optimal dose and its potential as a new therapeutic modality are warranted. Similarly, therapeutic potential of topical bexarotene gel 1% in psoriasis needs further evaluation^[196]. Oral Alitretinoin (9-cis-retinoic acid) 30 mg/d, alone or in combination with etanercept is another promising therapy for recalcitrant palmoplantar pustulosis or hyperkeratotic palmoplantar psoriasis but warrants confirmation of its efficacy and safety by controlled studies^[197,198].

Contraindications, drug interactions and monitoring guidelines

Absolute contraindications for the use of retinoids are pregnancy or woman who is likely to become pregnant, non-compliance with contraception, nursing mothers, or individuals with known hypersensitivity. Relative contraindications include leukopenia, moderate to severe cholesterol or triglyceride elevation, and significant hepatic or renal dysfunction. Monitoring of concomitant medications that may interact with retinoids is required (Table 6). Pregnancy test in women of childbearing age, complete blood count, liver and renal function tests, complete lipid profile and urinalysis if indicated should be performed at baseline and repeated monthly for the first 3-6 mo, and then every 3 monthly. X-ray of wrist, ankle or thoracic spine at baseline and periodically are needed if retinoids are required for a long duration. Ophthalmologic examination is done as and when required.

According to iPLEGE program, the patient is advised to have a negative pregnancy test before isotretinoin use, every month during treatment, at the end of treatment and 1 mo after stopping treatment. The women must use two form of contraception for at least 1 mo prior to initiation of isotretinoin, during and one month after discontinuing therapy. Women of childbearing potential must access the iPLEDGE system at the time of first prescription and then at each subsequent prescription.

Retinoid acid metabolism blocking agents

Retinoid acid metabolism blocking agents, liarazole and talarozole, are retinoid mimetic drugs that act by blocking cytochrome P-450 dependent 4-hydroxylation of all-trans-retinoic acid. They modulate intracellular levels of endogenous retinoids and in turn normalize aberrant epithelial growth and differentiation. As the plasma all-trans-retinoic acid levels do not increase beyond physiologic levels, the retinoid-associated adverse effects are less frequent despite their efficacy similar to that of retinoids. Talarozole is a more selective inhibitor of the enzyme retinoic acid 4-hydroxylase and is effective in lower doses causing less side effects. Due to their rapid metabolism and clearance unlike synthetic retinoids, these drugs are safer for women and children. Liarazole was found effective for both palmoplantar pustular psoriasis and chronic plaque psoriasis in double-blind, randomized, placebo-controlled trials^[199,200]. In a small pilot study, a noticeable improvement was observed in 4 of 7 patients with palmoplantar pustular psoriasis treated with liarazole (75 mg, twice daily) as compared to 1 in 8 patients receiving placebo^[199]. The lowest effective dose was 75 mg twice daily in a dose ranging, randomized, placebo controlled trial. A marked improvement occurred in 18% in liarozole 50 mg, 11% in 75 mg, 38% in 150 mg and 6% subjects in placebo group subjects, respectively^[200]. Verfaillie *et al*^[201] treated 19 patients of psoriasis with talarozole (1 mg) for 8 wk and observed significant reduction in PASI. No formal

Table 6 Drugs interacting with retinoids

Interacting drug	Mechanism/comments
Drugs that may increase retinoids levels and/or toxicity	
Vitamin A	Induces hypervitaminosis A like toxicities
Tetracycline, doxycycline and minocycline	Increase pseudotumour cerebri risk
Macrolides, Azoles, etc.	Other CYP 3A4 inhibitors increase its level
Drugs that may reduce retinoids level	
Rifampicin, rifabutin	Induction of CYP 3A4
Anticonvulsants-phenytoin, Phenobarbital, carbamazepine	Induction of CYP 3A4
Drugs that may synergistically increase hepatotoxicity	
Methotrexate	Common target organ for toxicity-liver
Alcohol	Common target organ for toxicity-liver
Drugs whose levels are changed by retinoids	
Cyclosporine A	Cyclosporine A levels are increased <i>via</i> competition for CYP 3A4

announcement has been made for the results of phase II clinical trial for of its oral formulation, and phase I clinical trial for topical formulation^[202].

FUMARIC ACID ESTERS

Although fumaric acid was found effective in systemic treatment of psoriasis as early as 1959, the drug is licensed only in Germany and Netherlands for short-term (< 6 mo) use in patients with severe psoriasis when topical therapy is not indicated^[203]. However, successful completion of a phase 3 study for use of its improved formulation in psoriasis has greatly renewed worldwide interest for this drug. The commercial preparations Fumaderm® initial and Fumaderm® have mixture of dimethylfumarate and three salts of ethyl hydrogen fumarate. (Fumaderm® initial contains dimethylfumarate 30 mg per tablet; Fumaderm® has dimethylfumarate 120 mg per tab).

The esters are used as fumaric acid itself is poorly absorbed after oral intake. They have almost complete absorption in the small intestines. The dimethylfumarate is rapidly hydrolyzed to more active metabolite monomethylfumarate by esterases. Dimethylfumarate and its metabolite monomethylfumarate are the principal active ingredients. Its interaction with intra- and extracellular thiols (glutathione) is considered the primary mechanism of action^[204]. This inhibits NF-κB-mediated transcription of intracellular mediators (TNF-α or IL-8) and adhesion molecules (E-selectin, ICAM-1, VCAM-1). Other work suggests their therapeutic benefit by shift of the Th1-cytokines pattern towards Th2-type cytokine pattern associated with reduction in peripheral lymphocytes (primary T cells) inhibiting proliferation of epidermal keratinocytes in psoriasis patients^[203,204]. Fumarates at higher concentrations inhibit induction of apoptosis and maturation of dendritic cells, which have an important role in immunologic reaction, and development and maintenance of an inflammatory response. These effects have been also demonstrated to be mediated by interference of the intracellular redox

system.

Clinical studies from 1990s have reported a substantial reduction in PASI score following treatment with fumaric acid. Its efficacy and safety have been reported frequently and reviewed comprehensively^[205-215]. Altmeier *et al*^[208,209] in two separate studies noted nearly 50% reduction in PASI in 50 patients with severe psoriasis and 80% in 83 patients respectively after 16 wk of treatment with Fumaderm®. Mrowietz *et al*^[210] also reported 80% reduction in PASI after a 16-wk open-label multicenter study. The efficacy of fumarates is also confirmed in recent years. Litjens *et al*^[211] reported nearly 53% reduction in PASI in 20 psoriasis patients while substantial improvement or clearance was observed by Carboni *et al*^[212] in 71% of 40 psoriasis patients after 12-wk treatment with fumarates. Twenty percent patients achieved a statistically significant reduction in PASI from 13.9 ± 9.0 to 11.3 ± 9.2 in a single center study from United Kingdom^[213]. The efficacy of fumaric acid ester in treating mild psoriasis too has been documented in a recent Italian study^[214]. Reich *et al*^[215] retrospectively analyzed the data of 984 patients with psoriasis for the long-term safety and efficacy of fumaric acid ester. Either the patients were on 24 mo of continuous treatment or at least 36 mo of intermittent treatment (mean duration 44 mo). Overall, 31%, 67%, 76%, 78% and 82% of the patients showed a substantial improvement or were clear of symptoms after 3, 6, 12, 24 and 36 mo, respectively, without significant laboratory abnormality or serious adverse effects. Although the efficacy of fumarates has been also demonstrated in psoriatic arthritis, nail psoriasis, and palmoplantar pustulosis, they are not recommended to treat psoriatic arthritis currently for lack of significant activity in arthritis, dactylitis, and enthesitis^[216-219].

The therapy is usually initiated with low dose and escalated weekly until clinical response (usually observed in 4-6 wk) or a maximum dose of 1.2 g/d is achieved. Treatment with fumaric acid esters can be maintained for up to 2 years. Short-term intermittent therapy until major improvement followed by drug withdrawal is another mode of therapy. Although no rebound phenomenon or pustular exacerbation occurs, gradual tapering to minimal threshold dose is recommended to prevent relapse in patients with high disease activity.

The comparative efficacy of fumaric acid esters vs other systemic therapies remains understudied and so is that of their combination with other systemic therapies. Methotrexate and fumarates were equally effective without significant adverse events in the treatment of patients with psoriasis in a small, short-term study. Fallah Arani *et al*^[83] in a first ever randomized controlled trial treated 60 patients with moderate to severe psoriasis vulgaris either with methotrexate (30 patients; 15 mg/Wk) or fumarates (30 patients; 30 mg, followed by 120 mg) for 16 wk. They reported 50% reduction in PASI at 12 wk of 42% and 60% patients in fumaric

acid esters and methotrexate group, respectively. PASI 75% was observed in 19% of fumaric acid esters and 24% of methotrexate group, respectively. Two patients in fumaric acid esters and 4 in methotrexate group dropped out due to adverse effects. Gollnick *et al*^[220] found combination of oral fumaric acid esters and topical calcipotriol significantly more effective and faster acting than monotherapy with slight fumaric acid esters-sparing effect imparting a superior benefit/risk ratio. Combination produced higher and early mean reduction in PASI (76% vs 52%) and PASI 50 in 3 wk vs 9 wk. Fumarates can be combined with UVA or UVB during initial 3 wk of therapy^[203]. There are reports of successful use in combination with methotrexate, acitretin, hydroxyurea or ciclosporin but combining retinoids have no additional benefit^[221]. However, their combination with other systemic therapies is not recommended currently.

The fumaric acid esters are safe in inducing remission in a reasonable time and retain it through extended periods. Gastrointestinal complaints (nausea, abdominal cramps, or diarrhea) occur in up to 60% of patients in first few weeks of therapy. These symptoms can be reduced by dose reduction, taking the drug with milk, or addition of aluminium hydroxide, metoclopramide, ranitidine or pentoxifylline^[222,223]. Flushing is seen in 30%-50% as feeling of warmth, facial flushing, and headache lasting for minutes to hours, and may be severe. It can be ameliorated with administration of acetylsalicylic acid. Leukocytopenia, lymphopenia, and eosinophilia can occur. The development of progressive multifocal leukoencephalopathy in two patients treated with Fumaderm® has been attributed to therapy associated prolonged severe lymphopenia^[224,225]. Leukopenia below 3000/ μ L and lymphopenia below 500/ μ L, thus, need drug withdrawal or reduced doses. Eosinophilia is transient, seen in 4-10 wk of therapy, and improves after the drug withdrawal/reduction^[226]. Occasional renal toxicity is observed and proteinuria when occurs will disappear following drug cessation or dose reduction^[227,228]. Isolated elevation of serum bilirubin, hepatic enzymes, serum creatinine or potassium, and dyslipidemia may occur but increased susceptibility for infections or development of malignancies is not observed. Progressive multifocal leukoencephalopathy is a potentially severe toxicity. Discontinuation of therapy from adverse effects may be needed in 30%-40% cases.

CALCINEURIN INHIBITORS

Calcineurin or protein phosphatase 3, a calcium-dependent serine-threonine phosphatase, activates the T cells of the immune system and can be blocked by drugs called calcineurin inhibitors that include cyclosporine, tacrolimus, pimecrolimus and voclosporine. Both cyclosporine and tacrolimus are chemically distinct molecules. They bind to the intracellular immunophilins cyclophilin and FKBP-12 respectively. Both inhibit the

phosphatase action of calcineurin required for the movement of nuclear factors in activated T cells to the chromosomes where subsequent cytokine synthesis occurs. They prevent IL-2 production in T cells and decreased secretion of IL-2 prevents proliferation of the inflammatory response *via* B cells and T cells. This attenuated inflammatory response greatly reduces the overall function of the immune system producing clinical response. Cyclosporine (cyclosporine A), a neutral cyclic undecapeptide, is derived from fungus *Tolypocladium inflatum* *gams*. It has been approved in the United States for 1-year and in Europe for 2-year of continuous therapy. Cyclosporine (2.5 to 5 mg/kg per day) has efficacy comparable to that of biologics in rapid control of severe, widespread, intensely inflammatory and erythrodermic psoriasis, cases resistant to other treatments, and nail psoriasis. Several studies have noted that 80%-90% of patients improve significantly after 12-16 wk of cyclosporine therapy^[229,230]. The drug is also useful in treating childhood psoriasis with results and adverse effect profile similar to that is seen in adults^[231-233]. However, early rebound flare up of psoriasis occurs after stopping the drug. Headache, tremors, and paresthesia/hyperesthesia are common adverse effects with short-term therapy. An irreversible nephrotoxicity and/or hypertension following long-term therapy especially in patients treated continuously with cyclosporine for > 2 years is of serious concern. Another major concern is almost six fold increased incidence of non-melanoma skin cancers like squamous cell carcinomas with long-term low-dose cyclosporine therapy especially when it is used in combination with PUVA (psoralen + UVA) therapy^[234].

Voclosporine

This relatively new member of calcineurin inhibitors has higher affinity for calcineurin, faster clearance of metabolites from the body, high efficacy and a better safety profile as compared to cyclosporine. Nearly 67% patients receiving 1.5 mg/kg per day of voclosporine achieved PASI 75 in phase II trial^[234]. Similarly, 16%, 25% and 47% patients achieved PASI 75 response at 12 wk after voclosporine 0.2, 0.3, and 0.4 mg/kg, respectively, in a phase III dose-finding placebo-controlled study comprising 451 patients with chronic plaque psoriasis as compared to 4% patients in the placebo group^[235]. No significant adverse events or alterations in blood pressure, lipids or triglycerides were observed.

Topical calcineurin inhibitors

After noticing incidental improvement of psoriasis following systemic tacrolimus to prevent rejection in one heart and three liver transplant recipients, the researchers reported good response to the drug in other three patients with severe, recalcitrant and treatment resistant psoriasis^[236]. Subsequently, European FK 506 multicenter psoriasis study group in a double-blind, placebo-controlled study comprising 50 patients with

severe recalcitrant plaque-type psoriasis randomized to receive treatment with either oral tacrolimus (FK 506) ($n = 27$) or placebo ($n = 23$) reported 83% PASI reduction in 27 psoriasis patients at the end of 9 wk^[237]. Similarly, Rappersberger *et al*^[238] used oral pimecrolimus with high clinical efficacy and good tolerability. The drug was well tolerated without clinically relevant laboratory abnormalities in a large, double-blind, dose-finding study^[239]. Oral pimecrolimus, given as 20 and 30 mg twice daily in psoriasis patients, demonstrated a mean percentage reduction in PASI by 51.3% and 54%, respectively, at week 7 from the baseline. However, availability of topical formulations of tacrolimus and pimecrolimus (approved for atopic dermatitis) renewed interest for their use in the treatment of psoriasis as an alternative to topical corticosteroids. Mrowietz *et al*^[240] used pimecrolimus (0.3% or 1%) to treat 10 patients with chronic plaque psoriasis in double-blind randomized-controlled study. Total scores decreased by 92% for clobetasol, by 82% for pimecrolimus (0.1%), by 63% for pimecrolimus (0.3%), and by 18% for control. They are most effective in recalcitrant psoriasis affecting the face, genitals, and intertriginous areas^[241-245]. Tacrolimus (0.1%) ointment completely cleared psoriasis of face, intertriginous skin or both in 81% of 21 patients at end of study period of 57 d^[242]. It also demonstrated complete clearing (24.8% vs 5.8%) in another randomized-controlled study at day 8, and 65.2% vs 31.5% at 8 wk in 80% of 167 patients with facial and intertriginous psoriasis^[243]. Other researchers also made similar observations for efficacy and safety of topical tacrolimus with nearly 80% of patients having complete clearance of psoriasis on the face, genitalia, intertriginous areas, and corporal plaques^[244]. Tacrolimus ointment improved plaque psoriasis in a microplaque assay^[246]. It has been also used with equal efficacy and safety in pediatric patients. Brune *et al*^[247] evaluated tacrolimus 0.1% ointment in a single-centre open-label trial by treating 11 children aged between 6 and 15 years having psoriasis of face, folds or both. All patients had clearance or achieved excellent response within first 30 d itself. However, it is less effective for hyperkeratotic plaques involving back, trunk, elbows, and knees, perhaps from poor penetration^[248]. Combining tacrolimus (0.1%) with salicylic acid (6%), or calcipotriene (0.005%) improves outcome in such cases^[249,250]. Using tacrolimus or pimecrolimus under occlusion is also associated with improved efficacy in treatment of psoriasis^[251]. Changing formulations for tacrolimus or pimecrolimus to improve its penetration and cutaneous bioavailability is another promising area for research. Topical liposomal tacrolimus was found nine times more effective than tacrolimus ointment in experimental studies^[252]. Polymeric micelles- methoxy-polyethylene glycol-dihexyl substituted polylactide (MPEG-dihexPLA), a biodegradable and biocompatible diblock copolymer, as a nanocarrier was highly efficient for selective cutaneous delivery of tacrolimus experimentally^[253].

Burning sensation and/or pruritus, usually in first few days of application of tacrolimus or pimecrolimus, is considered secondary to release of neuropeptides such as substance P^[254]. Although United States FDA has issued "black-box" warning considering the risk for lymphoma and skin cancer, there is no convincing data for enhanced risk for the development of either cutaneous or systemic malignancy after topical use in large number of patients with atopic dermatitis for up to 4 years^[255,256].

THIAZOLIDINEDIONES AND STATINS

Thiazolidinediones, pioglitazone, troglitazone, and rosiglitazone, are used for the treatment of non-insulin-dependent diabetes mellitus. They lower insulin resistance in peripheral adipose and muscle tissues, and decrease hepatic gluconeogenesis by binding to peroxisome proliferator-activated receptors (PPAR) γ . They also have cardiovascular benefits because of their property of lowering blood pressure, improving endothelial cell function/fibrinolysis, and increasing high-density lipoprotein. Increased expression of PPAR β/δ has been observed in activated T cells in human psoriatic lesions while experimental studies have shown that activation of PPAR β/δ in the epidermis could sustain a psoriasiform inflammation with keratinocyte hyperproliferation, accumulation of dendritic cells and endothelial activation^[257,258]. Experimentally, topical PPAR β/δ antagonists effectively reversed PPAR β/δ activation triggered psoriasis-like changes^[259]. The PPAR γ agonists said to act *via* modulating anti-inflammatory actions by decreasing inflammatory cytokines like IL-2, TNF- α and IFN- γ , and down regulating the expression of adhesion molecules like VCAM-1^[260]. They also inhibit the production of IL-17 by CD4⁺ cells, and neoangiogenesis/angiogenesis both *in vitro* and *in vivo*^[261,262]. Shafiq *et al*^[263] in a double-blind randomized placebo-controlled clinical trial evaluated pioglitazone monotherapy in 70 patients with moderate to severe psoriasis. Three groups of patients received placebo, pioglitazone 15 or 30 mg/d, respectively for 10 wk. Psoriasis cleared or almost cleared in 40% of treated patients compared to 12.5% of patients in placebo group at end of the study period. The results were better with higher dose of pioglitazone and mean percentage reduction in mean PASI score was 21.6%, 41.1% and 47.5% in the pioglitazone 15 mg, 30 mg, and placebo groups, respectively. Adverse events like decreased hemoglobin in one patient and elevation of liver enzymes in two patients did not warrant withdrawal from study. In another open-label study, Bongartz *et al*^[264] reported statistically significant reduction with pioglitazone 60 mg/d and non-steroidal anti-inflammatory drugs in average number of painful and/or swollen joints and a 38% reduction of PASI score in 10 patients after 12 wk of treatment. A 3-mo treatment period appears appropriate for any significant clinical response as most improvement occurred between 6 and 12 wk. The pioglitazone in combination with methotrexate or

acetrein seems more effective in improving plaque psoriasis in two recent studies than control groups receiving methotrexate or acetrein alone. Lajevardi *et al*^[265] in a randomized controlled, assessor-blinded study compared the efficacy of methotrexate and combination of methotrexate and pioglitazone in 22 patients in each group. The PASI 75 was achieved in 63.6% with combination treatment as compared to 9.1% with methotrexate alone at end of 16 wk study period. Mean percentage reduction was 70.3% vs 60.2% in combination vs methotrexate alone group. Mittal *et al*^[266] reported mean percentage reduction in PASI score of 64.2% in acetrein plus pioglitazone group as compared to 52.7% in acetrein plus placebo group after 12-wk study period. Its combination with other systemic therapy remains unevaluated. Troglitazone also normalized histological changes of psoriasis and reduced hyperplasia in experimental murine and human skin models. A substantial efficacy of troglitazone in psoriasis too has been reported in similar studies^[267,268]. However, rosiglitazone was no more effective than placebo in a recent study^[269]. Moreover, the drug has been withdrawn because of idiosyncratic hepatotoxicity.

Thiazolidinediones, due to their effect on lipid and glucose metabolism, appear to be therapy of choice for psoriasis associated with metabolic comorbidities like insulin resistance, obesity, dyslipidemia, or cardiovascular diseases. Pioglitazone 150 mg/d also led to complete remission of psoriasis in a 65-year-old man with non-alcoholic steatohepatitis and diabetes who had not responded to treatment with ursodeoxycholic acid^[270]. However, topical formulations of these agents need further evaluation as no change was observed in PASI scores in a study comprising 8 patients with plaque psoriasis treated with topical 0.5% rosiglitazone^[271]. Apparently, thiazolidinediones make useful therapeutic options for psoriasis and pioglitazone remains the most studied drug among its peers. Although more evaluation is needed for pioglitazone, alone or its combination with methotrexate, acetrein or other antipsoriatic drugs, it appears a relatively safe, convenient, and effective therapeutic option for psoriasis.

Statins

Statins include atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. They were developed originally to treat lipid disorders in patients with hypercholesterolemia. They have significant immuno-modulating properties and studies have shown that they modify Th1/Th2 response to Th1 response, inhibit MHC-II induction, cytokine release, inhibit mast cells degranulation, and induce apoptosis. CCL20/CCR6 interaction also plays an important role in the pathogenesis of psoriasis. Kim *et al*^[272] investigated an inhibitory effect of statins on CCL20/CCR6 interaction and could demonstrate that IL-1 β , TNF- α , and IL-17A significantly increased CCL20 production from HaCaT cells. Fluvastatin and simvastatin, but not pravastatin seemed to reduce this

effect. Statins have shown to reduce inflammatory markers and when added to standard psoriasis therapy may improve disease severity. Statins show a hierarchy in their anti-inflammatory activity (cerivastatin > atorvastatin > simvastatin > pravastatin > lovastatin > fluvastatin)^[273]. However, studies on their potential role in preventing psoriasis have yielded conflicting results. A decreased progression of psoriasis is shown to be associated with statin intake in several studies^[274-279]. Contrarily, statins have been implicated for deterioration of skin lesions as well^[280-283]. Shirinsky *et al*^[279] in an 8-wk pilot study for the efficacy of simvastatin (40 mg/d) observed beneficial effects in seven patients with plaque psoriasis. Brauchli *et al*^[275] observed no link between long-term use of statins and the decreased risk of psoriasis diagnosis in a case-control retrospective analysis of 36702 cases of psoriasis identified between 1994 and 2005 from United Kingdom based General Practice Research Database. However, they observed a reduced psoriasis risk for short-term statin users. Whereas, another retrospective cohort study assessed the relationship between adherence with statins and the risk of psoriasis among 205820 health plan enrollees in Israel (mean age 55 years; 54.1% female) and found that high and long-term adherence with statins is not associated with a meaningful reduction in the risk of psoriasis^[280]. Another aspect of statins use is their combination with other antipsoriasis therapy. It showed a trend toward greater improvements in psoriasis severity in a study comprising 232 patients using topical corticosteroids, topical vitamin D, and some anti-ischemic treatments^[274]. The patients on statins ($n = 66$) had more severe disease (BSA of 13.26%) before starting new psoriasis medication as compared with 12.25% for the patients in nonstatin ($n = 166$) group. Interestingly, the trend reversed after initiating medication, with a BSA of 5.21% vs 7.43% for the statin vs nonstatin users. There was overall 64% reduction in psoriasis severity in statin group as compared with 45% reduction in the nonstatin group. Although the difference was not statistical significance, trend for those treated with statins was toward greater improvement. Combined treatment with simvastatin and topical betamethasone also provided better clinical outcome in a double-blind study comprising 30 subjects with plaque-type psoriasis randomized to two groups^[278]. Oral simvastatin (40 mg/d) combined with topical betamethasone (50% in pet) ointment in first group, whereas the second group received topical betamethasone (50% in pet) ointment and oral placebo. PASI score decreased significantly in both groups after study period of 8 wk. However, the reduction in PASI score was more expressed in simvastatin group patients. The potential efficacy of adding topical simvastatin to topical calcipotriol in plaque psoriasis also needs confirmation^[284]. Effects of combined treatment with atorvastatin (40 mg/d) vs placebo and keratolytics and/or corticosteroids were studied by Faghihi *et al*^[276] in a prospective, randomized, double-blind, placebo-

controlled study. Oral atorvastatin was not associated with therapeutic benefit in patients with PASI scores < 12 points prior to addition of statin and the differences in mean PASI score were not statistically significant in two groups. Statins associated adverse effects like myopathy, proteinuria, elevated transaminases, or haemorrhagic stroke were not noted by these studies. Simvastatin presents the highest risk of toxicity *via* mechanism of CYP3A4 inhibition. It is not uncommon to find statins triggering/aggravating psoriasis. Cozzani *et al*^[281] reported worsening of psoriasis in a patient 3 mo after atorvastatin and considerable improvement after discontinuation of atorvastatin. There is also report of exacerbation of psoriasis following pravastatin use^[282]. Despite reduction in all-cause mortality among people without evidence of cardiovascular disease treated with statins, the major concern from wide use of statins in psoriasis is possible drug interactions between concomitant antipsoriatic or other therapies (methotrexate, cyclosporine, fibrates, macrolides, warfarin, digoxin, and azole antifungals)^[285,286]. Potential interaction between fluvastatin and cyclosporine, primarily metabolized by CYP2C9 and not CYP3A4, is low^[286].

It is perhaps too early to recommend use of statins in psoriasis as stand alone therapy as sufficient perspective data is lacking. The misinterpretation of available data is also possible as patients using statin are likely to change towards a healthier lifestyle as has been suggested by Brauchli *et al*^[275]. Nonetheless, statins seems reasonable adjuncts to psoriasis therapy in view of the fact that psoriasis patients have a significant risk for metabolic disturbances and cardiovascular diseases.

ANTI-INFLAMMATORY AND OTHER DISEASE MODIFYING DRUGS

The utility of anti-inflammatory drugs as monotherapy is limited. While some of these agents like sulfasalazine have well identified advantage especially in psoriatic arthritis, others may perhaps have just more than a placebo effect. Nevertheless, their significance is perhaps in "add-on" therapy to ameliorate accompanying symptoms of inflammation and being sick.

Sulfasalazine

Sulfasalazine, a sulfa drug, is a derivative of mesalazine formed by combining sulfapyridine and salicylate with an azo bond. Sulfasalazine is primarily used for the treatment of inflammatory bowel disease including Crohn's disease and ulcerative colitis. It is also indicated for the treatment of rheumatoid arthritis or other inflammatory arthritis such as psoriatic arthritis. The recommended dose is 500 mg three times daily and increased as needed/tolerated. Sulfasalazine metabolizes to sulfapyridine that is responsible for some of the anti-arthritis effects and side effects of sulfasalazine from high serum concentrations of sulfapyridine and

poor acetylation of the drug. Its other metabolite, 5-aminosalicylic acid (5-ASA), is considered responsible for its major therapeutic effect. However, its exact mechanism of action is not understood well but its anti-inflammatory effect is attributed to inhibition of dihydrofolate reductase and folate absorption. Sulfasalazine has been found effective in the treatment of psoriasis, spondyloarthritis and psoriatic arthritis^[287-299]. In a double-blind, randomized, controlled trial of sulfasalazine, intolerable adverse effects warranted discontinuation of treatment in 8 of 25 patients while other 7 of 17 patients, who continued treatment, showed 60%-89% improvement in their psoriasis^[288]. In a small study, 3 of 8 patients in sulfasalazine group had moderate (50% to 70%) improvement of PASI score as compared 70% (very good response) improvement in PASI score in 6 of 7 patients in methotrexate group^[293]. Significant improvement was observed in morning stiffness, number of painful joints, articular index, clinical score, and pain score, with the favourable response more pronounced in the polyarticular group and response became visible as early as 4 wk^[289,297]. In a large double blind, placebo-controlled study 58% of 221 patients with moderate to severe psoriasis improved with sulfasalazine (2 g/d) over 36 wk and showed improvement in their psoriatic arthritis compared with 45% in the placebo group^[290]. Rahman *et al*^[295] treated 36 patients with sulfasalazine (3 g/d). One or more side effects warranted discontinuation of drug in 14 of 16 patients within 3 mo. A 50% reduction in actively inflamed joint count was noted in 7/20 patients at 6 mo and 11/15 patients at 12 mo as compared to 7/19 patients in the control group at 6 mo and 10/20 patients at 12 mo. Combe *et al*^[299] also noted significant improvement in their study of 120 patients. Overall, the benefit remains marginal with no halt in radiographic progression in psoriatic arthritis and significant number of patients experience adverse effects. The axial disease also does not appear to improve significantly^[294]. Comparatively, cyclosporine was more effective than sulfasalazine in the treatment of psoriatic arthritis in an open trial^[298].

Although adverse effects are not serious, may occur in about 60% of patients requiring withdrawal from study in 15% patients^[295]. Gastrointestinal intolerance (nausea, heartburn, vomiting, and diarrhea), malaise, headache, arthralgia, drug fever, and reversible oligospermia are common while leukopenia and agranulocytosis, and haemolytic anemia in G6PD deficient individuals are more serious adverse effects^[296]. Skin eruptions can also occur and caused 4 of 23 patients receiving drug to drop out in a trial^[288]. As the effect of sulfasalazine remains variable, its usage must be weighed against risk vs benefit of the drug. It must not be combined with methotrexate due to enhanced hepatorenal toxicity.

Colchicine

Colchicine, an alkaloid extracted from the plant

Colchicum species (*C. autumnale*), has anti-inflammatory response by interfering neutrophil chemotaxis and inhibition of cell-mediated immune responses. It is mostly used to treat acute gout in a dose of 0.6 to 1.2 mg once or twice daily while its efficacy in psoriasis varies from being effective to having no effect on skin lesions. Wahba *et al*^[300] observed significant clearing of skin lesions in 11 of 22 patients treated with colchicine (0.02 mg/kg per day) with symptomatic improvement observed in four patients with arthralgias. No significant difference was reported in 25 patients treated with colchicine (0.6-1.8 mg/d) or placebo at 23 wk in a subsequent placebo controlled study while colchicine was also associated with more adverse effects necessitating withdrawal from study in three patients^[301]. Seideman *et al*^[302] in a double blind, placebo controlled, and cross over study found significant improvement in joint pain and swelling, and grip strength in 10 of 12 patients after 16 wk treatment with colchicine (1.5 mg/d). Complete remission of pustular psoriasis occurred in 3 of 4 patients after colchicine treatment^[303]. Palmoplantar pustulosis too has been treated successfully with some exceptions^[304-306]. However, the potential efficacy of topical colchicine needs further evaluation^[307]. Colchicine associated gastrointestinal adverse effects at doses above 2-3 mg/d are the major concern and may occur in 80% of patients and can be an indicator of maximum therapeutic dose. Myopathy and neuropathy may occur in long-term therapy while pancytopenia and renal failure results from overdose of the drug. Colchicine may be more useful in psoriatic arthritis, pustular psoriasis and palmoplantar psoriasis in a subset of patients, but more perspective data will be required to establish the role of colchicine in the management of psoriasis.

Dapsone

Therapeutic efficacy of this well-known antileprosy drug was first reported in a patient of generalized pustular psoriasis who was managed on a regimen of long-term systemic triamcinolone and dapsone^[308]. Subsequently, several reports of its successful use in the treatment of childhood pustular psoriasis appeared^[309-311]. An excellent response from dapsone was noted in 19 of 26 children while other five children had moderate response when treated with dapsone^[310]. The response improved further when dapsone was combined with triptolide (the active ingredient in a Chinese herb) and erythromycin. Dapsone (100 mg/d) was also effective in treating inverse psoriasis involving genital skin fold^[312]. The usual dose for pustular psoriasis in children is 1 mg/kg per day or 50-300 mg/d in adults and decreased to a low maintenance dose after effective control. The mechanism of its action in psoriasis has been postulated to be due to its anti-inflammatory effects by virtue of interference with neutrophil chemotaxis, blockage of prostaglandin- and leukotriene-mediated inflammation, and inhibition of myeloperoxidase in neutrophils and eosinophils, preventing tissue injury from oxygen radicals. Woolly headedness, anemia, dose-related methemoglobinemia,

hemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficient patients, agranulocytosis, hepatitis, dapsone hypersensitivity syndrome, peripheral neuropathy are some of its potential adverse effects requiring periodic evaluation. The utility of dapsone appears exciting but few well-controlled clinical studies are highly desirable to evaluate efficacy of this very versatile low-cost treatment in psoriasis.

Pentoxifylline

Pentoxifylline, a methylxanthine derivative, is a non-selective inhibitor that moderates the intracellular levels of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate by decreasing their hydrolysis and augments cyclic nucleotide-dependant signal transduction leading to variable effects on inflammation^[313,314]. It reduces blood viscosity, inhibits aggregation of platelets, erythrocytes and leukocytes, inhibits thrombus formation and improves microcirculation and tissue perfusion because of hemorheologic actions^[315]. It also suppresses *TNF α* gene transcription, expression of TNF mRNA and secretion of TNF protein in macrophages and monocytes. The anti-TNF effect and antiproliferative effect of pentoxifylline is speculated to be responsible for its efficacy in psoriasis^[293,316]. Magela Magalhães *et al*^[317] in a randomized, placebo-controlled trial treated 61 patients with active psoriasis with pentoxifylline 400 mg/d or placebo. Clinicopathologic evaluation 8 wk after treatment showed no statistically significant differences from pre-treatment features between the two groups. el-Mofty *et al*^[293] in a randomized controlled trial studied efficacy of sulfasalazine and pentoxifylline. They divided 32 patients in four groups treated either with sulfasalazine (group A), pentoxifylline (group B), both drugs (group C), or methotrexate (group D), respectively. Combination of sulfasalazine and pentoxifylline produced a better response than either drug used alone but methotrexate was superior in clearing the psoriasis at weeks 0, 2, 4, 6 and 8 of follow up. Its combination with fumaric acid esters is also said to reduce the severity and incidence of fumaric acid esters associated flushing and gastrointestinal side effects^[224]. Similarly, use of pentoxifylline with cyclosporine might reduce later's nephrotoxicity^[318]. Overall, its usefulness as monotherapy appears limited as compared to its combination with other antipsoriatic therapy. It is perhaps better to use it as only "add-on" therapy in the treatment of psoriasis^[319].

PHOTOTHERAPY RELATED PROCEDURES

Phototherapy using UV light from sun or artificial source is a well-established treatment option in psoriasis of moderate severity, palmoplantar psoriasis, guttate and small plaque variety. UV light of both, broadband (BB) UV-B (290-320 nm) and narrowband (NB) UV-B (311-313 nm), and UV-A (320-400 nm) wavelength is predominantly used in psoriasis therapy. Comparatively, NB-UV-B phototherapy is superior to BB-UV-B in efficacy

and remission periods but is equal or less effective than PUVA therapy^[320-325]. PUVA is useful in thick plaque psoriasis, palmoplantar psoriasis (particularly with topical psoralene), and for UVB phototherapy non-responders. However, UV-B phototherapy has added advantage of ease of administration and no psoralene toxicity (gastrointestinal intolerance, hepatotoxicity, phototoxicity, photodamage, premature aging, cataract, risk of skin cancers). Combination of PUVA or UV-B phototherapy has been used along with various topical (corticosteroids, calcipotriene, anthralin, tazarotene) or systemic treatments (methotrexate, retinoids) for enhanced therapeutic effect even at lower than recommended doses^[326-329]. A combination of PUVA and UV-B has cleared psoriasis more effectively with an average of 11.3 treatments at doses much lower than needed for monotherapy^[330]. The overall objective is to maintain minimum perceptible erythema for optimal dosing until 20-25 treatments, total or near total remission, or no further improvement is noticeable. The treatment is continued with reduced frequency to maintenance therapy once the remission is achieved. Nevertheless, the limitation is its contraindication in patients with erythrodermic or photo aggravated psoriasis, photosensitive disorders (systemic lupus erythematosus), personal or family history of melanoma or other skin cancers, and severe actinic damage. Eye protection is essential during UV phototherapy and ingestion of psoralene is contraindicated in children aged < 12 years.

Photodynamic therapy

Photodynamic therapy or photochemotherapy using topical aminolevulinic acid has been tried in psoriasis with inadequate clinical response in a randomized study comprising 29 patients^[331]. Results have been discouraging in a recent randomized double-blind trial of this modality in 12 patients with psoriasis^[332]. The therapy is frequently associated with severe pain and burning during and after treatment warranting its discontinuation. Topical hypericin, methylene blue, and systemic ALA and verteporfin are perhaps better tolerated photosensitizers for photodynamic therapy^[333]. Like photodynamic therapy, photopheresis and extra-corporeal photochemotherapy are ineffective for skin lesions or psoriatic arthritis^[334,335] and not preferred.

Grenz ray therapy

Grenz rays are essentially short-wavelength X rays with a wavelength of 0.07 to 0.4 nm, which is also in the range of long-wavelength ultraviolet radiation. They are produced at low kilovoltages with very limited penetration ability; up to the first half millimeter of the skin. Grenz ray therapy has been used effectively in many inflammatory dermatoses (eczemas, lichen planus, acne, Hailey- Hailey disease, mycosis fungoides) perhaps for their anti inflammatory effect and ability to decrease Langerhans cells in the epidermis^[336]. Many researchers have reported good response from grenz

rays (4 Gy weekly for 6 wk) therapy in psoriasis as well. Grenz rays therapy was effective in 14 of 16 patients with scalp psoriasis in a double-blind bilateral trial leading to complete clearing of scalp lesions treated with grenz rays for 6 wk and the remission lasted for 3 mo in 9 of these patients^[337]. Grenz rays combined with topical corticosteroids cleared scalp psoriasis faster than topical corticosteroids alone in 17 patients with symmetrical scalp psoriasis lesions in a double-blind study^[338]. The remission also lasted longer with combination therapy than when grenz rays were used alone. Lindelöf *et al*^[339] compared grenz ray therapy alone with combination of grenz rays and topical betamethasone dipropionate in 40 patients with scalp psoriasis randomized into two groups. One group received 4 Gy of Grenz rays administered on six occasions at intervals of 1 wk and the other group was given the same Grenz ray treatment plus topical corticosteroid. The patients were assessed before and after Grenz ray therapy. Psoriasis cleared significantly in 16 out of 19 (84%) of the patients in the Grenz ray group, and 13 out of 18 (72%) of the patients in the combination group but the remission did not differ significantly between the two groups at end of follow-up of 6 mo. Remissions were longer with combination of grenz rays and selenium sulphide shampoo in combination as compared to placebo shampoo and Grenz rays^[340]. Grenz ray therapy was also effective in a limited manner and appears to be a useful adjunct to other therapies for palmoplantar psoriasis and nail psoriasis particularly for nails with normal thickness^[341,342]. The grenz ray therapy (4 Gy weekly for 6 wk) showed moderated but significant improvement of palmoplantar pustulosis in 15 patients in a randomized placebo controlled bilateral study^[341]. The efficacy of grenz ray therapy was assessed in 22 patients with nail psoriasis in a randomized, bilateral controlled study^[342]. One hand was allocated to treatment group receiving 5 Gy of grenz rays at weekly interval on 10 occasions. The placebo group received simulated therapy. The patients receiving active treatment showed moderate but significant improvement when psoriatic nails of normal thickness as compared to the control group. Overall, current evidence on its efficacy for psoriasis remains limited and development of non-melanoma skin cancers is a concern in the long term in addition to reported adverse effects of erythema and pigmentation^[336,343].

Excimer laser

The monochromatic excimer laser used 308 nm xenon chloride light source and can deliver supra-erythemogenic doses up to 6 MED (2-6 MEDs) focally to the individual skin lesion for targeted phototherapy to minimize radiation and number of treatments. Initially used as three times weekly with an average of 10-12 treatments needed normally for improvement^[344]. Asawanonda *et al*^[345] reported at least 75% clearing of psoriasis in 72% of 124 patients after an average 6.2 treatments with excimer laser delivered twice

weekly. Higher response was noted with excimer laser in comparison with pulse-dye laser in a recent comparative study; few patients also responded better with the pulse-dye laser^[346]. Patients in both the groups had remissions lasting more than 3 mo to 1 year. Blistering, burning and pain, and postinflammatory hyperpigmentation are potential side effects of excimer laser.

Climatotherapy and balneophototherapy

Exposure to sunlight is well known to improve psoriasis in majority. Daily bathing in Dead Sea water followed by exposure to sunlight perhaps remains the most studied mode of climatotherapy. The efficacy of Dead Sea climatotherapy has been attributed to the, high mineral contents, climatic conditions, and its location at about 400 m below sea level. Exposure to UV light through a mineral haze surrounding the beaches for 15 min daily to begin with is increased gradually depending on skin type to a maximum of 3 h/d for 3-4 wk. A 2 wk therapy is also considered optimal by some workers^[347]. The therapy has been found effective in psoriasis decreasing PASI scores by 75% or more with long remissions^[348-350]. Harari *et al*^[351] observed 95.5% improvement of pre-treatment mean PASI score that decreased from 31.7 to 1.42 in 64 patients after 4-wk Dead Sea climatotherapy. All patients achieved PASI 50 and 75.9% of them reached PASI 75 during the same period. The median time of remission was 23 wk after a median duration of 33.6 wk. However, no long-term changes in psoriasis severity and quality of life were observed following Dead Sea climatotherapy in an earlier study^[352]. Nevertheless, improvement is considered comparable to that from NB-UVB or PUVA therapy and other treatment modalities^[351,353]. It was effective in psoriatic arthritis and has been used safely in pediatric patients^[354-357]. Although considered expensive and time consuming, Shani *et al*^[350] found it cost-effective considering the cost involved in travel, hotel accommodations, medical and laboratory charges, loss of productive days, adverse effects, and time taken for recovery of inpatient treatment. It has been combined safely and effectively with acitretin for psoriasis therapy^[355].

Balneophototherapy involves salt-water baths and artificial ultraviolet radiation as an alternative to climatotherapy at the Dead Sea. Although high clearance rates have been reported with balneophototherapy^[358,359], combination of Dead Sea bathing and sun exposure was more effective with 83% improvement as compared to 73% improvement with sun exposure alone and 28% improvement in psoriatics who only soaked in Dead Sea salts^[360]. Climatotherapy is considered safe and adverse effects of this non-drug therapy such as sunburn, pruritus, folliculitis, solar elastosis, solar lentigens, poikiloderma and wrinkles may occur^[349,350,361]. Photodamage, malignant melanoma and non-melanoma skin cancer are other potential risks associated with long-term therapy.

Phototherapy for treating psoriasis, as standalone therapy or in combination with other modalities,

remains as good an option as it was before therapies that were more effective became available. NB-UVB phototherapy is preferred being simpler and cheaper than all these procedures, virtually safer and free of adverse effects associated with psoralene ingestion.

PHYSICAL MODALITIES

Because of inherent complications, these physical treatment modalities should not be preferred to other therapeutic modalities or biologicals even in resistant debilitating disease.

Dialysis and related procedures

A report on incidental clearance of psoriasis lesions following haemodialysis in 1976 led several small studies reporting a variable response^[362-367]. Twardowski^[363] also performed hemodialysis for psoriasis in a non-uremic patient. A review of these reports reveals that peritoneal dialysis was more effective than hemodialysis. With 3-4 continuous ambulatory peritoneal dialyses per day, the psoriasis cleared completely in the two patients with renal failure and improved in the other two patients with normal renal function^[368]. However, continuous treatment is perhaps required to prevent relapse. In a randomized double-blind crossover study treatment with sham and real peritoneal dialysis was performed in severe chronic plaque psoriasis unresponsive to conventional therapies including methotrexate^[369]. Two patients cleared completely, two patients had more than 75% clearance and one patient had no significant response in peritoneal dialysis group while none of the 5 patients in the control group had any response. Sobh *et al*^[370] treated 40 patients with severe psoriasis after their random grouping for haemodialysis (group-1), peritoneal dialysis (group-2), and treatment with modified Goeckerman (group-3). Ten dialysis sessions showed better response in peritoneal than haemodialysis, and both were better than Goeckerman treatment. There were no significant changes in plasma, or tissue zinc and copper levels while there was a significant decrease in IgG deposits after treatment in the three groups. Contrarily, Nissenon *et al*^[371] in a randomized controlled trial of haemodialysis in seven patients with severe psoriasis observed no significant objective improvement. They performed a 24 h course of haemodialysis in three patients once daily for 4 d and repeat haemodialysis after 4 wk. Sham dialysis was performed in similar manner in four patients. In another study, 4/8 (50%) patients in haemodialysis group and 6/10 (60%) patients in peritoneal dialysis group, respectively, improved at the end of six months^[372]. The benefit was temporary and one patient developed exfoliative dermatitis 11 d after haemodialysis. Three patients of Llewellyn *et al*^[373] neither tolerated nor benefited from peritoneal dialysis. The exact mechanism of action of this procedure is poorly understood and is postulated to be from decreased IgG, increased fibronectin level, and postulated removal (from bloodstream) of growth-

promoting substances, psoriasis-related factors, activated polymorphonuclear leukocytes, interference with neutrophil migration^[371,372].

While some psoriasis patients with renal disease may benefit from dialysis, the severe psoriasis itself independently predicts chronic kidney disease^[374]. Haemodialysis may also cause relapse, worsening of pre existing psoriasis or trigger *de novo* psoriasis during chronic hemodialysis for renal disease. New-onset psoriasis may occur during both haemodialysis and peritoneal dialysis and factors implicated include dialysis-induced growth factor, cytokines, and chemokines in psoriasis development^[375-377].

The outcome of hemofiltration, leukopheresis, cardiopulmonary bypass, and exchange with fresh frozen plasma in psoriasis treatment has been variable^[378-381]. Plasma exchange gave no or only partial remissions but no controlled studies are available^[382,383]. However, a controlled study noted no beneficial effect from sham and true plasma pheresis and leucopheresis^[384]. Forced osmotic diuresis simply does not work^[385]. Among all, peritoneal dialysis may favourably influence psoriasis outcome but never preferred unless it is required for its well-defined indications.

Tonsillectomy

Exacerbation, persistence or new onset of chronic plaques psoriasis within a subset of psoriatics is often attributed to hyper-reactivity to super-antigens, usually viral or bacterial proteins. Streptococcal infection has been the most implicated trigger in such instances. It has been suggested that some auto-reactive T cells primed against streptococcal proteins may cross react with keratinocytes (molecular mimicry) causing exacerbation of psoriasis. Molecular studies have suggested that auto-reactive T cells from tonsils can enter the circulation with homing to the skin triggering exacerbations/persistence of psoriasis. Tonsillectomy perhaps offer a valuable treatment option for such patients. However, most reports in the literature on tonsillectomy comprise small case series or case reports pertaining to Japanese patients with acute guttate psoriasis, chronic plaque psoriasis or palmoplantar pustulosis. A complete clearance of guttate psoriasis and proteinuria was reported 2 and 6 mo after tonsillectomy in two patients, respectively^[386]. Similarly, complete clearance of recurrent guttate psoriasis with remissions lasting for 16 mo was observed in two patients 1-2 mo after tonsillectomy^[387]. Hone *et al*^[388] reported complete clearance in 5 (83%) patients in a retrospective study comprising six patients with guttate psoriasis. However, the effect of tonsillectomy in guttate psoriasis remains poorly studied despite strong suggestion for its association with streptococcal pharyngitis. The clinical improvement in plaque psoriasis and reduction of circulating streptococcal and keratin peptide-reactive IFN- γ -positive CD8-positive skin-homing T cells is closely related^[389]. However, the benefit of tonsillectomy

in chronic plaque psoriasis remains ambiguous at best. In a questionnaire based retrospective study of 74 Danish patients with plaque psoriasis, 32% patients each reported complete or significant clearance of recalcitrant psoriasis vulgaris while 39% patients had some improvement^[390]. Worsening of disease was reported by 7% and 22% experienced no improvement. There was also no statistical difference in the benefit of tonsillectomy for patients who reported flare up of their skin disease and who reported no effect from tonsillitis. Hone *et al*^[388] reported complete or partial clearance of psoriasis plaques after tonsillectomy in 29% patients each, respectively; three of seven (42%) patients did not benefit at all. Recently, Thorleifsdottir *et al*^[389] noted a significant reduction in PASI score ranging from 30%-90% in 86% of 29 patients vs 0% in controls in a randomized clinical trial of tonsillectomy in chronic plaque psoriasis. Nearly, 60% patients achieved PASI 50 and the improvement was apparent 2 mo after tonsillectomy that lasted for over 2 years. Rachakonda *et al*^[391] also made similar observations in a recent systematic review of 20 publications of last 53 years comprising 545 patients with psoriasis who were evaluated for or underwent tonsillectomy.

The therapeutic efficacy of tonsillectomy was also analysed in 12 patients among 385 patients with generalize pustular psoriasis in a 1999 report by Ozawa *et al*^[392]. The disease decreased in approximately 50% but only 2 (16.7%) patients showed clear-cut benefit. The exacerbation of palmoplantar pustulosis too has been imputed to acute tonsillitis pioneering its treatment with tonsillectomy^[393-399]. Subjective marked or complete remission after tonsillectomy was reported by 89% of respondents to a questionnaire who had been treated for palmoplantar pustulosis by tonsillectomy^[400]. Thirteen of 15 patients with palmoplantar pustulosis in another study reported effective to complete response 3 mo after tonsillectomy, no or partial response was also observed in one patient each^[401]. Takahara *et al*^[394,399] in two separate studies noted subjective improvement after tonsillectomy in 87% and 94% patients with palmoplantar pustulosis, respectively. Wu *et al*^[400] have recently reviewed available evidence for the benefit of tonsillectomy in treatment of psoriasis. Overall, tonsillectomy may be useful for a subset of these patients in view of high rates of reported response to the procedure. However, additional well-designed studies including patients of diverse ethnicities will be needed for any recommendations. Moreover, the benefit must outweigh the risk associated with the procedure as disease remission after tonsillectomy was only for over two years or so in the reviewed reports. Long-term antimicrobial therapy will perhaps be more useful in such cases unless tonsillectomy is required due to its well-established indications^[401].

Ichthyotherapy

Ichthyotherapy (Ichthys-Fish, Greek) means treatment

for skin by using fish *Garra rufa*, commonly known as “nibble fish” or “doctor fish of Kangal”, which is a natural inhabitant of river basins in Central Eurasia. It is widely used in beauty and foot spas, and for the treatment of wounds or skin disorders like psoriasis and dermatitis that has made Kangal (Turkey) a popular health resort^[402]. The treatment involves lying in the ponds/spas and let the fish nibble on the scales and loose skin on the affected areas. Although the utility of *Garra rufa* in the treatment of psoriasis was identified as early as 1989 by Turkish researchers^[403,404], no controlled studies have been carried out for its efficacy. The two recent short-term, uncontrolled studies report beneficial effects of ichthyotherapy in psoriasis. Özçelik *et al*^[405] followed up 14 of 87 patients with chronic plaque psoriasis having prolonged immersion (mean 7.4 ± 1.1 h/d, mean 11.5 ± 6.6 d) in warm spring spas of Kangal containing *Garra rufa*. They reported complete clearance at 21 d in 8 (57.14%) and partial clearance in 6 (42.85%) patients, respectively. Two patients with erythrodermic or pustular psoriasis could not use this mode of therapy due to pain. Thirty-five of 87 patients experienced significantly longer remissions as compared to patients treated with topical corticosteroids alone. The overall beneficial effect was attributed to descaling of skin lesions by the fish, high selenium content and jacuzzi effect in spa water, natural sunlight, and reverse Koebner’s phenomenon. Grassberger *et al*^[406] used ichthyotherapy in a controlled medical setting to eliminate potential risk of infections associated with this mode of therapy. They evaluated its efficacy in 67 Austrian patients with moderate to severe chronic psoriasis who had undergone fish spa therapy for 2 h/d for three weeks in a tub containing garra rufa combined with short-term UV-A exposure and emollient application after each session. The tub and the fish were used exclusively for one individual patient. The bath water temperature was maintained at 36°C – 37°C , filtered and disinfected constantly, and changed every 3–4 times a day. Overall, there was 71.7% reduction in PASI score and 87.5% patients reported a more favourable response vs other therapies. PASI ≥ 75 and PASI ≥ 50 were noted in 31 (46.3%) and 61 (91%) patients, respectively. Mean remission period was 8.58 mo and 65% patients reported decreased severity of relapse. They attributed beneficial effects to the relaxing effect of baths, decreased stress and psychological wellbeing contrary to the earlier belief.

Although no significant side effects were noted in these studies, pain, bleeding from nibbled skin lesions or transmission of viral and bacterial infections remains a potential risk^[406,407]. The main concern about the use of fish spas involves the transmission of infectious agents such as *Mycobacterium marinum*, *M. fortuitum* and *M. chelonae*, *Aeromonas* spp. (*Aeromonas* folliculitis), *Streptococcus* spp., *Salmonellae* (soft tissue infections, pustular dermatitis), *Vibrio cholerae*, *V. vulnificus*, or *Klebsiella* spp (wound infections) particularly among patients with diabetes, a common

psoriasis co-morbidity, causing significant morbidity.

COMMENTS

The usefulness of various therapies, systemic (methotrexate, cyclosporine, acitretin or various biological therapeutic agents) or topical (tar, anthralin, corticosteroids or vitamin D analog ointments, phototherapy with or without psoralens) has been well established. The utility of vitamin D analogs (calcipotriol, calcitriol, tacalcitol, maxacalcitol, becocalcidiol) in psoriasis needs a mention here since these are important in sequential therapy as monotherapy or in combination with topical corticosteroids (halobetasol, clobetasol, betamethasone dipropionate) for added benefit and steroid-sparing effect. Over the years several clinical studies across the regions have demonstrated efficacy and safety of topical calcipotriene without tachyphylaxis or skin atrophy observed with topical corticosteroids^[408–412]. Calcitriol is as effective as betamethasone propionate or short-contact dithranol therapy, and significantly more effective than calcipotriene for the treatment of facial, hairline, and flexural psoriasis with better tolerability. While several studies have demonstrated efficacy of tacalcitol in the treatment of mild to moderate plaque psoriasis, nail psoriasis and scalp psoriasis, maxacalcitol (25 $\mu\text{g/g}$) is considered more effective than once-daily calcipotriol^[413–418]. However, noncompliance for vitamin D analogs reported in 12%–20% patients is due to lesional and perilesional irritation with accompanying perilesional erythema, stinging, itching, and/or burning following topical application^[419–423]. Hypercalcemia, hypercalciuria and parathyroid hormone suppression are rare but potential systemic adverse effects and occur because of using more than recommended dose of 100 g/wk or in the presence of impaired calcium metabolism or underlying renal disease^[424–428]. Relatively high cost of therapy is another reason for noncompliance.

Emollients, especially petrolatum-containing products, remain a main stay of any treatment. They retain moisture in the stratum corneum and increase local penetration of topical medications. Petrolatum ointment has an antipsoriatic effect while combination with salicylic acid (3%–6%) will have descaling effect on psoriasis plaques and enhance penetration of corticosteroid. Ichthyol pale (4% sodium shale oil sulfonate), a substitute for coal tar with conventional moisturizing properties, also offers anti inflammatory, antipruritic and antimicrobial actions because of high sulphur content^[429,430]. All these can be used alternating with gradual withdrawal of topical steroids for the maintenance stage. Anecdotal efficacy of topical aminophylline 4% ointment could not be substantiated^[431,432]. Changing topical formulations for improved drug delivery and cutaneous bioavailability appears another area for future researchers.

Apremilast is recently FDA approved oral therapy of active psoriatic arthritis in adult patients. It was found superior over placebo in phase 3 randomised, placebo-controlled trial (PALACE 1–4 study) comprising patients with active psoriatic arthritis^[433]. Overall, it was also

equally effective as monotherapy as in combination with existing DMARDs. There was also improvement in the PASI 50 (51% vs 19%) and PASI 75 (21% vs 5%) compared with placebo. Headache, nausea, and diarrhea were the only significant adverse effects reported. Apremilast 30 mg twice daily was also effective in chronic plaque psoriasis in a phase 3 multicenter, randomized, placebo-controlled trial (ESTEEM 1 study)^[434]. Its exact mechanism of action needs elucidation but said to regulate inflammatory mediators by inhibition of phosphodiesterase 4 enzyme in immune cells leading to increase in intracellular cAMP levels.

Peptide-T, tyrosine kinase inhibitors (Erlotinib), p38 mitogen activated protein kinase inhibitors, protein kinase-C inhibitors, nerve growth factor receptor blocker, rapamycin inhibitors (sirolimus, everolimus) constitute experimental therapies^[435-441]. Alternative approaches (acupuncture, ayurvedic medicine, traditional Chinese medicine, homeopathic medicine, naturopathic medicine, etc.), and immunotherapy (heat-killed delipidated, deglycolipidated *Mycobacterium vaccae*, *Mycobacterium w* or anti-leishmania vaccines) forms other interesting area of research despite variable results^[442-445].

It is also interesting to note the evolution of psoriasis and its therapeutic modalities. The concept of keratinocyte dysfunction led to treatment with phototherapy, methotrexate, and retinoids before 1980s, whereas, cyclosporine was introduced after it was considered an immunologic disease during 1980s. Alefacept, efalizumab, and TNF- α blockers were developed during 1990-2005 as psoriasis evolved as a disease of altered cytokine profile (IL-12/Th1-mediated). In recent years, ustekinumab and secukinumab have been developed in view of IL-23/Th17-mediated cytokine profile in psoriasis. Normalization of angiogenesis, an important pathologic component of psoriasis lesions, appears emerging concept for novel antiangiogenic agents for more targeted therapy; may be in combination or as an alternative to conventional therapies. Calcium dobesilate inhibits VEGF and interferes with fibroblast growth factor-induced neoangiogenesis; the efficacy of topical 5% cream in limited plaque psoriasis appears promising^[446-448]. Neovastat, also a VEGF antagonist with anti-angiogenic and anti-inflammatory properties, has shown statistically significant reduction in PASI score in randomized phase I/II dose-comparison clinical trials comprising 29 patients with psoriasis^[449]. More well designed studies are required before these drugs are approved for the treatment of psoriasis. Finally yet importantly, the clinicians must be apprised of all available antipsoriasis therapies in view of variable therapeutic outcome(s) that may test one's ingenuity in managing some of the "difficult to treat" patients. It seems that nonstandard and off-label therapies will remain an important alternative in rotational/intermittent treatment(s) or to more widely used and evidence based treatments until a therapy that is affordable, safe, effective, and more importantly, remittiv becomes available.

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Treatment of mycosis fungoides, in the era of stem cell transplantation

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Abstract

Mycosis fungoides and Sèzary syndrome are the most common subtypes of cutaneous T-cell lymphomas. Even though, in early-stage disease, Mycosis fungoides commonly has a more indolent course, disease will progress in about 20% of such patients. About 30% of patients have been reported to develop advanced-stage disease and, at present, there is no cure for the

disease. A number of systemic approaches have been used for advanced-stage mycosis fungoides (IIB-IV) and transformed disease. Aggressive approaches seem to be warranted in such patients. The scope of this review is the stem cell transplantation in mycosis fungoides and its leukemic variant, Sèzary syndrome.

Key words: Mycosis fungoides; Sèzary syndrome; Stem cell transplantation

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Core tip: Some cutaneous T-cell lymphoma patients progress to advanced-stage disease or leukaemic stages. To date, there is no cure for those cases. In the last few years, several publications reported durable responses in some patients following allogeneic hematopoietic stem cell transplantation. Our aim is to define outcomes after hematopoietic stem cell transplantation for mycosis fungoides and Sèzary syndrome.

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INTRODUCTION

Cutaneous T-cell lymphomas (CTCL) are amongst a group of malignancies of T-lymphocytes which primarily involves the skin. Mycosis fungoides (MF) and Sèzary syndrome (SS) are the most common subtypes of CTCL^[1]. Based on the TNM classification, MF has four clinical stages, which has been translated further into early-stage and advanced-stage disease. Patients are considered to have "limited-stage" or "advanced-stage" disease if they have stage IA, stage IB, or stage IIA

Table 1 Summary of studies on auto hematopoietic stem cell transplantation and allo hematopoietic stem cell transplantation in patients with mycosis fungoides and Sèzary syndrome

Ref.	Year	Study location	Cases	Feature of study
AutoHSCT				
Bigler <i>et al</i> ^[11]	1991	United States	6	The first publication containing patient series with autoHSCT
Olavarria <i>et al</i> ^[9]	2001	United Kingdom	9	The analysis of autoHSCT with harvested cells post-T-cell depletion
Duarte <i>et al</i> ^[10]	2008	Spain	20	The use of auto and alloHSCT were summarized in this review
AlloHSCT				
Duvic <i>et al</i> ^[14]	2010	United States	19	The safety and efficacy of total skin electron beam with alloHSCT
Duarte <i>et al</i> ^[12]	2010	EBMT	60	The first large multicenter analysis of alloHSCT
Schlaak <i>et al</i> ^[15]	2012	Germany	-	To compare the efficacy and safety of conventional therapies with alloHSCT
de Masson <i>et al</i> ^[16]	2014	France	37	The largest multicenter analysis of alloHSCT for transformed MF
Duarte <i>et al</i> ^[13]	2014	EBMT	60	Updated with a prolonged median follow-up of 7 yr
Lechowicz <i>et al</i> ^[17]	2014	United States	129	The largest reported descriptive cohort of patients receiving alloHSCT
		United Kingdom		
		Australia		

HSCT: Hematopoietic stem cell transplantation; MF: Mycosis fungoides.

disease and stage IIB, stage III, or stage IV, respectively. Even though, in early-stage disease, MF commonly has a more indolent course, disease will progress in about 20% of such patients^[2]. About 30% of patients have been reported to develop advanced-stage disease and, at present, there is no cure for the disease^[3]. In terms of outcome, the most significant predictor appears to be clinical stage of the disease.

In most of advanced stage CTCL cases, short-term clinical responses can be achieved with the use of various therapies, with a median survival time of 2.9 years. Patients with SS, on the other hand, have shorter median survival, approximately 13 mo^[2,4,5]. A number of systemic approaches have been used for advanced-stage MF (IIB-IV) and transformed disease. These approaches include the use of retinoids, histone deacetylase inhibitors, interferon- α , bexarotene, the fusion toxin denileukin diftitox, extracorporeal photopheresis and chemotherapy without or in conjunction with stem cell transplantation. Despite of the limited data, the outcome is very poor in younger patients who have advanced-stage MF and are refractory to or relapsed after treatment with IFN- α , bexarotene, or histone deacetylase inhibitors. Aggressive approaches seem to be warranted in such patients^[6]. The scope of this review is the stem cell transplantation in MF and its leukemic variant, SS.

HEMATOPOIETIC STEM CELL TRANSPLANTATION

Overview

Hematopoietic stem cell transplantation (HSCT) is a procedure in which hematopoietic progenitor cells obtained from bone marrow or peripheral or umbilical cord blood, either autologous or allogeneic, is administered to the recipient with the aim of recomposing the bone marrow. It has been shown that conditioning regimen composed of chemotherapy and/or radiotherapy

combined with either autologous or allogeneic grafts was an efficient salvage treatment for a number of hematological malignancies that are unresponsive to conventional therapies. The most common indication for an HSCT in Europe is lymphomas. There has been an increase in the rate of allogeneic HSCT (alloHSCT) for lymphoma in recent years, largely owing to the introduction of reduced-intensity conditioning (RIC) alloHSCT^[7,8]. RIC is a procedure to reduce the tumor size prior to the transplant to refrain from standard regimes of high-dose therapy. RIC appears to be as effective as standard conditioning regimens but with significantly less toxicity. Even though we have sufficient experience with HSCT in other types of lymphoma, there is only a handful of cases and series available with regard to CTCL (Table 1).

Autologous HSCT for mycosis fungoides and Sèzary syndrome

Results with autologous HSCT (autoHSCT) did not particularly meet the expectations^[9,10]. As a matter of fact, autoHSCT is rarely, if ever, used for MF or SS. Bigler *et al*^[11] published the first paper on the advanced-stage MF and autoHSCT in 1991 and reported the outcome of six patients after autoHSCT. Later, in 2001, Olavarria *et al*^[9] published the analysis of autoHSCT with harvested cells post-T-cell depletion of nine patients with advanced-stage MF. Their data showed that complete clinical remission had been achieved in all patients and the median duration to achieve complete remission was 7 mo. However, the authors have reported that some of the cutaneous diseases relapsed, albeit in a less aggressive form. In 2008, the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation analyzed data of twenty patients with advanced MF/SS who received an autoHSCT since 1986 retrospectively. They calculated that the median estimated time to disease progression was only 2.3 mo^[11]. Unfortunately, high-dose chemotherapy with

autoHSCT showed only short-lived responses.

Allogeneic HSCT for mycosis fungoides and Sézary syndrome

AlloHSCT may be considered for patients with advanced disease (\geq stage IIB) whose disease fails to respond to all primary therapy options or who do not experience durable responses with any primary or salvage therapies.

The first large multicenter analysis of alloHSCT for advanced-stage MF came from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation in 2010 that reported sixty patients with MF and SS. Data showed that, estimated overall survival (OR) in patients with advanced-stage MF/SS at 1 year and 3 years were 66% and 54%, respectively. In MF/SS patients, disease status, donor type and type of conditioning regimen have been identified as the main determinants of the outcome of alloHSCT, with the disease status having the highest impact across all outcomes. An earlier phase of the disease time course independently predicted both lower relapse/progression and higher progression free survival and overall survival. Neither the differences in outcomes between MF and SS patients or between TNM stages were significant. RIC protocols appeared to lower the risk of non-relapse mortality (NRM) below to that associated with myeloablative conditioning (MAC) without apparently increasing the risk of relapse/progression. RIC alloHSCT continued to offer a better OS than MAC alloHSCT. AlloHSCTs from matched HLA-identical related donors had a better outcome than alloHSCTs from matched unrelated donors. There are only 15 cases in a series on matched unrelated donor in MF/SS, which makes our experience very limited. It is possible that the outcome would be better as our experience builds up^[12]. This original series were reanalyzed by the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation in 2014. New analyses revealed that OS at 5 and 7 years were 46% and 44%, respectively while PFS at 5 and 7 years were 32% and 30%, respectively, confirming that patients with advanced-stage MF or SS indeed benefited from alloHSCT. Data also showed that 27 patients (45%) had relapse or progression at a median of 3.8 mo after HSCT, indicating that disease relapse and progression comprised the main causes of post-transplant failure. It is worth noting that 8 of these 27 patients were alive at a median of 8 years after HSCT. This finding suggests that donor lymphocyte infusions (DLI) and/or other salvage therapies were very beneficial in rescuing some patients. At last follow-up visit, 27 patients were alive, and 26 of them were in CR. Seven year NRM was 22%, with the latest NRM occurring 14 mo after HSCT. Moreover, the risk of NRM is slightly higher if the patient has a poor performance score at HSCT (Karnofsky < 70) and the risk of relapse or progression is higher in patients who receive T-cell depletion. However, none of these alters survival significantly^[13].

Duvic *et al.*^[14] reported the results of their prospective study on 19 patients with advanced stage MF who underwent total skin electron beam irradiation, followed by alloHSCT with conditioning with fludarabine and melphalan. The authors calculated the 2-year OS and PFS and reported them as 79% and 53%, respectively. The authors also reported that was the main cause of failure of treatment among their patients who had advanced phase disease was progressive disease.

Further, Schlaak *et al.*^[15] planned to compare in patients with advanced primary cutaneous T-cell lymphomas the efficacy and safety of conventional therapies with alloHSCT. Unfortunately, an updated literature search in January 2013 did not reveal any randomised controlled trials. Therefore, the authors of this study could not come up with a validated conclusion or propose recommendations for clinical practice.

A retrospective multicenter analyses has been carried out by de Masson *et al.*^[16] in 37 patients who had advanced stage CTCL and treated with alloHSCT. These patients included 20 cases (54%) with transformed MF. Best to our knowledge, this study is the largest multicenter retrospective analysis of alloHSCT for transformed MF. Therefore, the estimated 2-year OS rate of 57% in this study indicates that alloHSCT is suitable in advanced stage primary CTCL, including transformed MF. Nineteen (51%) patients experienced progression, which translates into 56% 2-year cumulative incidence of progression. The relapse rate was higher than other studies which could be explained by the fact that most of our patients had transformed MF, which is associated with a higher risk of relapse.

Lechowicz *et al.*^[17] conducted a study on the outcomes of alloHSCT in MF/SS, using the data gathered from 129 subjects who presented in 2014 to the Center for International Blood and Marrow Transplant Research. To our knowledge, this analysis is the largest descriptive study on patients who received alloHSCT for MF/SS. However, due to the fact that 39% of the patients had stage IV MF/SS, this cohort represents the minority of patients with MF/SS with very aggressive disease. The result of that study confirms that alloHSCT is useful, delivering acceptable NRM (19%-28%) in MF/SS patients and that patients benefit from the treatment.

CONCLUSION

Based on the publications with limited evidence, HSCT has the potential to increase response in advanced-stage MF and the results are especially consistent and promising for alloHSCT. However, autoHSCT is not devoid of any disadvantages, one of which is the possibility of an early relaps. This may be due reinfusing the malignant cells, which contaminate the graft. Hence, T-cell depletion to get the graft free from tumor cells before autoHSCT is a feasible and safe option^[9]. Insufficient results achieved by autoHSCT means that alloHSCT should be listed as the treatment option for

advanced-stage MF. In contrast to autoHSCT, alloHSCT, which is obtained from a healthy donor, avoids the risk of tumor contamination of the graft and more importantly, has the potential to provide a ground for adoptive immunotherapy, leading to "graft-versus-tumor-effect" (GVT)^[18]. Based on previous reports, alloHSCT in advanced-stage MF appears to be superior to autoHSCT but relapse remains the major cause of mortality^[9-11]. Even though relapse is not uncommon, the course of the disease varies and some relapse with more indolent disease than others. It is obviously easier to manage relaps with indolent disease by non-chemotherapeutic agents. Duarte *et al*^[10] argued that DLI was beneficial in achieving complete remission after alloHSCT even if the patients had advanced-stage MF relapses and that this was an indication of the presence of GVT effect^[10]. Even though high grade graft-versus-host disease (GvHD) following alloHSCT is one of the greatest challenges for a clinician, low grade GvHD is a desired situation as a positive relationship has been found between disease-free survival and low grade GvHD. Therefore especially low grade skin GvHD, which often involves the skin in MF might increase the effectiveness of alloHSCT in MF^[19].

Limited number of studies in this area calls for caution while interpreting the results and implementing the findings in planning the treatment. To date, we have not been able to accumulate sufficient data from randomized controlled trials, which would otherwise clearly demonstrate the efficacy of alloHSCT in advanced-stage MF. We need more research, especially, prospective studies to enhance our knowledgebase in newer therapeutic modalities and establish a protocol on when to use alloHSCT.

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Clinical pharmacokinetics profile of ivermectin 1% cream after dermal applications on the face

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Abstract

AIM: To investigate the pharmacokinetics profile of Ivermectin 1% cream after topical treatment in patients with papulopustular rosacea (PPR).

METHODS: Ivermectin 1% cream is a new, effective, and safe treatment for PPR. The human pharmacokinetic (PK) profile of ivermectin and its circulating metabolites were assessed following topical application of ivermectin 1% cream to the face. Clinical PK assessments were conducted after 4 wk of treatment using healthy volunteers and PPR subjects. Additionally, PK sampling was conducted up to 1 year of treatment in clinical phase 3 studies. Plasma concentrations of ivermectin and ivermectin metabolites were determined using high-performance liquid chromatography with fluorescence detection after a specific derivation to increase sensitivity.

RESULTS: Systemic exposure to ivermectin was quantifiable at low levels in healthy and moderate to severe PPR subjects following the first topical application of ivermectin 1% cream (mean C_{max} of 0.5 ± 0.2 ng/mL and 0.7 ± 0.5 ng/mL in healthy volunteers and PPR subjects, respectively). Ivermectin plasma levels reached a plateau after 2 wk of repeated topical application, indicating that steady-state concentrations had been reached. No further ivermectin plasma accumulation was observed during the long-term clinical studies that investigated ivermectin treatment up to 1 year. Investigation of ivermectin metabolites indicated that 2 circulating metabolites represented

more than 10% of parent drug systemic exposure at steady state. Repeated topical application of ivermectin 1% cream resulted in lower systemic exposure levels when compared with orally administered ivermectin, suggesting limited transdermal absorption of ivermectin. Topically applied ivermectin is cleared from the plasma slowly (with a prolonged plasma half-life when compared to the oral route).

CONCLUSION: Applications of ivermectin 1% cream result in low systemic exposure levels. Steady-state conditions are achieved by 2 wk without further accumulation under chronic treatment.

Key words: Ivermectin; Pharmacokinetic maximal usage trial; Metabolites; Plasma and rosacea

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Core tip: Papulopustular rosacea (PPR) is a chronic skin disease affecting patients face, with a dramatic impact on social and professional interactions. Ivermectin 1% cream is a new effective and safe treatment for PPR recently approved in many countries. This article presents the clinical pharmacokinetics (PK) assessments conducted during the drug development of Ivermectin 1% cream. Usually, for topical products, PK assessments are incomplete due to the low systemic exposure. For ivermectin cream, a comprehensive PK and metabolism program was conducted in healthy volunteers and PPR patients up to 1 year treatment. These provided valuable information to better assess ivermectin safety profile.

Benkali K, Rony F, Graeber M, Jacovella J, Chappuis JP, Peirone MH, Poncet M, Delage S, Bouer R, Wagner N. Clinical pharmacokinetics profile of ivermectin 1% cream after dermal applications on the face. *World J Dermatol* 2016; 5(1): 57-64 Available from: URL: <http://www.wjgnet.com/2218-6190/full/v5/i1/57.htm> DOI: <http://dx.doi.org/10.5314/wjd.v5.i1.57>

INTRODUCTION

Ivermectin is a semi-synthetic derivative that belongs to the avermectin family of macrocyclic lactones with anti-parasitic activities and is thought to have an anti-inflammatory effect by decreasing cellular and humoral immune responses^[1]. The efficacy of oral ivermectin in human and animal demodicidosis and its anti-inflammatory properties suggest that ivermectin may also be effective in the treatment of papulopustular rosacea (PPR)^[2,3]. Ivermectin 1% cream development has shown that this treatment is effective and safe in treating inflammatory lesions of papulopustular rosacea^[4,5]. Therefore, ivermectin is now approved in the United States and in European Union member states as Soolantra® Cream 1% for treatment of papulopustular

rosacea in adults^[6].

Ivermectin pharmacokinetics (PK) data are well documented but mainly available for the oral marketed product for the treatment of onchocerciasis, strongyloidiasis of the intestinal tract and lymphatic filariasis^[7]. In addition, ivermectin is indicated for scabies treatment in some countries^[7]. After single or repeated oral dosing, peak plasma concentrations are achieved at approximately 4 to 10 h after dosing^[8-10]. The plasma systemic exposures increase proportionally with doses between 6 and 120 mg^[8,9]. After single 12 mg doses of oral ivermectin (tablet) in healthy volunteers, the mean peak plasma concentrations were from 23.5 to 50 ng/mL^[10]. Ivermectin elimination curve might be subject to an enterohepatic recycling^[11,12]. Ivermectin is widely distributed in the body with a volume of distribution about 3.1 and 3.5 L/kg, after ingesting 6 and 12 mg of ivermectin, respectively^[13]. In addition, ivermectin is approximately 93% bound to plasma proteins, mainly to serum albumin^[14].

Ivermectin is extensively metabolized in vitro by liver microsomal cytochrome P450 3A4 to hydroxylated and demethylated metabolites^[15]. Ivermectin and its metabolites appear to be eliminated mainly in the faeces, with minimal urinary excretion ($\leq 1\%$ of the administered dose). The mean half-life of ivermectin when administered orally is ranging from about 15 to 20 h^[9].

Recently, ivermectin has been approved for use in human as a topical treatment of head lice infestations with a short contact therapy (10 min application, single use)^[16]. The ivermectin transdermal absorption was evaluated in a clinical study in subjects aged from 6 mo to 3 years after a single application of ivermectin 0.5% lotion on the head. The resulting systemic exposure levels after a single 10-min application were very low in comparison to the oral administration, the mean maximum exposure (C_{max}) being 0.24 ± 0.23 ng/mL^[17].

The present work summarizes the human PK behavior of ivermectin and its metabolites following topical applications of ivermectin 1% cream as developed recently for the treatment of PPR. A comprehensive assessment of the clinical PK profile of ivermectin following topical application was performed in healthy volunteers and PPR subjects after 4 wk of treatment. In addition, due to the anticipated chronic use of this treatment, systemic exposure levels were further investigated in long term studies of up to 1-year treatment.

MATERIALS AND METHODS

PK study in healthy volunteers

A single-centre, open-label study to assess the pharmacokinetics and safety of ivermectin 1% cream has been conducted in healthy volunteers. Thirty-two male or female volunteers were enrolled in the study. A maximized dose (1 g of ivermectin 1% cream) was applied under nurses' supervision on the whole face as

a single application (Group 1: 8 subjects) or as repeated applications once (Group 2: 12 subjects) or twice (Group 3: 12 subjects) daily for 28 d. The treatment was followed by a 28 d or 56 d follow-up treatment-free period for the single and repeated dose respectively.

For the single application group (Group 1), blood samples for the determination of ivermectin plasma levels were collected over a 24 h period post dose and during a 28 d follow-up period.

For the repeated application groups [Group 2 (QD) and Group 3 (BID)], blood samples for the determination of ivermectin plasma levels were collected over a 24 h period on day 0 (first drug application), 14 and 28. In addition, pre-dose blood samples (residual levels) were collected on day 7 and 21. Blood samples were also collected during the 56 d follow-up period.

Maximal use PK study in subjects with severe papulopustular rosacea

This study was a multi-centre, open label study, involving approximately 15 adult male or female subjects with severe PPR, *i.e.*, with at least 25 inflammatory lesions and an Investigator Global Assessment (IGA) of rosacea of severe (score 4 on a 5-point rating scale from 0 to 4). Subjects were treated by nurses once daily on the whole face with 1 g of ivermectin 1% cream during a 4 wk period. The treatment was followed by a 28 d treatment-free follow-up period.

Blood samples were collected over 24 h in day 0 (first drug application), 14, and 28 to investigate the pharmacokinetics of ivermectin (and its related metabolites) in the plasma. In addition, pre-dose samples were collected at day 7 and 21. Blood draws were also sampled during the 4 wk following the last treatment application.

Long term use clinical studies

Two phase 3 studies of same design (Study #1 and Study #2) enrolled a total of 1371 adult subjects with moderate to severe PPR. The design of these studies has been previously described by Stein *et al.*^[4]. Overall, 1 group of subjects was treated with ivermectin 1% cream once daily for 52 wk, the remaining subjects were treated with the vehicle (during the first 12 wk of treatment) followed by an active treatment, azelaic acid 15% gel twice daily (from wk 13 to 52 of the study). Blood samples to assess ivermectin systemic levels were collected in a subset of subjects at approximately 12 h after the drug application at week 12, 32, 52 and at week 56 (4 wk after treatment stop).

Ivermectin and metabolites plasma concentrations measurement and PK analysis

In all clinical trials, ivermectin plasma concentrations were measured, after a solid-phase extraction, using the same validated high-performance liquid chromatography method (using fluorescence detection after a specific derivation to increase sensitivity). The limit

Table 1 Demographic characteristics of subjects enrolled in pharmacokinetic studies

	Healthy volunteers PK study (n = 32)	PPR subjects maximal use PK study (n = 17)
Age (yr)		
Mean \pm SD	30 \pm 8	54 \pm 12
(Min-max)	(18-45)	(35-74)
Gender (male/female)	16/16	6/11
IGA score: 4 (n %)	NA	17 (100%)
Inflammatory lesion count		
Mean \pm SD	NA	40.5 \pm 14.3
(Min-max)		(27.0-88.0)

NA: Not applicable; PK: Pharmacokinetic; PPR: Papulopustular rosacea.

of quantification of the method was 0.05 ng/mL. In addition, an estimation of concentration levels of the ivermectin metabolites was performed from the human plasma samples collected in the maximal use PK study.

Pharmacokinetic parameters (C_{min} , C_{max} , T_{max} , AUC and $t_{1/2}$) were calculated for each subject using a non-compartmental method (Kinetica™ software, version 4.3, InnaPhase Corporation, Philadelphia, United States). Descriptive statistics were performed on PK parameters. In addition, selected PK parameters (from healthy volunteers and PPR PK studies) were transformed into natural logarithms (Ln) and submitted to an analysis of variance including subject and time as factors in the model to assess the steady state conditions. The statistical review of the study was performed by a biomedical statistician.

RESULTS

PK study in healthy volunteers

Thirty-two healthy volunteer subjects were enrolled. There was an equal repartition of males (50%) and females (50%) in each group. The mean age (\pm SD) was 30 \pm 8 years (Table 1).

Single dose application

After a single topical application of ivermectin 1% cream, ivermectin plasma levels were quantifiable in all subjects (Figure 1). The mean values of AUC_{0-12h} and AUC_{0-24h} were 3.8 \pm 1.4, 8.3 \pm 2.5 ng \times h/mL, respectively (Table 2). The mean maximum plasma concentration of ivermectin peaked at 9 h after dosing (mean C_{max} : 0.49 \pm 0.15 ng/mL) and slowly decreased thereafter (Figure 1). The mean plasma terminal half-life was 45 h (range 32 to 130 h).

Repeated applications

Following repeated topical applications of ivermectin 1% cream, systemic exposure was higher than that found after a single application (Table 2 and Figure 1). However, ivermectin systemic levels reached a plateau at day 14 of treatment for both QD and BID dosage regimen groups (Table 2 and Figure 1). In addition, the

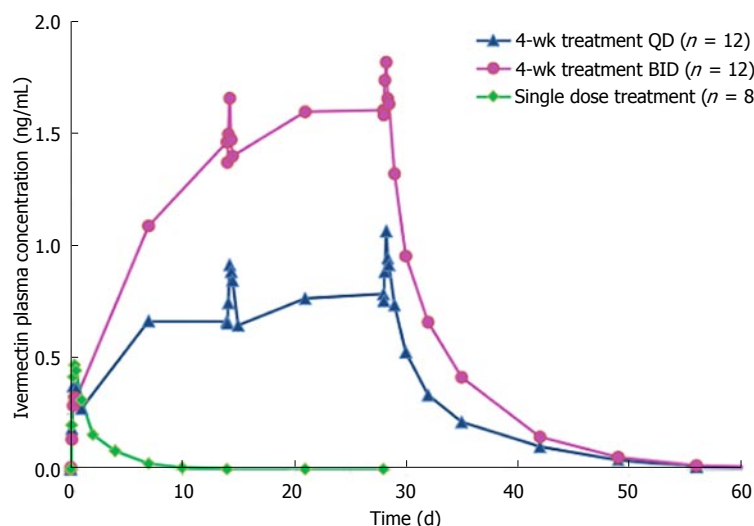


Figure 1 Plasma concentration-time curves after application of ivermectin 1% cream in healthy volunteers (means). QD: Once a day; BID: Twice a day.

Table 2 Pharmacokinetic parameters obtained after topical applications of ivermectin 1% cream in healthy volunteer subjects

Group	Time Point	C _{max} (ng/mL)	T _{max} (h)	AUC _{0-12 h} (ng × h/mL)	AUC _{0-24 h} (ng × h/mL)
1: Single dose	NA	0.49 ± 0.15	9 ± 3	3.8 ± 1.4	8.3 ± 2.5
2: QD 4 wk treatment	Day 0	0.41 ± 0.17	10 ± 5	3.1 ± 1.5	6.9 ± 2.9
	Day 14	0.93 ± 0.35	NA	9.8 ± 3.4	19 ± 7
	Day 28	1.08 ± 0.43	NA	11 ± 5	21 ± 8
3: BID 4 wk treatment	Day 0	0.34 ± 0.16	11 ± 2	2.6 ± 1.5	NA
	Day 14	1.70 ± 0.66	NA	18 ± 6	NA
	Day 28	1.90 ± 0.76	NA	20 ± 9	38 ± 17

NA: Not applicable; AUC_{0-12 h}: Area under the plasma concentration-time curve from pre-application (T₀) through to 12 h; AUC_{0-24 h}: Area under the plasma concentration-time curve from pre-application (T₀) through to 24 h.

comparison of PK parameters (AUC and C_{max}) calculated at d 14 and 28 have shown that there were no statistical differences in both dosage regimen groups, evidencing that the steady-state was already reached at day 14 (Table 2 and Figure 1).

After twice daily repeated topical applications of ivermectin 1% cream, the systemic exposure parameters (C_{max} and AUC_{0-24 h}) were 1.8-fold higher than parameters calculated for the once daily dosage regimen, suggesting a dose proportionality trend with the applied dose (Table 2). In addition, no gender effect on PK parameters was observed in this study (data not shown). After the last topical application, ivermectin was slowly eliminated with a mean half-life of 87 h (range 28 to 180 h) and 97 h (range 55 to 163 h) for the QD and the BID groups respectively.

Maximal use PK study in subjects with PPR

From the 17 subjects enrolled, 2 discontinued the study prematurely, and 15 subjects completed the study. The mean age of all 17 subjects was 54 ± 12 years, and the majority of subjects were females (64.7%). All subjects presented a severe PPR with an IGA score of 4 and mean facial lesion count of 40.5 ± 14.3 (Table 1).

After 1 single topical application of ivermectin 1%

Table 3 Pharmacokinetic parameters of ivermectin obtained after topical application of ivermectin 1% cream once a day in subjects with papulopustular rosacea (maximal use pharmacokinetic study)

Parameters Mean ± SD	Day 0 ¹	Day 7 ²	Day 14	Day 21	Day 28
Pre-dose/C _{min} (ng/mL)	0.37 ± 0.21	1.17 ± 0.88	1.26 ± 0.53 ³	1.36 ± 0.66 ³	1.36 ± 0.63
C _{max} (ng/mL)	0.69 ± 0.49	NA	2.10 ± 1.04	NA	1.74 ± 0.77
T _{max} (h)	9 ± 6	NA	10 ± 8	NA	11 ± 4
AUC _{0-24 h} (ng × h/mL)	9.3 ± 5.4	NA	36 ± 16	NA	35 ± 14

NA: Not applicable; Pre-dose/C_{min}: Residual drug concentration (pre-dose level); AUC_{0-24 h}: Area under the plasma concentration-time curve from pre-application (T₀) through to 24 h; ¹N: 17; ²N: 13; ³N: 14.

cream, quantifiable ivermectin levels (> 0.05 ng/mL) were detected in the plasma of all subjects (Figure 2). Maximum plasma concentrations of ivermectin were observed within 9 h post dose with a mean C_{max} of 0.69 ± 0.49 ng/mL and then slowly decreased thereafter to 0.37 ± 0.21 ng/mL, 24 h post dose (C_{min}) (Table 3). After repeated topical application, ivermectin maximum concentration reached a plateau with a C_{max} of 2.10 ± 1.04 ng/mL and 1.74 ± 0.77 ng/mL at day 14 and 28 (Figure 2). In addition, residual concentrations (C_{min}) were also stable from day 7 to day 28 ranging from 1.17 ± 0.88 ng/mL to 1.36 ± 0.63 ng/mL.

Overall, all assessed systemic exposure PK parameters (C_{min}, C_{max} and AUC_{0-24 h}) were stable through the treatment duration (Table 3). Indeed, after repeated topical applications of ivermectin 1% cream in subjects with severe PPR, exposure to ivermectin was similar at day 14 (AUC_{0-24 h} of 36 ± 16 ng h/mL) and at day 28 (AUC_{0-24 h} of 35 ± 14 ng h/mL), indicating that steady-state conditions were reached by 2 wk of treatment. Furthermore, the statistical analysis demonstrated that steady state conditions were achieved after 2 wk of treatment, as evidenced by the

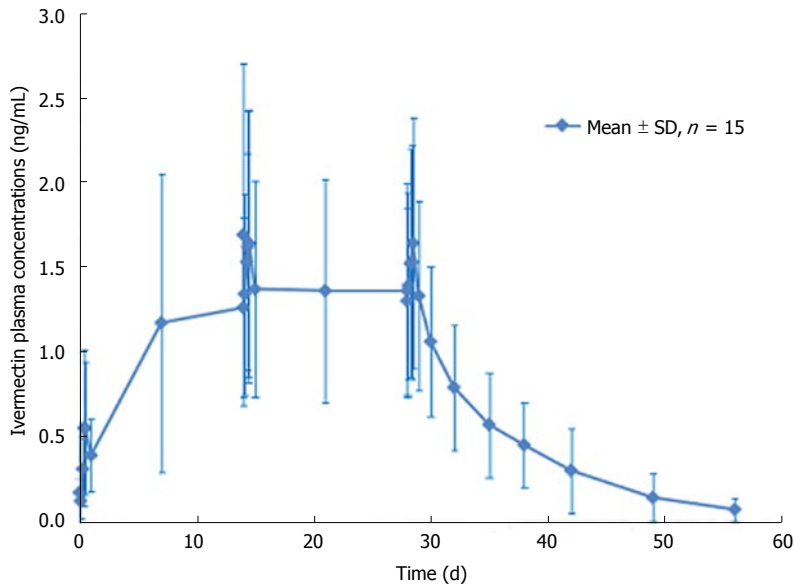


Figure 2 Plasma concentration-time curves after application of ivermectin 1% cream once a day in subject with severe papulopustular rosacea.

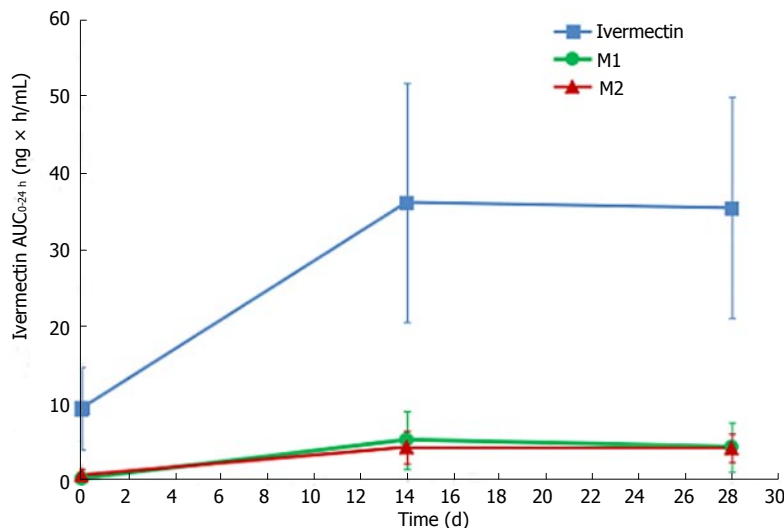


Figure 3 Mean AUC_{0-24 h} of ivermectin and its circulating major metabolites versus study days in subject with severe papulopustular rosacea. AUC_{0-24 h}: Area under the plasma concentration-time curve from pre-application (T₀) through to 24 h.

geometric mean ratio of AUC_{0-24 h} of day 28-14 (0.99, 90%CI: 0.82-1.18).

At the end of the 28 d application period, ivermectin was slowly cleared from the plasma (Figure 2). The mean value for the apparent terminal half-life was 145 h (range 92 to 238 h).

Ivermectin metabolites investigation has shown that 2 circulating metabolites represented more than 10% of parent drug systemic exposure at steady state. According to FDA guidance on safety testing of drug metabolites, these 2 metabolites are considered as major^[18]. These 2 metabolites were identified as a 3'' O-demethyl ivermectin (M1) and 4a hydroxy ivermectin (M2). The systemic exposures of M1 at day 14 (AUC_{0-24 h} of 5.2 ± 3.8 ng × h/mL) and at day 28 (AUC_{0-24 h} of 4.3 ± 3.2 ng × h/mL) were similar, indicating that steady state was already reached by day 14. The same tendency was observed with M2, which had similar systemic exposures at day 14 (AUC_{0-24 h} of 4.2 ± 2.1 ng × h/mL) and day 28 (AUC_{0-24 h} of 4.1 ± 1.8 ng × h/mL) (Figure 3). At the end of the 28 d application period, the

metabolites were slowly cleared from the plasma, with the last quantifiable concentration being observed 4 to 8 d after the last application.

Long term use studies

Blood samples for the assessment of ivermectin levels were collected in 197 subjects in the 2 phase 3 studies (Study #1 and Study #2). Ivermectin concentrations were stable through the 1-year treatment duration with concentrations means ranging from 0.3-0.5 ng/mL (Table 4 and Figure 4). Four weeks after the last treatment application (at week 56), ivermectin plasma concentration had decreased to mean concentrations of 0.07 and 0.1 ng/mL in Study #1 and #2, respectively (Figure 4). In addition, only 26% of subjects still had quantifiable low levels of ivermectin 4 wk after the last application, ranging from 0.05-0.89 ng/mL.

Overall, ivermectin 1% cream was safe and well tolerated after repeated topical treatment in both healthy volunteers and PPR subjects after 4 wk or 1 year treatment periods. With regards to ivermectin

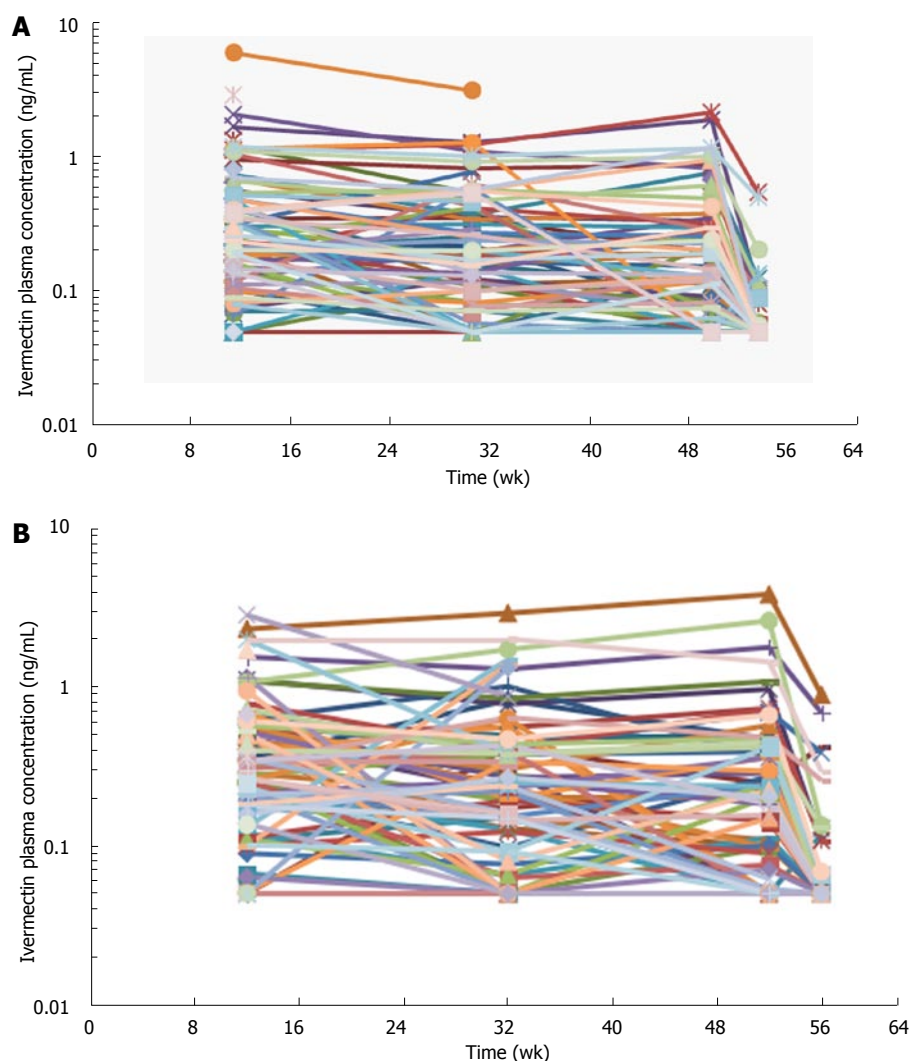


Figure 4 Individual ivermectin plasma profiles in a semi-logarithmic scale. (A: Study #1; B: Study #2) in subject with severe papulopustular rosacea.

Table 4 Ivermectin plasma concentrations (ng/mL) obtained after repeated topical applications of ivermectin 1% cream QD in subjects with papulopustular rosacea (maximal use pharmacokinetic trial and phase 3 studies #1, #2)

Treatment duration	Maximal use PK study ¹	Study #1 ²	Study #2 ³
Week 2	1.3 ± 0.5 (0.6 to 2.3)	NA	NA
Week 4	1.4 ± 0.6 (0.5 to 3.0)	NA	NA
Week 12	NA	0.5 ± 0.7 (< 0.05 to 6.0)	0.4 ± 0.5 (< 0.05 to 2.8)
Week 32	NA	0.4 ± 0.4 (< 0.05 to 3.1)	0.4 ± 0.5 (< 0.05 to 2.9)
Week 52	NA	0.3 ± 0.4 (< 0.05 to 2.2)	0.4 ± 0.6 (< 0.05 to 3.80)

PK: Pharmacokinetic; NA: Not applicable; ¹N: 14 (week 2), *n* = 15 (week 4); ²N = 105 (week 12), *n* = 77 (week 32), *n* = 73 (week 52); ³N = 92 (week 12), *n* = 84 (week 32), *n* = 65 (week 52); Note: Data represent Mean ± SD, and minimum to maximum, as available. BLQ data were imputed to the LOQ of 0.05 ng/mL for the maximal use PK study C_{min} concentration is displayed. For Study #1 and #2 blood samples were taken approximately 12 h after drug application.

exposure, systemic levels were low and stable through the 1-year treatment duration without any further accumulation.

DISCUSSION

The pharmacokinetics investigation of ivermectin 1% cream was conducted on both healthy volunteers and subjects with moderate to severe rosacea (PPR). In addition, to assess ivermectin systemic levels under chronic use conditions, blood samples were collected during a treatment period up to 1 year. The PK studies conducted in healthy volunteers and PPR subjects showed that after the first topical administration ivermectin was not completely eliminated at the time of the second application (24 h after the first dose when considering a once daily dosage regimen). Subsequently, ivermectin plasma concentrations were higher during the second dosing interval. However, after repeated topical application, plasma concentrations of ivermectin increased progressively until reaching a plateau after 2 wk (*i.e.*, steady state conditions).

(Figures 1 and 2). After repeated topical applications of ivermectin 1% cream in healthy subjects, the PK behavior of ivermectin could be accurately predicted from single dose data, confirming that the PK profile of ivermectin was not affected by the repeated topical applications (time stationarity). Moreover, systemic exposure in healthy volunteers increased proportionally to the daily dose of ivermectin (dose proportionality) (Figure 1 and Table 2).

The PK study in PPR subjects was conducted under maximal use conditions to ensure the assessment of the maximal exposure. Then, the maximum body surface area involved in the pathology (whole face) and the maximum therapeutic dose (1 g) were used. In addition, subjects with PPR presented the upper level of severity (at least 25 lesions and IGA score of 4 in all subjects). Overall, ivermectin systemic exposure levels obtained in PPR subjects under maximized conditions were much lower than those observed after oral administration. The mean C_{max} in PPR subjects treated under maximal use conditions was 1.74 ± 0.77 ng/mL after 4 wk treatment, while the means C_{max} after 12 mg oral dose were from 23.5 to 50 ng/mL^[10]. Overall, these data evidenced the limited ivermectin transdermal absorption.

The repeated topical applications of ivermectin 1% cream in this study resulted in similar exposure after 2 or 4 wk of treatment ($AUC_{0-24\text{ h}}$ of 36 ± 16 ng \times h/mL at week 2 and $AUC_{0-24\text{ h}}$ of 35 ± 14 ng \times h/mL at week 4), confirming that steady state was reached by 2 wk as was observed in healthy volunteers. In addition, at steady state levels, 2 metabolites, 3'-O-demethyl ivermectin and 4a hydroxy ivermectin, were considered as "major" because their systemic exposures were greater than 10% of ivermectin systemic exposure (parent compound)^[18]. These 2 metabolites were previously characterized consecutive to oral administration of ivermectin^[15]. In addition, these 2 metabolites were present in the same ratios (metabolite/parent) after oral ivermectin administration (data not shown).

With regard to impact of disease severity on ivermectin systemic exposure, no trend of correlation was observed between the number of inflammatory lesions and systemic ivermectin levels. From the maximal use PK study, the patient presenting the highest level of severity (subject with 88 inflammatory lesions) had a lower systemic level of ivermectin (C_{max} of 1 ng/mL and an $AUC_{0-24\text{ h}}$ of 23 ng \times h/mL) than the most exposed subject who had 35 inflammatory lesions at baseline (C_{max} of 4 ng/mL and an $AUC_{0-24\text{ h}}$ of 75 ng \times h/mL). In addition, the time to reach the peak of exposure (T_{max}) and the time to reach the steady state conditions were similar between healthy volunteers and subjects with PPR. However, ivermectin systemic exposure levels in PPR subjects were slightly higher than those observed in healthy volunteers (1.6-fold higher). Nevertheless, considering the high variability and the limited number of subjects, no firm conclusions could be drawn on

the impact of rosacea skin on ivermectin transdermal penetration.

At the end of the 4 wk treatment period, ivermectin was slowly cleared from the plasma in both healthy subjects and subjects with severe PPR. Under maximal use conditions, the half-life ($t_{1/2}$) of ivermectin was approximately 6 d (range: 92-238 h), and the last quantifiable concentration was observed approximately 24 d after ivermectin application. This prolonged apparent half-life indicates that ivermectin was slowly cleared from plasma after the last treatment application. This terminal half-life is more prolonged than the one published for an oral administration of ivermectin oral tablets (15 to 20 h)^[9]. This increase in terminal half-life observed by topical route suggests that absorption is the limiting step for ivermectin elimination. The term flip flop is used to describe this phenomenon^[19]. Therefore, ivermectin elimination is limited by its slow absorption process through the skin (absorption dependent elimination): After the last application, ivermectin is slowly cleared from plasma, the low absorption phase becoming the limiting factor for its elimination. However, to confirm that no accumulation of ivermectin occurred in deeper body compartments and to confirm that steady state conditions are achieved, plasma samples were collected over longer treatment duration (up to 52 wk) in subjects with moderate to severe PPR. Overall, the ivermectin mean plasma concentrations measured at weeks 12, 32, and 52 were similar (Table 4 and Figure 4), supporting the assumption that steady state was achieved after 2 wk of treatment with no further accumulation.

Repeated topical application of ivermectin 1% cream resulted in lower systemic exposure levels in comparison to those observed after ivermectin oral administration, evidencing the limited ivermectin transdermal absorption. In addition, the steady state conditions were achieved by 2 wk of treatment and no accumulation occurred under chronic treatment as evidenced in long term use clinical studies for up to 1-year treatment. The pharmacokinetic behavior of ivermectin applied topically (prolonged plasma half-life) is consistent with a slow release of ivermectin from the skin rather than an accumulation in a deeper body compartment.

COMMENTS

Background

Pharmacokinetics investigations of topical drugs are of a high interest during drug development. The characterization of the transcutaneous penetration helps to assess the pathology effect of drug systemic exposure; and therefore, define accurately safety margins and the potential for drug-drug interactions.

Research frontiers

For a long time due to the limited sensitivity of analytical methods, the pharmacokinetics behaviors of dermatological drugs were not investigated thoroughly. Therefore, limited information on drug safety was available. However, recent technological innovations in the bioanalytical field now allow the accurate quantification of very low levels of circulating compounds. Then, pharmacokinetics of topical drugs and their metabolites became feasible.

Innovations and breakthroughs

This article describes the comprehensive assessment of the ivermectin's pharmacokinetics, a topical drug, recently approved for the treatment of papulopustular rosacea. This assessment includes metabolites investigation and the determination of the drug exposure in chronic use up to 1 year.

Applications

Pharmacokinetics results presented in this article will provide prescribers with valuable information about the systemic safety of this new treatment.

Terminology

Pharmacokinetics is the study of the drug absorption, distribution, metabolism and elimination. These information are useful to establish treatment conditions and bring important knowledge on the drug safety.

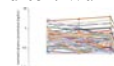
Peer-review

This is an interesting and well written article regarding the pharmacokinetics of 1% ivermectin cream.

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**DIAGNOSIS ADVANCES**

- 65 CD34+ dermal dendritic cells and mucin deposition in dermatomyositis
Yokoyama E, Nakamura Y, Okita T, Nagai N, Muto M

REVIEW

- 72 P2X7 receptor in skin biology and diseases
Geraghty NJ, Watson D, Adhikary SR, Sluyter R
- 84 Unraveling oral psoriasis and its relationship with geographic tongue: A literature review
Piccianni BLS, Teixeira-Souza T, Curty AA, Izahias LMS, Pessoa TM, Carneiro S, Gonzaga HFS, Dias EP
- 93 Review of narrowband ultraviolet B radiation in vitiligo
Attwa E

MINIREVIEWS

- 109 Pediatric ocular rosacea, a misdiagnosed disease with high morbidity: Proposed diagnostic criteria
Arriaga C, Domingues M, Castela G, Salgado M
- 115 Actinic keratosis and field cancerization
Emre S

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CD34+ dermal dendritic cells and mucin deposition in dermatomyositis

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Abstract

Dermal mucinosis is often associated with collagen diseases

such as rheumatoid arthritis, lupus erythematosus, and dermatomyositis, in addition to autoimmune thyroiditis. We report eight cases of dermal mucin deposition secondary to typical dermatomyositis with cutaneous lesions known as heliotrope rash and Gottron's papules. Striking mucin deposition was observed in both the papillary dermis and reticular dermis of all biopsy specimens. Immunohistochemical analysis showed that CD34+ dermal dendritic cells (DDCs) in the perilesional area in combination with vimentin+ cells within the mucinous lesion might be important in giving rise to abnormal deposition of dermal mucin. On the other hand, numbers of factor X IIIa+ DDCs and tryptase+ mast cells were reduced within and surrounding the mucin deposition, as compared with those in the dermis of normal controls. A pathogenic mechanism of dermal mucin deposition is proposed.

Key words: Mucin deposition; Dermatomyositis; CD34+ dermal dendritic cell

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Core tip: Immunohistochemical analysis of skin biopsy specimens with dermatomyositis showed the involvement of CD34+ dermal dendritic cells, α -smooth muscle actin+ myofibroblasts and possibly mast cells, as well as vimentin+ fibroblasts for abnormally dermal mucin production. Further pathophysiological studies are required to more precisely clarify secondary cutaneous mucin deposition by CD34+ dermal dendritic cells. CD34+ dermal dendritic cells and mast cells might be important in giving rise to deposition of dermal mucin in dermatomyositis.

Yokoyama E, Nakamura Y, Okita T, Nagai N, Muto M. CD34+ dermal dendritic cells and mucin deposition in dermatomyositis. *World J Dermatol* 2016; 5(2): 65-71 Available from: URL: <http://www.wjgnet.com/2218-6190/full/v5/i2/65.htm> DOI: <http://dx.doi.org/10.5314/wjd.v5.i2.65>

INTRODUCTION

Dermal mucin deposition has been seen in several skin diseases, including granuloma annulare, autoimmune thyroiditis, and collagen diseases (dermatomyositis, scleroderma, and lupus erythematosus). These observations led us to imagine dermal mucinosis as a heterogeneous group of pathologies showing a common factor of dermal mucin deposition.

We have previously reported a rare case of self-healing papular mucinosis (SHPM) in a patient with rheumatoid arthritis^[1]. We suggested that CD34+ or Factor X III a+ (FX III a+) dermal dendritic cells (DDCs) and tryptase+ mast cells (MCs) in the perilesional area in combination with vimentin+ cells in the mucinous lesion might have been involved in the dermal deposition of mucin. DDCs and MCs would then presumably play a key role in the development of mucinosis.

The present study tentatively defined DDCs as all the cells in connective tissue morphologically showing a dendritic shape. These fibroblast-like cells in the connective tissue have been classified into the following groups^[2-8]: (1) true fibroblasts; (2) myofibroblasts; (3) CD34+ DDCs; (4) FX III a+ DDCs; and (5) others. Fibroblasts are regarded as those cells positive only for vimentin, and myofibroblasts as those positive for both vimentin and α -smooth muscle actin (α -SMA)^[2,8]. DDCs are divided into CD34+ and FX III a+ DDCs^[2-7]. Other fibroblast-like cells (*i.e.*, not categories 1-4) are not specified further, and are collected as other fibroblast-like cells.

The aim of the present study was to elucidate the involvement of DDCs and MCs in the dermal mucin deposition seen in dermatomyositis.

DIAGNOSIS

Participants comprised 8 patients who had been clinicopathologically diagnosed with dermatomyositis. This study followed eight cases of dermatomyositis showing clear mucin deposition in biopsied skin tissues taken at the time of the first medical examination. Fifteen volunteers who underwent removal of nevus cell nevi (including normal skin) were used as site-matched controls. Mean (\pm standard deviation) ages in the patient and control groups were 53 ± 26 years (range, 34-86 years) and 22 ± 20 years (range, 12-64 years), respectively. Male-to-female ratios were 3:5 in the patient group and 6:9 in controls.

Skin biopsy specimens from the 8 patients with dermatomyositis were obtained from the thigh in 3 cases, from the chest in 3 cases, and from the dorsum of the hand in 2 cases. Normal skin consisting of the remaining unaffected portion of surgically removed nevus cell nevus was derived from various corresponding control sites. Informed consent was obtained from all subjects prior to participation in the present study.

RESEARCH

Archival paraffin embedded tissues from dermato-

Table 1 Antibodies used in immunohistochemical analysis

Antibody	Type	Source	Dilution
Vimentin	Mouse	Dako	1:40
CD34	Mouse	Nichirei	1:1
Factor XIIIa	Rabbit	Biogenesis	1:50
α -smooth muscle actin	Mouse	Dako	1:50
Desmin	Mouse	Dako	1:1
Tryptase	Mouse	Dako	1:50

myositis and normal skin were utilized for this study. In each case, formalin-fixed, paraffin-embedded, 4- μ m-thick sections were stained by the periodic acid-Schiff (PAS) technique, with Alcian blue (pH 2.5). Fibroblast-like cells were immunohistochemically recognized using antibodies for vimentin, CD34, FX III a, α -SMA, and desmin. MCs were identified by immunohistochemical staining for tryptase.

Sections from all cases were stained with an avidin-biotin peroxidase technique, using an ENVISION kit (Dako, Carpinteria, CA). Antibodies used in the present study are shown in Table 1. Cells were stained with mouse monoclonal and rabbit polyclonal antibodies. Sections were deparaffinized in xylene and rehydrated in a graded alcohol series. Endogenous peroxidase activity was removed by immersion in methanol with 3% hydrogen peroxide for 10 min. Non-specific binding was blocked by incubation for 5 min at room temperature with non-immune goat serum. Primary antibodies were then applied to sections and incubated for 45 min at room temperature. Secondary rabbit anti-mouse immunoglobulin (Ig) was applied for 45 min at room temperature. Finally, specimens were developed with 3,3'-diamino benzidine solution and 1% hydrogen peroxide, then counterstained with Mayer's hematoxylin.

DDC and MC counts were assessed as the number of positive cells per 10 high-power fields ($\times 400$) on each skin specimen by a single observer. Statistical significance was analyzed using Student's *t*-test. Student's *t*-test was applied for comparisons of mean numbers of positive cells between dermatomyositis and normal skin samples. Values of $P < 0.05$ were considered significant.

RESULTS

The profiles of eight patients with dermatomyositis are shown in Table 2. No patients had yet received any treatments (including steroids) for dermatomyositis at the time of biopsy. The interval between observation of the first skin symptom to first medical examination ranged from 1 to 6 mo (1 mo, $n = 2$; 5 mo, $n = 2$; 6 mo, $n = 1$; 3 mo, $n = 1$; 2 mo, $n = 1$; unknown, $n = 1$). Three cases (cases 2, 3 and 6) had muscle weakness, two cases (cases 3 and 7) had arthralgia, and one case (case 1) developed respiratory failure. Only one case (case 8) showed lung cancer; this patient died after 1 year. None of the other seven patients had internal malignancy.

Table 2 Profiles of eight patients with dermatomyositis

No	Age	Sex/period	Clinical findings	Sight of skin biopsy	Pathological findings
1	86	Male One month	Rash erythema of whole body respiratory failure	Right thigh	Vacuolar change, mucin in papillary and reticular dermis
2	59	Female One month	Lilac rash of eyelids, erythema rash of limbs, dorsal hands of Gottron's papules arthralgia	Right thigh	Vacuolar change, subepidermal blister, mucine in papillary dermis
3	53	Female Two months	Dorsal hands of Gottron's papules, scary erythema of face, chest, limbs, arthralgia, muscle weakness	Light thigh	Vacuolar change, periadnexal infiltration mucin in papillary and reticular dermis
4	63	Female Five months	Lilac rash of eyelids, dorsal hands of Gottron's papules, scary erythema of face, neck, chest	Chest	Vacuolar change, periadnexal infiltration mucin in papillary and reticular dermis
5	46	Male Unidentified	Dale reddish erythema of face, edematous erythema of neck	Limbs	Vacuolar change, melanine incontinen mucin in papillary and reticular dermis
6	34	Female Five months	Dorsal hands of Gottron's papules rash erythema of eyelid, nasal grooves muscle weakness	Chest	Hyperkeratosis, vacuolar change, mucin in papillary dermis
7	46	Female Three months	Dorsal hands of Gottron's papules, scary erythema of knee and hip, arthralgia	Light dorsal hand	Hyperkeratosis, vacuolar change, mucin in papillary and reticular dermis
8	57	Male ¹ Six months	Edematous erythema of face, neck, chest and shoulder	Chest	Vacuolar change, mucin in papillary and reticular dermis

¹Only the 57-year-old male (case 8) was found lung cancer, the other seven patients had no internal malignancy.

Table 3 Number of positive cells in normal skin and dermatomyositis

	Normal skin (<i>n</i> = 15) mean \pm SE cells/high-power field (\times 400)	Dermatomyositis (<i>n</i> = 8) mean \pm SE cells/high-power field (\times 400)	<i>P</i> value
Mast cells tryptase	12.320 \pm 0.997	5.788 \pm 0.805	0.000270
Dendritic cells			
Vimentin	9.654 \pm 1.374	16.0125 \pm 3.257	0.0524
CD34	10.933 \pm 1.131	14.937 \pm 3.257	0.177
Factor XIIIa	8.708 \pm 2.172	4.40 \pm 1.619	0.166
α -SMA	0	0.488 \pm 0.447	0.141
Desmin	0	0	

In terms of histopathology, mucin deposition was in the papillary dermis in two cases, and in the papillary and reticular dermis in six cases. All cases showed vacuolar change and one had subepidermal blistering (case 2). Two cases (cases 3 and 4) had periadnexal infiltration.

Our findings are shown in Figures 1 and 2 and Table 3. PAS-negative and Alcian blue-positive mucin deposition was identified in all 8 skin samples from dermatomyositis patients. Histologically, mucin deposition demonstrable with Alcian blue staining was distributed diffusely but not focally in the papillary dermis, and to a lesser extent between collagen bundles of the reticular dermis with or without sparse lymphocytic infiltrates. Vimentin+ fibroblasts (16.01 \pm 3.23 in dermatomyositis vs 9.65 \pm 1.37 in controls; *P* = 0.052), CD34+ DDCs (14.94 \pm 3.35 in dermatomyositis vs 10.93 \pm 1.13 in controls; *P* = 0.18), and α -SMA+ myofibroblasts (0.48 \pm 0.45 in dermatomyositis vs 0 in controls; *P* = 0.14) tended to be moderately increased in numbers, whereas numbers of FX IIIa+ DDCs were decreased in dermatomyositis skin, compared to normal skin (4.40 \pm 1.62 in dermatomyositis vs 8.71 \pm 2.17 in control; *P* = 0.17), although no significant differences were evident between diseased and control groups. In contrast, significant differences between the two groups were only

seen for numbers of tryptase-positive MCs (5.79 \pm 0.81 in dermatomyositis vs 12.32 \pm 1.00 in controls; *P* = 0.00027). MCs were diffusely scattered without forming cell clusters. DDCs and MCs were counted separately in areas of periadnexal matrix and interstitial portions of the dermis. However, no significant differences were seen between groups. Furthermore, histopathological examination revealed no increase in vascularization within the dermis among the 8 patients with dermatomyositis. We examined the tryptase(+) MC count according to progress before performing a biopsy after the onset of exanthema (Figure 3). For 3 mo, a tendency to increase was seen, followed by a gradual decrease, and, for 1 mo, it is with a low value most in 6 mo. Unfortunately, the extremely limited number of cases adversely impacted the statistical power of our comparisons.

DISCUSSION

The present immunohistochemical analysis of dermatomyositis showed a moderate increase in CD34+ DDCs and vimentin+ cells lacking CD34 or FX IIIa related to mucin deposition in the dermis. We have previously reported a rare case of self-healing papular mucinosis (SHPM) in a patient with rheumatoid arthritis^[1]. In that lesion, well-circumscribed mucin deposition was

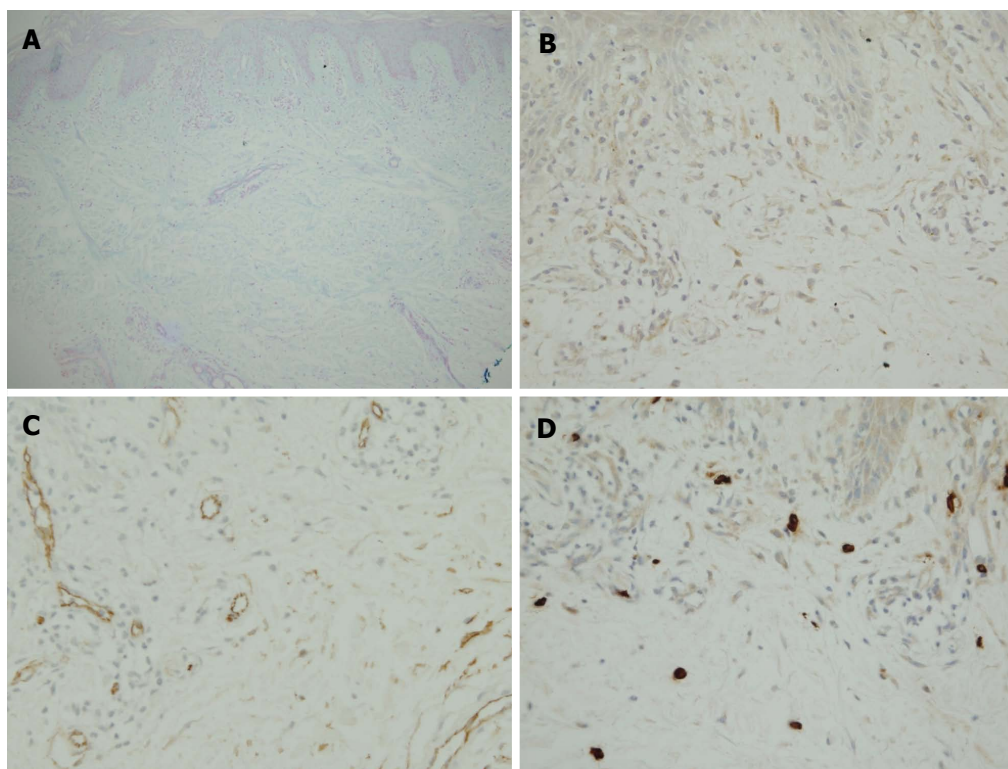


Figure 1 Representative histological findings in active skin lesions of dermatomyositis. A: Alcian blue (pH 2.5); B: Vimentin; C: CD34; D: Tryptase for mast cell staining.

demonstrated in the papillary dermis with Alcian blue staining. The overlying epidermis showed the formation of an epidermal collarette. On the other hand, in the case of dermatomyositis, diffuse mucin deposition was demonstrated with Alcian blue staining in the papillary dermis and between collagen bundles of the reticular dermis with or without sparse lymphocytic inflammatory infiltrates. Mucin deposition was particularly prominent in the papillary dermis. At the time of clinical diagnosis of dermatomyositis and immunohistochemical study, seven of the patients with dermatomyositis had no internal malignancies such as gastric or breast cancer, while one 57-year-old male patient showed lung cancer. There was also no evidence to support thyroid abnormalities among any of the eight patients.

Interstitial mucin deposition is a well-known occurrence in dermatomyositis^[9]. However, the pathogenic mechanisms responsible for dermal mucin deposition remain unclear (Figure 4). Mucin is normally produced in small amounts by dermal fibroblasts, and chemically consists of acidic glycosaminoglycans. Rapoport *et al.*^[10] hypothesized that the overproduction of mucin results from autoantibodies against thyroid-stimulating hormone receptor stimulating dermal fibroblasts to produce deposition of mucin, mainly as hyaluronic acid. However, our cases showed no evidence of thyroid dysfunction. Another hypothesis is that interleukin (IL) 1 β can induce glycosaminoglycan synthesis by fibroblasts *via* the prostaglandin E2 pathway through cyclooxygenase-2, an enzyme responsible for prostaglandin E2 synthesis^[11].

IL1 β can be produced by many cells, including fibroblasts, myofibroblasts, and MCs^[12]. In our study, a small number of α -SMA+ DDCs were observed in dermatomyositis, whereas none were present among normal controls. The possibility that α -SMA+ myofibroblasts could produce mucin thus remains plausible. A third hypothesis is that Tominaga *et al.*^[13] observed an increased hyaluronan content in lesional skin compared to non-lesional skin in a patient with reticular erythematous mucinosis and proposed that the cells responsible for the deposition of hyaluronan in lesional skin were FX III a+/hyaluronan synthase 2+ DDCs rather than dermal fibroblasts. However, we found no evidence for an increase in FX III a + DDCs in the patient group with dermatomyositis (Figure 2).

Finally, Pugashetti *et al.*^[14] noted that local tissue hypoxia in response to chronic venous insufficiency could potentially increase the biosynthetic activity of fibroblasts and thus dermal mucin deposition. Our data offered no clinicopathological evidence for venous insufficiency. Since the numbers of vimentin+ spindle-shaped cells were increased in our cases, mesenchymally derived vimentin+/CD34- fibroblasts, histologically indistinguishable from CD34+ and FX III a+ DDCs, appeared likely to represent the source of mucin deposition.

What are the CD34+ cells? In the present study, numbers of CD34+ DDCs tended to be increased, although no significant difference was evident between the patient and normal control groups at the 5% level.

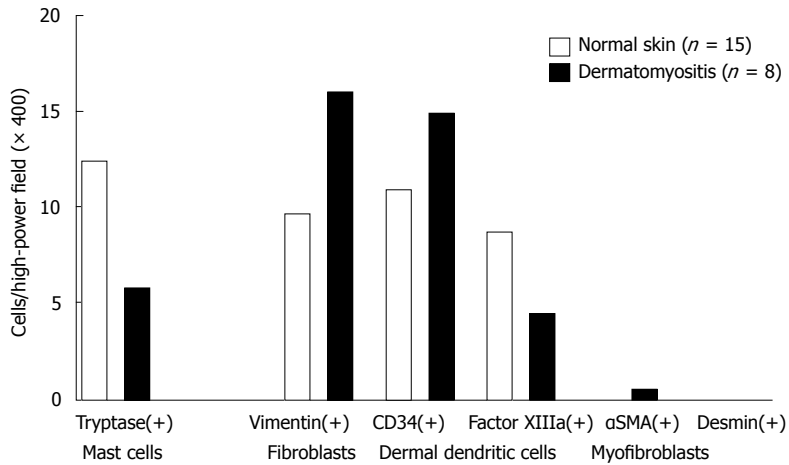


Figure 2 Number of positive cells in active skin lesions of patients with dermatomyositis. Vimentin+ fibroblasts, CD34+ DDCs and αSMA+ myofibroblasts are increased, but factor XIIIa+ DDCs are decreased in diseased skin compared to normal skin. A significant difference is evident for tryptase-positive mast cells between the diseased and control groups ($P < 0.0003$). DDCs: Dermal dendritic cells; α-SMA: α-smooth muscle actin.

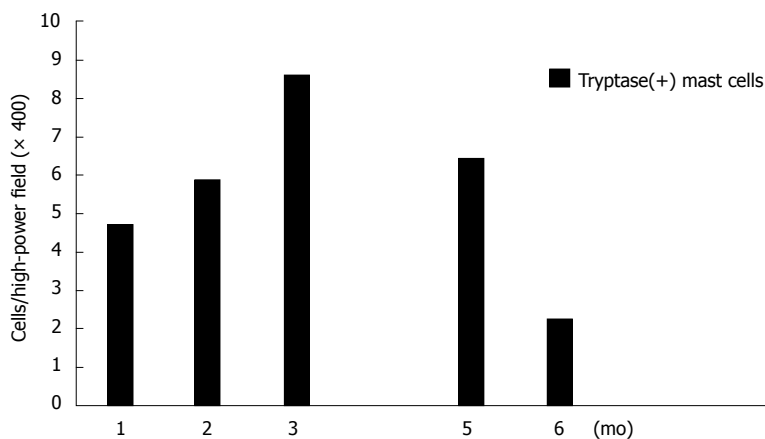


Figure 3 Progress at monthly intervals and mast cell count after occurrence of exanthema.

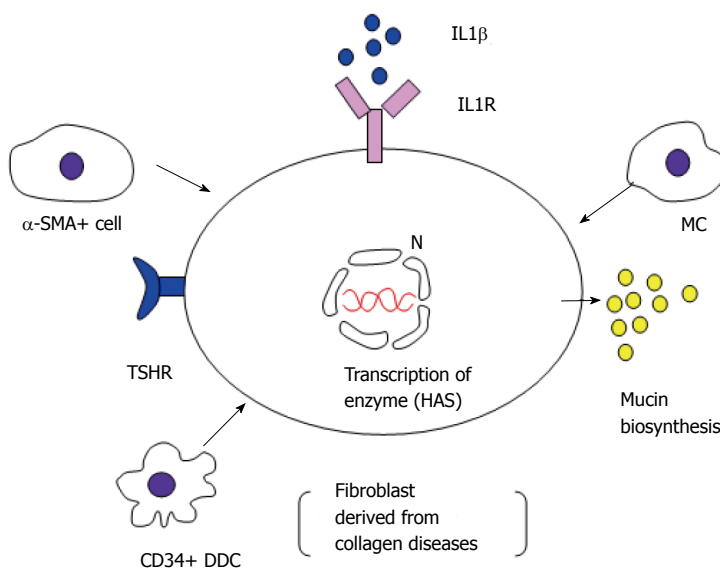


Figure 4 Proposed pathogenic mechanism underlying dermal mucin deposition in dermatomyositis. α-SMA: α-smooth muscle actin; N: Nucleus; TSHR: Thyroid-stimulating hormone receptor; HAS: Hyaluronan synthase.

Immunohistochemically, CD34 is a human progenitor cell antigen expressed not only on vascular endothelial cells but also on a population of dendritic fusiform cells around cutaneous appendages and in the interstitium, principally in the deep dermis^[2,6]. In contrast, FX III a immunoreactivity is noted on populations of dendritic cells in the upper portion of the dermis and around blood vessels and cutaneous appendages. Taken together with our data regarding collagen disease involving

dermatomyositis and rheumatoid arthritis^[1], CD34+ DDCs seem to play important supportive functions in the production of mucin within diseased skin.

Much remains to be learned about CD34-expressing cells in the skin regarding the functional relationships of dermal mucin production between CD34+ DDCs and other cells (FX III a+ DDCs, α-SMA+ myofibroblasts, vimentin+ fibroblasts, and tryptase+ MCs). Although we did not identify the DDCs in dermatomyositis more

precisely, use of specific antibodies for DDCs such as blood dendritic cell antigens [BDCA-1 for myeloid DCs, BDCA-2 for plasmacytoid DCs (PDCs)] might be valuable for subtyping DDCs, as Shrestha *et al.*^[15] recently reported. Using juvenile patients with dermatomyositis, they suggested that increased numbers of mature PDCs with CD34 markers as well as MCs are the major producers of interferon (IFN) α , in which IFN α itself can conversely modulate DCs subsets. The major infiltrating DDCs around mucin-deposited skin lesions in dermatomyositis might plausibly represent PDCs, subsequently influencing the subsequent effector functions of T cells.

MCs positive for tryptase were frequently seen in the perilesional area of predominantly the papillary dermis, although a significant reduction in total numbers of tryptase+ MCs were seen compared to numbers in normal controls. With respect to quantification of MCs, our data did not show any significant increase in the number of MCs at sites of dermatomyositis, as compared with the skin of controls. However, the present study also found greater numbers of MCs in the papillary dermis than in the reticular dermis for both control subjects and patients with dermatomyositis having mucin deposition. Abd El-Aal *et al.*^[16] reported that increased numbers of MCs could stimulate dermal fibroblasts to produce mucin in lichen myxedema. Martins *et al.*^[17] speculated mucin production from fibroblasts derived from patients with cutaneous mucinosis through the interaction of elevated serum levels of IgE between MCs bearing Fc ϵ RI α . We cannot discard this possibility, because we did not examine serum IgE levels for our 8 patients with dermatomyositis.

According to Smith *et al.*^[18], colloidal iron stain-positive mucin is present in 97% of skin biopsy samples from dermatomyositis cases and is a characteristic finding on views of dermatomyositis examining the pathological organization, but is not seen in all cases. Mucin deposition can represent an important sign of dermatomyositis, and its association with convalescence is unknown. This study examined the presence of MCs and DDCs in clear cases of mucin deposition with dermatomyositis.

The dermatomyositis and normal skin groups in this study showed similar results, with only MCs counts showing a significant difference. MCs tended to be decreased in our 8 dermatomyositis cases, who had not received treatment as of the time of biopsy. MCs may thus decrease at some stage during the progress of dermatomyositis. We showed this in the tryptase(+)MC count according to progress before performing biopsy after exanthem appeared. A tendency toward an increase was seen for three months after presentation, followed by a decrease.

CONCLUSION

Immunohistochemical analysis of skin biopsy specimens with dermatomyositis showed the involvement of CD34+ DDCs, α -SMA+ myofibroblasts and possibly

MCs, as well as vimentin+ fibroblasts for abnormally dermal mucin production. Further pathophysiological studies are required to more precisely clarify secondary cutaneous mucin deposition by CD34+ DDCs.

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P2X7 receptor in skin biology and diseases

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Abstract

The P2X7 receptor is a trimeric ligand-gated cation channel present on immune and other cells. Activation of this receptor by its natural ligand extracellular adenosine triphosphate results in a variety of downstream responses, including the release of pro-inflammatory mediators

and cell death. In normal skin, P2X7 is present on keratinocytes, Langerhans cells and fibroblasts, while the presence of this receptor on other cutaneous cells is mainly inferred from studies of equivalent cell types present in other tissues. Mast cells in normal skin however express negligible amounts of P2X7, which can be upregulated in cutaneous disease. This review discusses the potential significance of P2X7 in skin biology, and the role of this receptor in inflammatory skin disorders such as irritant and chronic dermatitis, psoriasis, graft-versus-host disease, as well as in wound healing, transplantation and skin cancer.

Key words: P2X7 receptor; Purinergic receptor; Extracellular adenosine triphosphate; CD39; Skin biology; Skin immune system

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Core tip: The P2X7 receptor is present on immune, stromal and epithelial cells. Activation of this receptor by its natural ligand, extracellular adenosine triphosphate, causes a variety of downstream effects including release of inflammatory mediators and growth factors, as well as cell death. P2X7 has various functions on skin cells, and studies of mouse models of disease and of human cells and tissues highlight emerging roles for this receptor in common skin disorders.

Geraghty NJ, Watson D, Adhikary SR, Sluyter R. P2X7 receptor in skin biology and diseases. *World J Dermatol* 2016; 5(2): 72-83 Available from: URL: <http://www.wjgnet.com/2218-6190/full/v5/i2/72.htm> DOI: <http://dx.doi.org/10.5314/wjd.v5.i2.72>

INTRODUCTION

Overview

The skin fulfils important roles such as barrier protection, thermoregulation, sensation, vitamin D synthesis^[1] and immunological protection^[2]. Extracellular nucleotides

Table 1 Events downstream of P2X7 receptor activation

RONS formation
Shedding of CD23, CD27, CD62L and E-cadherin
Up-regulation of CD80 and CD86 expression
PGE-2 synthesis and release
IL-1 β and IL-18 maturation and release
IL-6 release
IL-2 and IL-17 synthesis and release
VEGF release
Killing of intracellular pathogens
Cell death

IL: Interleukin; PGE-2: Prostaglandin E2; RONS: Reactive oxygen and nitrogen species; VEGF: Vascular endothelial growth factor.

and nucleosides function through a signalling network comprising cell-surface purinergic (P2X, P2Y and adenosine) receptors and ecto-nucleotidases^[3]. This network plays important roles in both physiology and pathophysiology, and as such is an emerging therapeutic target to combat many diseases^[3]. Evidence indicates that the extracellular nucleotide adenosine triphosphate (ATP) and cell surface purinergic receptors and ecto-nucleotidases play important roles in skin biology^[4,5]. Within this context the P2X7 receptor has a major role. This review aims to describe the cellular distribution of P2X7 in skin, and the potential significance of this receptor in skin biology and diseases.

Purinergic signalling

Purinergic signalling comprises a complex network of cell-surface receptors, where activation is mediated by extracellular signalling molecules such as ATP, which can act as a danger associated molecular pattern (DAMP) when released into the extracellular milieu after cell stress, damage or death^[6]. Extracellular ATP or other nucleotides can subsequently lead to activation of two purinergic P2 receptor subtypes; P2X and P2Y receptors. P2X receptors are a family of seven trimeric ATP-gated cation channels (P2X1-7); while P2Y receptors are a group of eight G protein-coupled receptors (P2Y1, 2, 4, 6, 11-14). P2 receptors are expressed on numerous cell subtypes, and activation of these receptors by extracellular ATP, or other nucleotides for some receptor subtypes, are important in inflammation and immunity^[7]. Activation of P2 receptors by ATP is regulated by the ecto-nucleotidases CD39 and CD73. CD39 degrades ATP into adenosine diphosphate (ADP) and subsequently adenosine monophosphate (AMP) before AMP is converted to adenosine by CD73^[8]. Adenosine can then activate P1 receptors; a family of purinergic receptors selective for adenosine^[3].

The P2X7 receptor

The P2X7 receptor belongs to the family of P2X receptors, which as noted above, are trimeric ATP-gated cation channels. Each P2X7 subunit is composed of intracellular amino and carboxyl termini, as well as two trans-membrane domains connected by a long glycosylated

extracellular loop, containing the ATP-binding site^[9]. Activation of the P2X7 receptor by extracellular ATP results in K⁺ efflux, and Na⁺ and Ca²⁺ influx, as well as the flux of organic cations and anions including dyes^[10]. P2X7 is present on leukocytes, but is also found on other cell types including epithelial cells and fibroblasts^[7]. P2X7 activation results in the stimulation of numerous pathways including the release of various pro-inflammatory mediators, modulation of various cell-surface receptors, formation of reactive oxygen and nitrogen species, killing of intracellular pathogens and cell death^[11] (Table 1). As a result of various studies in humans and animals, P2X7 is emerging as an important molecule in various biological processes^[12] and is attracting considerable interest as a therapeutic target in a wide-range of diseases^[13]. Due to this, and the increasing knowledge about the expression and function of P2X7 within the skin (Figure 1), there is a growing interest in the role of P2X7 in skin biology and related disorders.

P2X7 IN SKIN BIOLOGY

Keratinocytes

Keratinocytes comprise the majority of cells within the epidermis to provide a physical and immunological barrier^[14]. It is well established that human and rodent keratinocytes express P2X7. Immunohistochemistry reveals that P2X7 is expressed in the upper layer of human and rat skin^[15,16] suggesting that this receptor may be involved in the death of terminally differentiated keratinocytes. Consistent with this concept, human keratinocyte P2X7 co-localises with markers of apoptosis^[16], while P2X7 activation induces human keratinocyte death *in vitro*^[17] and increases murine keratinocyte death *in vivo*^[18]. P2X7 has been reported to be present on human HaCaT keratinocytes^[19] and can mediate ATP-induced death of these cells^[20], although the presence of P2X7 in these cells has not been confirmed in all studies^[21]. Nevertheless over-expression of protein kinase C alpha (PKC α) can result in increased expression of P2X7 in these cells^[19] indicating that this kinase may be involved in the up-regulation of keratinocyte P2X7 in the upper layers of the epidermis. Despite the apparent localisation of keratinocyte P2X7 to the upper layers of the epidermis, functional studies (using ATP-induced dye uptake measurements) show that the majority of human and murine keratinocytes express P2X7^[22,23]. Thus, these immunohistochemistry and functional studies combined suggest P2X7 may be present in all layers of the epidermis, with receptor expression increasing with keratinocyte differentiation and its upregulation resulting in the death of terminally differentiated keratinocytes.

In addition to cell death, P2X7 activation can induce interleukin (IL)-6 release from human keratinocytes^[24], and can mediate ultraviolet radiation-induced IL-1 β release from both human and murine keratinocytes^[25,26]. P2X7 activation on HaCaT keratinocytes has also been implicated in the activation of disintegrin-like metalloprotease-mediated shedding of E-cadherin and transforming growth factor alpha (TGF- α) induced by the major bee venom

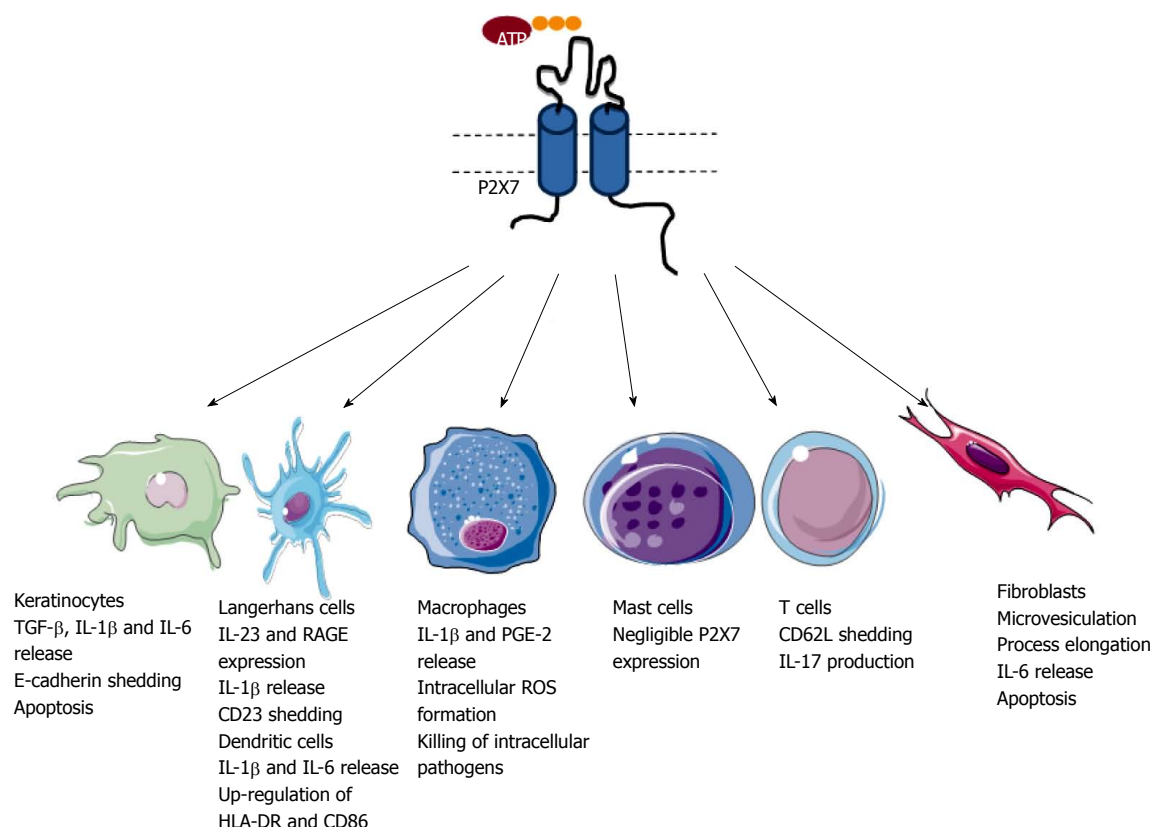


Figure 1 Expression and function of the P2X7 receptor on skin cells. P2X7 is present on keratinocytes, Langerhans cells, dermal dendritic cells, dermal macrophages, skin T lymphocytes and dermal fibroblasts. P2X7 activation on these cells induces a number of downstream events as indicated. P2X7 is absent on mast cells in normal skin, but can be upregulated during cutaneous disease. P2X7 may also be present on skin B cells, neutrophils, eosinophils and basophils (not shown), but direct evidence is lacking. Cell images were obtained from Servier Medical Art (www.servier.com). ATP: Adenosine triphosphate; HLA: Human leukocyte antigen; IL: Interleukin; PGE2: Prostaglandin E2; RAGE: Receptor for advanced glycation end products; ROS: Reactive oxygen species; TGF: Transforming growth factor.

component melittin^[27]. Collectively, these results indicate that P2X7 on keratinocytes may also be important in inflammatory and immune functions of these cells.

Langerhans cells

Langerhans cells (LCs) are professional antigen-presenting cells located in the epidermis, and are important in the establishment of adaptive immunity and the maintenance of peripheral tolerance^[28]. P2X7 is present on both human and murine LCs from skin^[22,23,29], as well as on migratory LCs [langerin⁺ dendritic cells (DCs)] from human skin explants^[30]. Although functional studies of P2X7 on LCs are largely limited to ATP-induced dye uptake measurements^[22,23,29], P2X7 activation of migratory LCs causes increased cell-surface expression of the IL-23 receptor and the alarmin receptor for advanced glycation end products (RAGE)^[30]. Further, P2X7 is present on human LCs derived from monocytes *in vitro* and activation of this receptor results in the rapid shedding of CD23 (the low affinity IgE receptor) from these cells^[22]. Finally, P2X7 is present on the murine LC-like line, XS106, and activation of this receptor results in the release of IL-1 β from these cells^[31]. Collectively, these studies support a role for P2X7 activation on LCs in promoting inflammation and immunity.

The relative amount of P2X7 activity on LCs appears

to be negatively modulated by the ecto-nucleotidase CD39 (Figure 2). It has long been known that LCs express high ecto-ATPase and ecto-ADPase activities^[32], which is almost completely due to CD39^[33]. Comparison of human monocyte-derived LCs and monocyte-derived DCs generated from the same subjects reveals that the relative P2X7 activity is lower on monocyte-derived LCs compared to monocyte-derived DCs despite similar amounts of cell-surface P2X7 expression^[22]. This difference in activity between these two cell types is inversely associated with cell-surface CD39 expression^[22]. These observations are consistent with the negative regulation of P2X7 activation by CD39 on murine peritoneal macrophages^[34] and murine bone marrow-derived mast cells^[35] (Figure 2). Notably, CD39 on LCs has been implicated in facilitating a protective or tolerogenic role for these cells in dermatitis^[33,36]. Collectively, variations in CD39 activity may play important roles in the regulation of P2X7 activation on LCs, and in determining the relative contribution of these cells in immunity or peripheral tolerance.

Dermal DCs

Dermal DCs are a heterogeneous population of professional antigen-presenting cells, and like LCs are important in the establishment of adaptive immunity and the maintenance of peripheral tolerance^[37]. It is well documented that

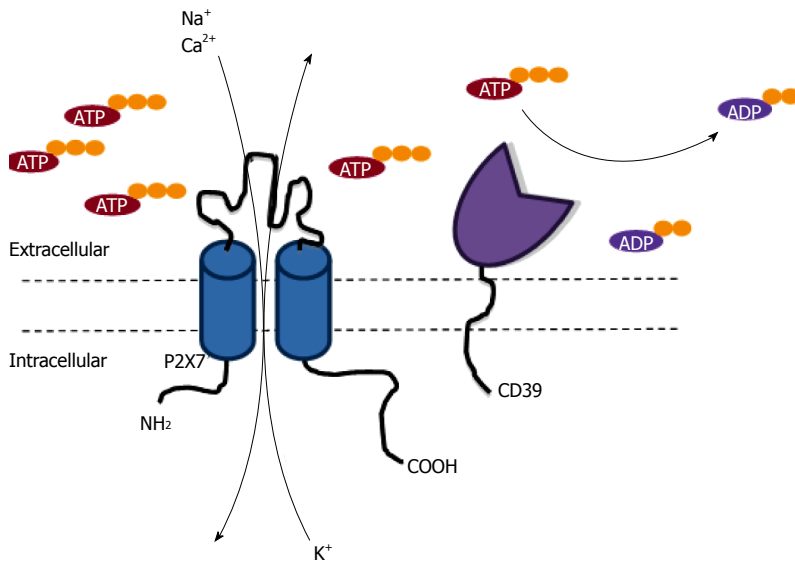


Figure 2 Activation of the P2X7 receptor and its regulation by CD39. Activation of P2X7 by extracellular ATP causes an influx of Ca^{2+} and Na^+ , and efflux of K^+ . Extracellular ATP can be degraded by cell surface CD39 to limit P2X7 activation on Langerhans cells, macrophages and mast cells. ATP: Adenosine triphosphate.

P2X7 is present on human and murine DCs derived from monocytes^[38-41] or within lymphoid tissues^[42,43], but direct evidence for P2X7 on dermal DCs is limited. P2X7 is present on foetal skin-derived DCs, where it may be involved in T cell stimulation^[44], however direct evidence for DC P2X7 in this process is not well established. Interpretation of these results is complicated by subsequent findings that extracellular ATP can induce human and murine T cell proliferation *via* P2X7 in an autocrine fashion^[45]. Thus, the role of P2X7 in T cell stimulation by dermal DCs remains to be elucidated.

P2X7 is also expressed on migratory DCs from human skin explants^[30]. Activation of P2X7 on skin migratory DCs resulted in the release of IL-1 β and IL-6, as well as the up-regulation of IL-23 and vascular endothelial growth factor (VEGF) mRNA and cell-surface expression of HLA-DR, and the co-stimulation molecule CD86^[30]. Finally, P2X7 activation on these cells promotes the development of T helper 17 (Th17) cell responses^[30].

Dermal macrophages

Dermal macrophages are a heterogeneous population of cells important in innate and adaptive immunity, as well as in tissue homeostasis and wound healing^[37]. Direct evidence for P2X7 on dermal macrophages is lacking, but it is well established that this receptor is present on human and murine macrophages derived from monocytes^[46-48] or isolated from tissues^[49,50]. P2X7 activation on human and murine macrophages results in the release of pro-inflammatory mediators such as IL-1 β and prostaglandin E_2 ^[51], as well as the production of reactive oxygen species^[52], and killing of intracellular mycobacteria^[53], chlamydia^[54] and toxoplasma^[55]. Of note, P2X7 activation eliminates *Leishmania amazonensis*, the causative agent of human cutaneous leishmaniasis^[56], within murine peritoneal macrophages^[57], supporting the potential importance of macrophage P2X7 in skin biology.

Mast cells

Mast cells are present in the dermis, and play important

roles during inflammation and immunity^[58]. In contrast to other tissues, mast cells in normal human and murine skin express negligible amounts of P2X7^[59,60], and ATP incubation of these cells fails to cause IL-1 β release despite inducing IL-1 β release from murine bone marrow-derived mast cells^[61]. This negligible P2X7 expression on skin mast cells is due to fibroblasts expressing the retinoic acid-degrading enzyme Cyp26b1^[61]. Although the exact mechanism by which these fibroblasts prevent P2X7 expression on skin mast cells is not known, exogenous retinoic acid upregulates P2X7 expression on bone marrow-derived mast cells^[61]. This suggests that Cyp26b1-expressing fibroblasts in mice regulate retinoic acid concentrations to suppress P2X7 expression on skin mast cells. Whether this same inhibitory mechanism operates for human skin mast cells or limits P2X7 expression on other dermal cell populations remains to be determined.

Granulocytes

Granulocytes (neutrophils, eosinophils and basophils) are circulating innate immune cells that infiltrate the skin to promote inflammation and immunity^[62]. Small numbers of neutrophils also circulate through normal skin, where they are presumed to function as sentinels^[63]. Direct evidence for P2X7 on granulocytes within the skin is lacking, but P2X7 is present on human blood eosinophils^[64,65] and murine bone marrow-derived basophils^[66]. P2X7 activation on human eosinophils results in cation fluxes, increased expression of the integrin CD11b and reactive oxygen species formation, as well as chemotaxis of these granulocytes^[64,65]. P2X7 activation is involved in the IgE-dependent activation of murine bone marrow-derived basophils^[66], which may have implications for cutaneous allergic inflammation. Collectively, these results suggest P2X7 may play important roles in the pro-inflammatory actions of these granulocytes.

In contrast to eosinophils and basophils, P2X7 appears to be absent on neutrophils. Repeated evidence demonstrates that P2X7 is not present in human blood

neutrophils^[67,68]. Neutrophil infiltration however is reduced by P2X7 deficiency in murine models of skin inflammation^[69] suggesting that P2X7 may be present on murine neutrophils or that P2X7 activation on other skin cells indirectly promotes neutrophil infiltration. Nonetheless future studies are required to determine if P2X7 is present on murine neutrophils or on neutrophils within skin.

T cells

Both human and murine skin contains populations of tissue-resident and recirculating T cells, which are key cellular mediators of adaptive immunity^[70]. Direct evidence for P2X7 on these skin T cells is lacking, however it is well known that human and murine T cell subsets from blood and lymphoid tissue express P2X7^[71]. P2X7 activation induces the rapid shedding of CD62L (L-selectin) from both human and murine CD4⁺ and CD8⁺ T cells^[72,73]. This cell adhesion molecule can regulate the migration of certain T cell subsets to sites of skin inflammation^[74]. Thus, the possibility remains that P2X7-induced CD62L shedding may regulate T cell migration within the skin. There is also evidence that P2X7 activation promotes Th17 cell development in humans^[75] and mice^[76]. Thus, a further possible role for P2X7 on skin T cells is in the generation of cutaneous Th17 responses.

Dendritic epidermal T cells (DETCs) are resident T cells found in the epidermis of mice, but not humans, and have important roles in inflammation, immunity and wound healing^[77]. Murine DETCs express low amounts of P2X7 mRNA^[26] but an earlier study, using an anti-P2X7 monoclonal antibody and ATP-induced dye uptake measurements, failed to observe P2X7 on DETCs, despite the presence of P2X7 on keratinocytes and LCs^[23]. Nevertheless ATP, released from keratinocytes, can enhance IL-17 release from CD3-activated DETCs^[26]. A direct role for P2X7 activation on DETCs in this process was not established, and these cells express high amounts of mRNA for P2X1, P2X2, P2X3 and P2X5^[26], thus it remains to be established if DETCs express functional P2X7. It also remains to be established if P2X7 is present on resident T cells in human skin, which are considered to be the equivalent cell type to murine DETCs^[77].

B cells

B cells are key cellular mediators of adaptive immunity, but their role in the skin immune system is poorly understood. Emerging evidence indicates the presence of B cells in normal skin, although it is unknown if they are skin-resident or circulating B cells^[78]. Further evidence indicates roles for B cells in cutaneous immunity and inflammation, and skin cancer^[78]. As for T cells, evidence for P2X7 on skin B cells is lacking, but P2X7 is present on human and murine B cells from blood and spleen^[79,80]. P2X7 activation results in the rapid shedding of CD62L from human B cells^[79] suggesting that this mechanism

may regulate B cell migration within the skin. P2X7 activation also results in the rapid shedding of CD23 from human and murine B cells^[80]. Although the functional significance of this process is yet to be established, soluble CD23 can regulate IgE production^[81]. Thus, P2X7-mediated release of soluble CD23 may regulate the development or severity of atopic dermatitis.

Fibroblasts

Fibroblasts are a heterogeneous population of cells located in the dermis with a variety of functions including tissue homeostasis, wound healing and inflammation^[82]. Human skin fibroblasts express P2X7^[83,84]. In addition to cation fluxes, dye uptake and membrane depolarisation, P2X7 activation in these cells results in microvesiculation, process elongation, IL-6 release and apoptosis^[84]. High concentrations of glucose potentiate these P2X7-mediated responses^[84]. This effect of glucose is attributed to a redistribution of P2X7 on the cell surface rather than increased expression of this receptor^[84]. Of note, skin fibroblasts from type 2 diabetic subjects demonstrate enhanced P2X7-mediated responses compared to skin fibroblasts from normal subjects^[85]. This enhanced P2X7 activity is suggested to be an important mechanism in the pathogenesis of vascular damage in diabetic subjects^[85], but this concept is yet to be developed. P2X7 may also be expressed on murine skin fibroblasts, but observations are limited to the subcutaneous fibroblast cell line L929^[86]. This study demonstrated that P2X7 activation mediates cation fluxes, membrane depolarisation and cytotoxicity in these cells.

P2X7 IN SKIN DISEASES

Allergic contact dermatitis

Allergic contact dermatitis (ACD) is a type IV delayed-type hypersensitivity (DTH) reaction characterised by a T cell-mediated response to allergens^[87]. A role for P2X7 in ACD in humans is supported by the up-regulation of this receptor in the epidermal basal layer of inflamed skin of atopic dermatitis patients compared to normal human skin^[88], while other experimental evidence supports a role for P2X7 in murine models of ACD. ACD is commonly studied using animal models of contact hypersensitivity (CHS)^[87]. Both pharmacological blockade and genetic deficiency of P2X7 impairs CHS responses in mice^[89]. This impaired CHS response is due to the absence of P2X7-mediated IL-1 β release from DCs abrogating the sensitising capacity of these cells^[89]. Intradermal injection of the hydrolysis-resistant nucleotide, adenosine gamma-thiotriphosphate (ATP γ S), can also enhance the CHS response in mice^[31] indirectly supporting a role for P2X7 in ACD. However, ATP γ S cannot activate murine P2X7 *in vitro*^[90] despite activating other mammalian P2X7^[90,91]. This raises the possibility that ATP γ S acts on other P2 receptors in this model of murine CHS^[31]. Notably, non-metal haptens can induce ATP release from primary human and HaCaT keratinocytes^[92] providing a possible

source for extracellular ATP in ACD.

Irritant contact dermatitis

Irritant contact dermatitis (ICD) is an inflammatory reaction to chemical irritants involving cells of the innate immune system^[93]. Experimental evidence in mice supports a role for P2X7 in ICD. Both pharmacological blockade and genetic deficiency of P2X7 impair oedema, IL-1 β production and neutrophil infiltration in croton oil-induced ICD^[69]. Furthermore, clodronate-depletion of DCs and macrophages, or pharmacological inhibition of caspase-1 reduced ICD in this model^[69] suggesting that P2X7 on DCs and macrophages may contribute to the pathogenesis of ICD through IL-1 β production. In addition to a role for P2X7 on DCs and macrophages in ICD, P2X7 on mast cells is involved in retinoid-induced ICD. This form of ICD is mediated by aberrant release of ATP within the skin and increased P2X7 expression on skin mast cells^[61]. A role for mast cell P2X7 in chemical-induced ICD remains to be determined.

Consistent with a role for P2X7 in ICD, chemical irritants can induce ATP release from murine and human keratinocytes^[33,94,95], and genetic deficiency of CD39 exacerbates croton oil-induced ICD in mice^[33,94]. Croton oil also decreases ATPDase activity in mice^[20] indicating that chemical irritants may further potentiate P2X7-mediated responses by causing a sustained increase in ATP concentrations during chemical irritant exposure. Of note, zinc deficiency, which is often associated with increased cutaneous inflammation, enhances ICD in mice and augments chemical irritant-induced ATP release from murine keratinocytes and in murine skin^[36]. Further, zinc deficiency in murine ICD is associated with loss of LCs^[36], which play a protective role in ICD through CD39 expression^[33]. This suggests that both increased ATP release from keratinocytes and impaired hydrolysis of ATP by LCs may contribute to the pathogenesis of ICD.

Psoriasis

Psoriasis is a chronic inflammatory disorder manifesting as plaque or pustular-like lesions of the skin. Psoriasis emerges due to excessive keratinocyte renewal, caused by an innate immune cell response and subsequent engagement of the adaptive immune response, resulting in a feed forward mechanism of inflammation^[96]. Although the role of P2X7 has not been investigated in animal models of psoriasis, *in vitro* studies support a role for P2X7 in psoriasis pathogenesis. Interferon gamma (IFN- γ), a pro-inflammatory cytokine implicated in psoriasis development^[96] can upregulate the expression of P2X7 in primary keratinocytes^[88]. Moreover, injection of the P2X7 agonist 2',3'-O-(4-benzoyl)benzoyl ATP (BzATP) into normal human skin explants induces increased expression of cytokines and other molecules commonly associated with psoriasis, including IL-1 β , IL-6 and TNF- α ^[30]. Importantly, these responses could be prevented through pharmacological blockade of P2X7^[30]. Of note, P2X7 expression in this model also caused the

functional maturation of cutaneous DCs and promoted the development of Th17 responses^[30], both of which are important contributors to psoriasis pathogenesis^[96].

Cutaneous graft-vs-host disease

Graft-vs-host disease (GVHD) is a common complication following bone marrow transplantation used to treat haematological malignancies^[97]. Two types of GVHD develop in patients; acute GVHD emerges early after transplantation, while chronic GVHD is a persistent long-lasting inflammation, with both forms causing inflammatory damage to the skin, as well as the gastrointestinal tract, liver and lungs^[97]. Pharmacological blockade and genetic deletion of P2X7 attenuates the development of disease in murine models of allogeneic GVHD^[98,99]. Additionally, experimental evidence establishes a model whereby ATP released at the site of tissue damage causes upregulation of the co-stimulatory molecules, CD80 and CD86 on DCs to promote T cell responses^[98]. P2X7 deficient mice receiving allogeneic bone marrow transplants demonstrated reduced serum concentrations of the pro-inflammatory cytokines IFN- γ , TNF- α , and IL-6^[98], which was replicated through blockade of the P2X7 receptor *in vivo* using the nucleoside reverse transcriptase inhibitor stavudine^[99]. Although the effect of P2X7 deficiency or blockade on acute skin GVHD was not directly reported in either study^[98,99], skin is a known target organ of GVHD in these models of allogeneic bone marrow transplantation^[100]. Of note, P2X7 blockade failed to prevent the development of chronic skin GVHD^[98], suggesting P2X7 may not play a role in skin inflammation in chronic GVHD, or longer periods of P2X7 blockade are required for prevention of chronic skin GVHD.

Wound healing

Wound healing is classically defined by the disruption of haemostasis, migration of platelets resulting in blood clotting, followed by inflammation, cell proliferation and tissue remodelling^[101]. Studies both *in vitro* and *ex vivo* have demonstrated a role for P2X7 in the process of wound healing. P2X7 is important for early cell migration and infiltration of immune cells required for wound healing, with P2X7 deficient cells showing a reduced migratory ability in an *in vitro* wound repair model suggesting that lack of P2X7 affects chemotaxis^[102]. P2X7 also promotes the release of VEGF from primary monocytes, important for control of angiogenesis and wound healing^[103]. Conversely, P2X7 is down-regulated on keratinocytes during wound healing^[104], suggesting that this reduced expression may be linked with reduced apoptosis of keratinocytes to promote healing of the epidermis. Mast cells also play an important role in wound remodelling and repair^[105], but express negligible P2X7 in normal skin^[59,60]. It remains to be determined if P2X7 on mast cells is upregulated during wound healing.

Skin transplantation

Transplantation is an important therapy for many end-stage diseases and rejection of transplants remains

Table 2 Roles of the P2X7 receptor in mouse models of skin disease

Disease	Observations
Allergic contact dermatitis	P2X7 blockade or deficiency impairs CHS ^[89]
Irritant contact dermatitis	P2X7 blockade or deficiency impairs croton oil-induced oedema, IL-1 β production and neutrophil infiltration ^[69]
Psoriasis	ND
Cutaneous graft- <i>vs</i> -host disease	P2X7 blockade or deficiency increases survival and reduces disease severity, serum concentrations of IFN- γ , TNF- α and IL-6 in allogeneic mouse models ^[98,99]
Wound healing	P2X7 deficient macrophages display reduced migration in an <i>in vitro</i> wound repair model ^[102]
Skin transplantation	P2X7 blockade or deficiency prevents allogeneic skin transplant rejection ^[109]
Melanoma	ATP injection impairs A375 melanoma cell growth in immuno-compromised mice ^[120] P2X7 blockade inhibits B16 melanoma cell growth in immuno-competent mice ^[121,122] P2X7 deficiency impairs B16 melanoma cell migration <i>in vitro</i> ^[102] P2X7 deficiency in host leads to increased B16 melanoma growth and metastasis ^[102]
Basal cell carcinoma	ND
Squamous cell carcinoma	P2X7 deficiency in host enhances chemical-induced carcinogenesis ^[18] BzATP injection led to tumour apoptosis ^[18]

ATP: Adenosine triphosphate; BzATP: 2',3'-O-(4-benzoyl) benzoyl ATP; CHS: Contact hypersensitivity; IFN: Interferon; IL: Interleukin; ND: Not determined; TNF: Tumour necrosis factor.

Table 3 Roles of the P2X7 receptor in human skin diseases

Disease	Observations
Allergic contact dermatitis	Increased P2X7 expression in atopic dermatitis lesions ^[88]
Irritant contact dermatitis	ND
Psoriasis	Increased P2X7 expression in psoriatic skin lesions ^[30,88]
Cutaneous graft- <i>vs</i> -host disease	ND
Wound healing	P2X7 activation promotes VEGF release from monocytes ^[103]
Skin transplantation	ND
Melanoma	P2X7 is present on melanoma cells ^[117,118] and cell lines ^[119] , with increased expression compared to normal melanocytes ^[119] P2X7 activation induces A375 melanoma ^[118] but suppresses HT168-M1 melanoma cell death ^[119]
Basal cell carcinoma	P2X7 is present in necrotic tumour centres and apoptotic tumour cells, and correlates inversely with tumour aggressiveness ^[123]
Squamous cell carcinoma	P2X7 is present in apoptotic tumour cells and its activation causes A431 SCC cell death ^[123]

ND: Not determined; SCC: Squamous cell carcinoma; VEGF: Vascular endothelial growth factor.

a major problem. Studies in transplantation have shown upregulation of P2X7 expression on infiltrating lymphocytes in transplanted hearts in human patients^[106]. Pharmacological blockade and genetic deletion of P2X7 in murine models leads to a delay in allograft rejection, which has been demonstrated in several transplant models including models of islet^[107], heart^[106] and lung^[108] transplantation. However, with the exception of one preliminary report^[109], there are limited studies investigating P2X7 in skin transplants. In this study^[109], ATP is released in allogeneic but not syngeneic skin grafts. This ATP release involved macrophages and the pannexin-1 hemichannel, and was impaired by pharmacological blockade or genetic deletion of P2X7. This inhibition or absence of P2X7 delayed allogeneic skin graft rejection. Collectively, these results support a role for P2X7 in ATP release and tissue rejection in allogeneic skin graft transplantation.

Skin cancer

Skin cancers are common cancers within humans and include three main forms: Basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and melanoma^[110].

Ultraviolet radiation is the major causative factor of these skin cancers^[110]. P2X7 is emerging as an important receptor in many forms of cancers, with various and contradictory roles attributed to this receptor in tumour biology^[111]. These include but are not limited to tumour cell proliferation^[112], death^[113], and invasiveness^[114], as well as anti-tumour immunity^[115] and cancer pain^[116].

The role of P2X7 in skin cancer has been studied most widely in melanoma. Immunohistochemistry reveals expression of P2X7 in human melanoma^[117,118] and in various melanoma cell lines^[119]. Further, this receptor is expressed at higher quantities in melanoma cells compared to normal melanocytes^[119]. Importantly, P2X7 in melanoma and melanoma cell lines is functional^[118,119]. Paradoxically, P2X7 activation promotes and suppresses ATP-induced apoptosis in human A375^[118] and HT168-M1 melanoma cells^[119], respectively. These differences remain to be reconciled, but opposing effects with P2X7 have also been observed in murine models of melanoma. ATP injection impairs the growth of A375 melanoma cells in (athymic) immuno-compromised mice^[120] supporting an anti-tumour effect for P2X7 presumably through ATP-induced cell death.

Conversely, injection of P2X7 antagonists inhibits the growth of murine B16 melanoma cells (which express P2X7^[121]) in immuno-competent mice^[121,122]. Additional data from these studies demonstrated that this pro-tumour effect of P2X7 was due to enhanced ATP-induced proliferation of B16 melanoma cells^[121,122]. P2X7 on immune cells also plays an important role in preventing melanoma progression by promoting anti-tumour immune responses. B16 melanoma growth and metastasis is increased in P2X7 deficient mice or wild-type chimeric mice transplanted with P2X7-deficient bone marrow compared to control mice^[102].

P2X7 may also play an important role in BCC and SCC. Immunohistochemistry of human samples reveals expression of P2X7 in the necrotic centre of BCCs and within apoptotic cells in both BCCs and SSCs, suggesting that P2X7 activation may mediate killing of malignant cells within these tumours^[123]. Evidence for this process in BCC is wanting, but P2X7 can mediate the killing of the human A431 SCC line^[123]. Another report however attributed this cytolytic effect to adenosine resulting from ATP hydrolysis rather than ATP directly^[124]. Thus, the role of P2X7 in this cell line remains uncertain. As noted above, P2X7 is also present on immortalised HaCaT keratinocytes^[19] and mediates ATP-induced death in these cells^[20]. Notably, ultraviolet B irradiation down-regulates P2X7 expression in HaCaT keratinocytes, potentially leading to survival of cells with a reduced ability for ATP-induced apoptosis, and allowing for malignant transformation and survival of malignant cells^[125]. Consistent with this concept, in BCC patients, more aggressive tumours have lower P2X7 expression, suggesting that loss of P2X7 can act as a marker for increased tumour aggressiveness^[123]. Finally, in a murine model of chemically-induced skin papilloma/SCC carcinogenesis, injection of BzATP reduces the frequency and size of papillomas and skin cancers, a response that is absent in P2X7 deficient mice, indicating a role for P2X7 in this process^[18]. P2X7 activation in these tumours is associated with apoptosis^[18]. Of note, P2X7 expression is reduced in papillomas and skin cancers compared to normal skin^[18], suggesting that down-regulation of P2X7 in skin tumours is a possible escape mechanism to avoid ATP-induced apoptosis.

Summary

In summary, P2X7 is present on immune, stromal, epithelial and malignant cells in diseased skin, and is up-regulated in some skin disorders. Activation of P2X7 cells and the resulting downstream effects are implicated in numerous skin diseases including allergic and irritant contact dermatitis, psoriasis, cutaneous GVHD, as well as in skin transplantation and skin cancer. In some instances the role of P2X7 in skin disease is supported by mouse models (Table 2) and human studies (Table 3), but for other skin diseases evidence is limited to only one species. Nevertheless, P2X7 represents a potential biomarker and target for treatment of various skin disorders, but further studies are required before the clinical value of P2X7 can be utilised.

CONCLUSION

The P2X7 receptor is present on numerous immune and other cell types in the skin including keratinocytes, Langerhans cells, and dermal dendritic cells, and may be present on T and B cells. P2X7 expression is negligible on mast cells, but can be upregulated in skin disease. Activation of P2X7 by ATP results in numerous downstream effects including cytokine release and apoptosis. P2X7 may play a role in homeostatic skin biology and has been implicated in a number of skin disorders, including contact dermatitis, psoriasis, cutaneous GVHD, and is involved in other skin processes including transplantation and wound healing. Thus, P2X7 represents a potential target for therapy of skin diseases.

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Unraveling oral psoriasis and its relationship with geographic tongue: A literature review

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Abstract

Differentiating between oral psoriasis and geographic tongue is difficult and controversial because some patients with geographic tongue do not necessarily have psoriasis. Furthermore, the number of clinical studies, reporting histopathological and genetic evidence for the definitive diagnosis of oral psoriasis, is limited. The aim of this literature review was to obtain data for supporting the diagnosis of oral psoriasis with particular emphasis on the relationship between psoriasis and geographic tongue. Based on the current data, it can be concluded that geographic tongue is the most common oral lesion in psoriasis, and histopathological, immunohistochemical, and genetic similarities have been observed between the two diseases. This review also emphasizes the importance of conducting oral examinations in patients with psoriasis and skin examinations in patients with geographic tongue.

Key words: Psoriasis; Geographic tongue; Oral psoriasis; Benign migratory glossitis

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Core tip: The occurrence of oral lesions in psoriasis is rare; however, some authors consider geographic tongue as an oral manifestation of psoriasis. Furthermore, the number of clinical studies, providing histopathological and genetic evidence for the definitive diagnosis of oral psoriasis, is limited. The aim of this literature review was to investigate the current data on oral psoriasis with an emphasis on the relationship between psoriasis and geographic tongue.

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INTRODUCTION

Psoriasis is a chronic, inflammatory, cutaneous-articular disease that affects 1%-3% of the world's population^[1,2]. The occurrence of oral lesions in psoriasis is rare, and the relationship between these lesions and the disease is controversial because of a limited number of cases with definitive histopathological diagnosis^[3-7]. Schultz first reported oral lesions in psoriasis in 1898; he presented three cases of psoriasis on the buccal mucosa^[8]. Subsequently, Oppenheim provided evidence of oral psoriasis in 1903 when he confirmed a clinical diagnosis by histopathology^[9]. There is substantial variability in the location and presentation of these lesions, and they are often described as plates or white patches, ulcers, pustules, papules, and erythematous lesions^[8,10-17]. In general, oral lesions in psoriasis can be divided into the following two categories: the first category includes true psoriatic lesions (confirmed by biopsy) accompanied by a parallel clinical course of skin lesions^[3,18,19] and the second category, which includes majority of oral findings in psoriasis, contains non-specific lesions, including fissured tongue and geographic tongue^[3,4,7,18-20]. Patients with psoriasis frequently exhibit geographic tongue, showing clinical, microscopic, and genetic similarities between the two diseases. However, the condition still does not have a well-defined etiology^[21-24]. The diagnosis of geographic tongue as oral psoriasis is controversial and difficult as some patients with geographic tongue do not suffer from psoriasis^[3]. Additionally, the number of clinical studies, providing histopathological and genetic evidence on a plausible definitive diagnosis of oral psoriasis is limited^[3,18,22]. Considering the importance of obtaining accurate data, the aim of this literature review was to assess the current data on oral psoriasis with particular emphasis on the relationship between the disease and geographic tongue.

LITERATURE RESEARCH

A systematic literature search was conducted using PubMed and the Cochrane Library. The search terms used were "geographic tongue", "oral psoriasis", "psoriasis", and "benign migratory glossitis". In total, 65 relevant studies were included in the review.

ORAL MANIFESTATIONS OF PSORIASIS

Although psoriasis affects up to 3% of the world's population, there are a limited number of studies that focus on involvement of the oral mucosa^[1,5].

Psoriatic lesions have mostly been observed in the jugal mucosa, labial mucosa, skin of the lips (vermilion),

hard and soft palate, floor of the mouth, gums, and tongue. The presentation of these lesions is highly variable, and they have been described as striae, white plaques, grayish white spots, white scales, mottled erythema, brown plaques, ulcers, pustules, papules, and atrophic lesions (Table 1)^[8,10-17]. In 1933, Usher examined 100 patients with cutaneous psoriasis and found that the oral mucosa was affected in two of them. Years later, Pisanty and Ship^[10] (1970) described a case of a male patient who exhibited an asymptomatic white plaque in the upper and lower lips for a duration of 2 mo. The patient had a personal and family history of psoriasis. Using histopathological analysis, the authors confirmed a diagnosis of oral psoriasis.

DeGregori *et al.*^[25] described a 53-year-old psoriasis patient with a family history of the disease and diffused erythema on the gingiva and tongue, symptoms that were histopathologically compatible with oral psoriasis. The authors demonstrated that up to the date of publication of their study, only 15 cases of oral psoriasis had been reported, and only two of them showed involvement of the gingival tissue.

Salmon *et al.*^[9] reported a case of psoriasis with oral involvement where the patient reported pain and itching in the lips and tongue. The tongue and lips exhibited irregular ulcers with erythematous borders, and a diagnosis of oral psoriasis was confirmed by histopathology.

White *et al.*^[12] described a case of a 43-year-old patient with psoriasis and erythematous lesions in the attached gingiva, labial mucosa, and soft palate, whereas Cataldo *et al.*^[26] described a case of a 47-year-old patient with white and raised lesions on their tongue and lips.

Hietanen *et al.*^[21] evaluated the oral mucosa of 200 patients with psoriasis, most of whom presented with disseminated skin psoriasis. Amongst these, fissured tongue was present in 9% of the patients, geographic tongue was observed in 1%, and angular cheilitis in 3%. Biopsies were performed in 20 patients, four of which had outcomes that were consistent with psoriasis.

Hubler^[27] reported five cases from three families who presented with generalized pustular psoriasis and tongue injuries. The author concluded that geographic tongue was an oral manifestation of generalized pustular psoriasis and that the two diseases were polygenic and episodic, had identical clinical histopathology, and manifested due to the influence of external factors.

Sklavounou *et al.*^[28] reported a case where intraoral examination revealed white lesions with erythematous areas that were slightly raised, well circumscribed, and located on the dorsum of the tongue. Lesions similar to geographic tongue were also observed on the lateral edge of the tongue. Although no skin disorder was diagnosed until the evaluation, the daughter was a carrier of psoriasis. A biopsy and HLA typing were performed, and the results of the microscopic analysis and the presence of B13 antigen confirmed a diagnosis of oral psoriasis.

Younai *et al.*^[29] reported an unusual case of oral lesions with the characteristics of psoriasis. The intraoral

Table 1 Oral psoriasis - case reports

Ref.	Age (yr)	Sex (M/W)	Affected areas	Clinical aspects	Histopathological diagnosis	Cutaneous psoriasis
Pisanty <i>et al</i> ^[10]	47	Man	Labial mucosa	White plaques	Yes	Yes
DeGregori <i>et al</i> ^[25]	53	Man	Tongue gingiva	Diffuse erythema	Yes	Yes
Salmon <i>et al</i> ^[9]	45	Woman	Tongue labial mucosa	Erythematous ulcers	Yes	Yes
White <i>et al</i> ^[12]	43	Woman	Gingiva labial mucosa soft palate	Erythematous spot	Yes	Yes
Cataldo <i>et al</i> ^[26]	47	Woman	Tongue lip	White plaques	Yes	Yes
Sklavounou <i>et al</i> ^[28]	42	Woman	Tongue	White plaque with erythematous areas	Yes	No ¹
Younai <i>et al</i> ^[29]	65	Woman	Tongue lip	Multiple pustules within the atrophic and erythematous areas	Yes	No
Rozell <i>et al</i> ^[30]	18	Man	Gingiva	Erythematous lesions	Yes	No ¹
Brice <i>et al</i> ^[14]	77	Man	Tongue, palate and gingiva	Erythematous lesions	Yes	Yes
	51	Man	Labial mucosa and gingiva	Erythematous plaques with white border		
Ariyawardana <i>et al</i> ^[31]	11	Woman	Buccal mucosa	Erythematous plaque	Yes	Yes
Binmadi <i>et al</i> ^[15]	72	Man	Tongue	Ulcers associated with fissured tongue	Yes	Yes
Reis <i>et al</i> ^[32]	35	Woman	Gingiva palate	Erythematous patches	Yes	No
Mattsson <i>et al</i> ^[33]	52	Woman	Buccal mucosa and gingiva	Diffuse patchy erythema	Yes	Yes
	40	Man	palate	red areas		

¹Patient with familiar history of psoriasis.

examination revealed geographic and fissured tongue, as well as an injury on the upper lip that was covered by a crust which could be easily removed by scraping to reveal a surface with minimal bleeding and white dots. No skin lesions were observed in the extra-oral examination. Lip biopsies were performed and the histopathological results were suggestive of psoriasis.

Rozell *et al*^[30] showed that the presence of skin lesions was not necessary for the manifestation of oral psoriasis in some cases. For example, an 18-year-old male who was studied for 12 years showed no clinical signs of cutaneous psoriasis during this period, although he exhibited erythematous lesions in the gums. An initial biopsy performed when he was 6 years old yielded classic histopathologic results of psoriasis. A second biopsy performed 12 years later gave the same result. His family history was positive for psoriasis, but none of the family members with dermal psoriasis presented any oral manifestations.

Brice *et al*^[14] reported two cases with an initial diagnosis of cutaneous psoriasis who exhibited injuries in the attached gingiva. Histopathological examination revealed signs that were compatible with psoriasiform mucositis. Although rare, oral involvement of psoriasis may occur and the correct diagnosis depends on clinical and histopathological evaluation.

Ariyawardana *et al*^[31] reported a case of intraoral psoriatic psoriasis in an 11-year-old child with red lesions in the jugal mucosa, and psoriasis was histopathologically confirmed in this case.

Binmadi *et al*^[15] described a case of a psoriasis patient presenting with painful ulcers and fissured tongue for

5 wk. Histopathological examination revealed evidence supporting a diagnosis of psoriasis. In this study, the authors emphasized the importance of an oral examination in patients with psoriasis.

Yesudian *et al*^[5] concluded that oral lesions are rare, with evidence found in fewer than 100 publications in the literature. They also suggested that it is unclear whether oral psoriasis is a distinct entity, or if, indeed, it exists at all.

Reis *et al*^[32] reported a case of a non-psoriatic patient with diffuse erythematous taint on their gums and palate. A histopathological examination of the lesions revealed a diagnosis of psoriasis.

Mattsson *et al*^[33] described two cases of lesions in the gums and jugal mucosa with psoriasiform histopathological characteristics, which clinically presented as erythema and serpiginous white areas, respectively. These patients reported a history of cutaneous psoriasis.

In 1993, Gonzaga *et al*^[34] concluded that the prevalence of oral lesions in patients with psoriasis would be much greater if a rigorous intraoral examination was carried out. Similarly, Picciani *et al*^[4] studied the prevalence of oral lesions in 203 psoriatic patients and found a high frequency of nonspecific oral lesions, thereby demonstrating the relationship between geographic tongue/fissured tongue and psoriasis.

Despite the aforementioned reports of lesions where clinical and histopathological examinations were compatible with oral psoriasis, the most common oral manifestations include nonspecific lesions such as geographic tongue and fissured tongue. Therefore, additional studies are required in order to define geographic tongue as a true oral lesion



Figure 1 Clinical aspects of geographic tongue (black arrow) and fissured tongue (white arrow).

of psoriasis^[4,35].

ASSOCIATION OF GEOGRAPHIC TONGUE AND/OR FISSURED TONGUE WITH PSORIASIS

Clinical aspects

Several authors suggest an association between psoriasis and geographic tongue or fissured tongue (Figure 1)^[4,7,18,19,22,36]. Approximately 10% of patients with psoriasis present with geographic tongue^[4], and it is more commonly associated with the pustular form of the disease^[37].

Fissured tongue is the oral condition most commonly associated with geographic tongue, and the prevalence of the condition is increased in patients with psoriasis. Although most injuries in psoriasis are transient, some lesions can have a more permanent course. Therefore, it is possible that geographic tongue is a transient expression of oral psoriasis, while fissured tongue is a delayed and more permanent expression of the disease. However, a common genetic marker for the three conditions is yet to be found^[38].

Previous studies have demonstrated that the prevalence of fissured tongue ranges from 9.8% to 47.5%, whereas that of geographic tongue ranges from 5.6% to 18.1%^[4,7,19,20,24,36,37].

Geographic tongue, also known as benign migratory glossitis, was first described by Reiter in 1831. Although this condition has no defined etiology, it has a chronic profile with inflammatory and immune-mediated elements. It affects approximately 0.6%–4.8% of the world's population, and occurs most commonly in children and women^[39–41]. It is clinically characterized by erythematous lesions (due to loss of filiform papilla) with whitish irregular edges, particularly on the dorsum and side edges of the tongue. The white border consists of filiform papilla on regeneration and a mixture of keratin and neutrophils. The lesions tend to change location, pattern, and size over time due to epithelial peeling at one location along with simultaneous proliferation elsewhere. There are periods of exacerbation as well as remission, the latter being asymptomatic and

not requiring treatment. Some patients complain of pain or burning, particularly during intake of spicy or acidic foods. Diagnosis of geographic tongue is based on patient history and a physical examination. However, histopathology may be necessary in unusual cases^[41–44].

Very rarely, other sides of the tongue may be affected, and this is known as geographic stomatitis or benign migratory erythema^[45,46].

Gonzaga *et al.*^[47] examined the association between alcohol, tobacco, and stress in 129 patients with psoriasis, 399 patients with geographic tongue, and 5472 healthy individuals. Their results showed high levels of alcohol consumption in psoriatic patients and a strong relationship between psoriasis and geographic tongue and psychosomatic factors. They concluded that the interactions between environmental factors and psoriasis differed from those that occur with geographic tongue, and they suggested that these differences accounted for the different manifestations of the two diseases. However, they considered both conditions to be part of the same disease.

Daneshpazhooh *et al.*^[37] conducted a case-control study, studying oral lesions in 200 psoriasis patients; These patients were divided into the following two groups: patients with psoriasis ($n = 87$, 43.5%) and the control group ($n = 39$, 19.5%). Fissured tongue was more frequently seen in the psoriatic group ($n = 66$, 33%) than the control group ($n = 19$, 9.5%). Geographic tongue was observed in 28 cases (14%) from the psoriatic group and 12 cases (6%) in the control group.

Zargari^[36] conducted a prospective study examining the prevalence of lesions on the tongue of patients with psoriasis. The author observed that 47 patients (15%) had tongue lesions, 25 (8%) had fissured tongue, and 17 (6%) had geographic tongue (of which 7% of patients had early psoriasis and 1% with late psoriasis). The author concluded that the incidence of geographic tongue in early psoriasis was an indicator of disease severity.

Hernández-Pérez *et al.*^[24] examined 80 patients with psoriasis and 127 healthy individuals and found that the number of patients with fissured tongue was more in patients with psoriasis (47%) than that in the control group (20%). Geographic tongue was present in 12% and 5% of patients in the psoriasis and control groups, respectively. The authors concluded that these lesions may be a predecessor of psoriasis or a marker of severity.

Picciani *et al.*^[4] also reported that the prevalence of geographic tongue was at its highest in early psoriasis, whereas the prevalence of fissured tongue was highest in late psoriasis.

Singh *et al.*^[7] evaluated 600 patients with psoriasis and concluded that prevalence of geographic tongue is increased in these patients and is related to the severity of the disease.

Picciani *et al.*^[48] also examined the relationship between disease severity and the presence of geographic tongue in 284 patients with psoriasis through the PASI. They

found that severe psoriasis occurred in 25% of patients without geographic tongue and in 58% of patients with this oral lesion. The authors concluded that geographic tongue could be considered a marker for the severity of psoriasis.

Gonzaga *et al.*^[49] conducted a study with 118 psoriasis carriers and 88 patients with benign migratory glossitis, and their results suggested that this lesion is a preceding manifestation of the cutaneous condition. They also identified the similarity between the fundamental lesions and symptoms of these diseases. In this tongue lesion, the erythematous lesions correspond to dermal peeling and, similar to psoriasis, follow a chronic course presenting periods of remission and exacerbation^[49]. The chewing and speech processes, which are constant trauma factors in the tongue that could correspond to the Koebner phenomenon, may stimulate the emergence of geographic tongue. The authors concluded that the prevalence of oral lesions of psoriasis may be much higher than currently reported because, in general, patients are not subjected to a thorough oral examination^[49].

Histopathological aspects

For several authors, the clinical and histopathological similarities between psoriasis and geographic tongue support the theory that the latter is an oral manifestation of the former (Figure 2)^[13,17,18,24].

The histopathological features of psoriasis include uniform elongation of the rete ridges, dilated blood vessels, thinning of the supra-papillary plate, intermittent parakeratosis, perivascular infiltration of lymphocytes, and the presence of occasional neutrophil aggregates in the epidermis. Histopathological diagnosis is made by comprehensively evaluating these findings^[50].

Since the diagnosis of geographic tongue is based on clinical examination, few histopathological studies have been conducted on this condition, and this has hindered the general understanding of the etiopathogeny of the oral lesion and its relationship with psoriasis.

Femiano^[18] conducted a histopathological comparison of 40 patients with geographic tongue: 20 with psoriasis and 20 without the cutaneous disease. In the psoriasis group, all the fragments showed the histopathological features of psoriasis, while only 80% of the patients in the non-psoriasis group exhibited these characteristics. Thus, the author concluded that geographic tongue is an oral lesion of psoriasis and can exist as a subclinical form of the condition.

Picciani evaluated and compared the histopathological aspects of geographic tongue lesions as well as dermal lesions in patients with and without psoriasis. The study found that most of the classic histopathological features of psoriasis were observed in all cases as parakeratosis, acanthosis, suprapapillary epithelial atrophy, spongiosis, basal layer hyperplasia, crest fusion, exocytosis, and the presence of papillary superficial and inflammatory infiltrate. However, remarkable differences were observed in the peripheral areas of the geographic tongue lesions

in the two groups, with the oral lesions of patients with psoriasis showing hyperplastic, inflammatory, and vascular changes in the periphery. Examination of these peripheral changes could perhaps help distinguish geographic tongue from true oral psoriasis^[51].

The importance of angiogenesis in the pathological process of psoriatic lesions is well recognized. The balance between pro- and anti-angiogenic factors regulates the genesis of new blood vessels. Angiogenesis facilitates the disease progress in pathological processes such as tumor growth or chronic inflammation^[52]. The vascular system is increased due to vasodilation and lengthening of existing vessels and also by the formation of new vessels. These morphological changes are observed even before epithelial hyperplasia of the psoriatic plaques^[52]. Santos^[53] qualitatively compared the geographic tongue lesions in patients with and without psoriasis and found that vascular ectasia associated with vascular tortuosity were the major changes associated with psoriasis accompanied by frequent geographic tongue lesions.

The evaluation of these aspects, especially in the peripheral areas of oral lesions, could perhaps help distinguish between geographic tongue and true oral psoriasis^[53].

Munro's micro-abscess (neutrophil collections in the corneal layer) is present in over 75% of psoriasis cases, whereas pustule of Kogoj (also a collection of neutrophils, but in the spinous layer) is mainly present in pustular psoriasis cases^[54]. Picciani^[51] recently demonstrated a high prevalence of pustules of Kogoj in geographic tongue injuries, and this finding strengthens the theory that geographic tongue represents a pustular manifestation of psoriasis^[37]. Evaluating oral and cutaneous lesions in patients with pustular psoriasis could help improve the current understanding of this relationship.

Immunogenetic similarities

Although there is a paucity of studies examining immunogenetics in geographic tongue, the results of those that exist demonstrate that it is the oral lesion most commonly associated with psoriasis.

The inflammatory infiltrate in psoriasis consists mainly of T cells: CD4⁺ in the dermis and CD8⁺ in the epidermis. Macrophages are the major antigens observed in psoriatic cells, and the infiltrate in oral psoriatic lesions consists of macrophages and T cells, especially CD4. The few immunohistochemical studies conducted in patients with geographic tongue showed a similar abundance of CD4⁺ cells^[13,17,55].

An immunohistochemical study of patients with geographic tongue demonstrated the presence of dilated and tortuous capillaries and intense cell proliferation (as evidenced by antibody Ki-67), similar to psoriatic lesions. However, a diagnosis of oral psoriasis was not established because of the absence of cutaneous manifestations^[17].

Espelid *et al.*^[55] conducted an immunohistochemical study in geographic tongue lesions with CD3, CD4, CD8, CD22, and CD11c antibodies and HLA-DR. They demonstrated

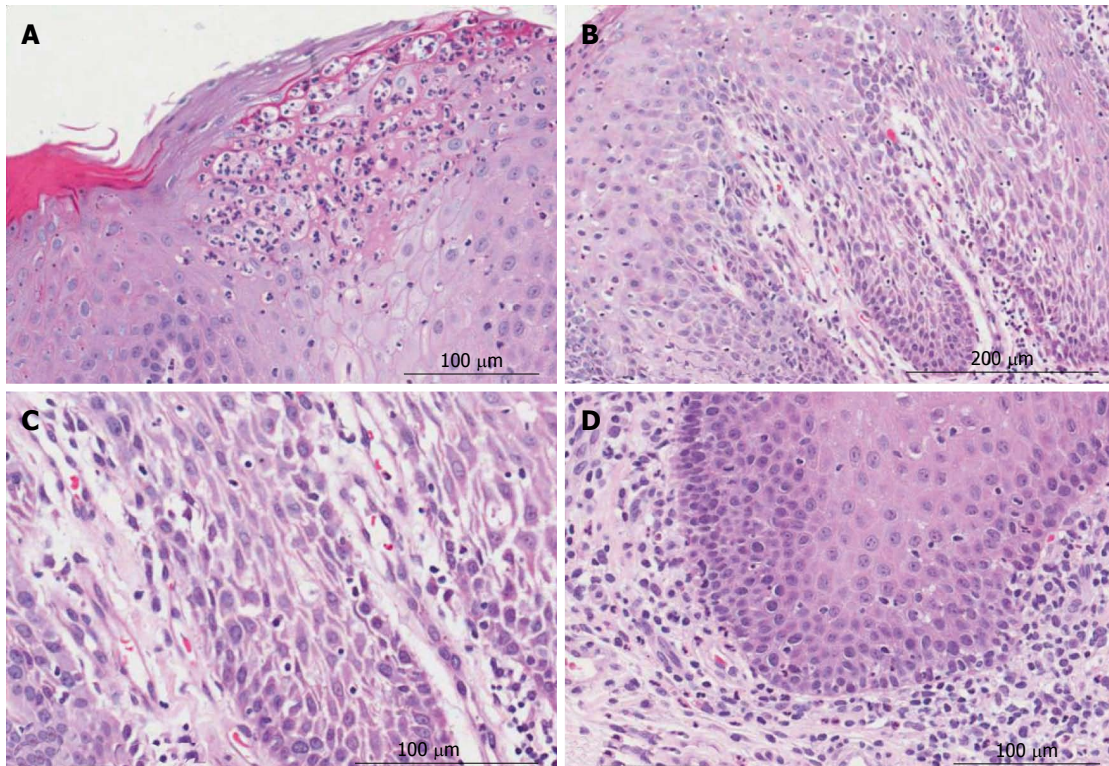


Figure 2 Histopathological aspects of geographic tongue. A: Histopathologic appearance exhibiting parakeratosis, exocytosis of polymorphonuclear leukocytes, and Munro micro-abscesses; B: Acanthosis, elongation, and fusion of rete ridges; C: Dilated tortuous vessels and espongiosis; D: Basal layer hyperplasia and superficial lymphocytic chronic inflammatory cells (hematoxylin and eosin).

that sub-epithelial inflammatory infiltrate is predominantly composed of CD4⁺ T lymphocytes, along with the presence of macrophages.

Ulmansky *et al.*^[13] showed that CD4⁺ T lymphocytes are the main cells in the inflammatory infiltrate from geographic tongue.

Based on this, the authors of the aforementioned studies concluded that there was a connection between geographic tongue and psoriasis^[13,55].

Picciani^[51] investigated the inflammatory responses of patients with geographic tongue who either did or did not have psoriasis (using CD1a, CD3, CD4, CD8, CD20, and CD68 antibodies). They found that the oral and cutaneous lesions had similar qualitative and quantitative standard markings, regardless of the antibody used. Oral and skin lesions of patients with psoriasis revealed a higher prevalence of TCD3, CD4, and CD8 T cells.

With psoriasiform lesions such as geographic tongue causing difficulties in diagnosis, the measurable difference in the amount and pattern of distribution of CD4⁺ and CD8⁺ cells could aid diagnostic decision making, especially in cases with very similar histopathological features^[56].

In a recent study, the concentration of TNF- α and IL-6 in the saliva of patients with geographic tongue and healthy individuals was examined. The results showed an increase of both proteins in patients with geographic tongue, and this finding strengthens the link between this condition and psoriasis^[57].

In the past decade, Th1 cytokines such as inter-

feron- γ (IFN- γ) and tumor necrosis factor- α (TNF- α) were considered to play a major role in psoriasis, but recent evidence points toward a greater role of IL-23 and IL-17A in the physio-pathogenesis of psoriasis^[58].

Domingos^[59] (2015) conducted an analysis of the immunopositivity to antibodies directed against IL-6, IL-17, and IL-23 in skin lesions of psoriasis and geographic tongue lesions of patients with and without the cutaneous disease. The three antibodies showed a similar pattern of cytoplasmic labeling, predominantly basal and parabasal, in psoriasis as well as geographic tongue. In the sections where the basal layer hyperplasia was most significant, the markings were longer and more prominent^[59].

Cytokeratins are the main structural component of keratinocytes in various groups, and they are expressed during various stages of cellular differentiation^[60,61]. In psoriasis, the present cytokeratins change in the pattern of expression, and they have been identified by immunohistochemical methods as differentiation markers and hyper-proliferation of keratinocytes^[61]. Activated keratinocytes express keratins that differ from normal skin, such as CK6, CK16, and CK17. Santos^[53] also evaluated the correlation between the patterns of distribution of CK6, CK16, and CK17 in skin lesions of psoriasis and in oral lesions of geographic tongue, and the immunohistochemical analysis showed a similar distribution in both lesions. A greater quantitative similarity was observed between geographic tongue lesions and skin lesions in patients with psoriasis, reinforcing the

association between the diseases.

In 1996, the association between psoriasis and geographic tongue was supported by genetic analysis for the first time when a common genetic marker, the human leukocyte antigen (HLA-Cw6) was determined. Thus, these two conditions apparently have a common genetic basis^[22]. The genetic determinant of geographic tongue pathogenesis is under-reported in the literature, with only five papers correlating this oral lesion to HLA genes which are known to be important for susceptibility to psoriatic disease. Specifically, relationships were demonstrated with the HLA-B13, -B15, -B58, -CW6, -DR5, and -DRW6 alleles^[22,62-65].

Picciani *et al.*^[65] conducted the first study using molecular methodology for HLA typification. They found associations between HLA-B × 57 and psoriasis vulgaris and HLA-B × 58 and geographic tongue. Both alleles are serological divisions of HLA-B17. The findings of this study strengthen the link between the two conditions.

The same authors^[17] evaluated an isolated case of a patient with a family history of psoriasis and geographic tongue in association with benign migratory erythema and found histopathological, immunohistochemical, and immunogenetic features similar to those observed in dermatitis. However, a diagnosis of oral psoriasis was not completed because of the absence of cutaneous lesions in the patient.

Historically, the difficulty in accepting a diagnosis of geographic tongue as oral psoriasis arose from the fact that some patients with geographic tongue did not have psoriasis^[3]. However, a detailed family analysis of these patients, including insights into the family history of psoriatic disease, may introduce new genetic markers that show increasingly significant correlations between the two conditions.

CONCLUSION

Geographic tongue is the most prevalent oral lesion in psoriasis, with histopathological, immunohistochemical, and genetic similarities observed between the diseases. In order to confirm the relationship between geographic tongue and psoriasis, it will be necessary to conduct new studies that combine histopathology and immunogenetic analysis. This review also highlights the importance of conducting oral examinations in patients with psoriasis and skin examinations in patients with geographic tongue.

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Review of narrowband ultraviolet B radiation in vitiligo

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Abstract

Vitiligo is a common, acquired pigmentary disorder of unknown etiology with great impact on patient's appearance and quality of life. It presents a therapeutic challenge to many dermatologists. Photochemotherapy using psoralen and ultraviolet A (UVA) therapy, topical and oral immunosuppressants, as well as cosmetic camouflage are also commonly employed with varying clinical efficacy. Phototherapy is a popular treatment option, which includes

both of the generalized ultraviolet B (UVB) therapies, broadband UVB and narrowband UVB (NB-UVB). It has been used favorably, both alone as well as in combination with other agents like topical calcineurin inhibitors, vitamin-D analogs. Combination therapies are useful and may provide quicker repigmentation and treat vitiligo with an additive mechanism of action than UVB phototherapy. Advances in technology may lead to the continuing use of UVB phototherapy as a treatment for vitiligo through the development of sophisticated devices and delivery systems as well as innovative application methods. These will provide increased therapeutic options for all vitiligo patients, particularly those with refractory disease. In this article, I have reviewed the available data pertaining to efficacy and safety issues for NB-UVB as monotherapy, its comparison with psoralen plus UVA and other modes of phototherapy, combination regimens that have been tried and future prospects of NB-UVB in vitiligo.

Key words: Narrow-band ultraviolet B; Phototherapy; Vitiligo

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Core tip: Vitiligo is a procured depigmentation issue with great effect on patient's appearance and his satisfaction. Till date, the etiology of vitiligo remains elusive, which makes it difficult to have curative therapies. Narrowband ultraviolet B (UVB) phototherapy is generally utilized and delivers great clinical results. In this manuscript, I review the excursion of narrowband UVB from its prior days of advancement until this time as monotherapy, its comparison with psoralen and ultraviolet A and other modes of phototherapy and in combination with other therapies in the management of vitiligo.

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INTRODUCTION

The principal investigation of the use of light in the therapy of dermatologic issue dates from 1400 BC when patients with vitiligo were taken sure concentrates of the plants *Psoralea corylifolia* in India and *Ammi majus* linnaeus in Egypt as topical application or ingestion, trailed by introduction to the sun^[1]. The genuine enthusiasm for the utilization of ultraviolet (UV) light in the remediation of different cutaneous illnesses began in the nineteenth century when Niels Finsen got the Nobel Prize in 1903 for his helpful outcomes with UV illumination in lupus vulgaris^[2].

In 1977, Fischer^[3] observed that light at a wavelength of 313 nm was viable in clearing psoriatic plaques. Diffey and Farr^[4] in the wake of concentrating on the impacts of UV radiation (UVA, UVB and UVC), recommended that more drawn out wavelengths added nothing to the helpful event, that shorter wavelengths really cheapened the adequacy of remediation, and that UVB was practically viable at 311 nm.

A couple of years after the fact it was resolved that the best wavelengths were somewhere around 295 and 313 nm; inside of that range, the proportion of the most reduced viable every day dosage to the negligible erythema measurement was littlest for 313 nm, demonstrating that this wavelength might have the ideal "phototherapy index" for clearing psoriasis^[5]. These ponders prompted the advancement of the Phillips TL-01 fluorescent light, which radiates a slender crest around 311-312 nm (Figure 1)^[6].

Narrowband UVB (NB-UVB) is a subset of the UVB wideband or broadband range. The UVB band includes the scope of wavelengths between 290 nm and 320 nm while UVB narrowband has a restricted range of emanation (310-315 nm) wavelengths with a crest at 311 nm^[7].

NB-UVB phototherapy lodges comprise fluorescent TL-01 (100 W) tubes as the wellspring of light. The expense of a chamber and lights show extensive varieties in the middle of nations and wholesalers. NB-UVB lodges accessible industrially either join TL-01 alone or in blend with UVA tubes. Blend chambers take more time to control a medication measurements. Along these lines, in spite of the fact that they give adaptability, they might speak to an unacceptable tradeoff for a bustling phototherapy unit^[8].

Smaller containers of NB-UVB have additionally gotten to be accessible in little range treatment types of gear (hand and foot unit, NB-UVB brush) for the treatment of restricted body sites^[9].

NB-UVB calendars can be customized by skin sort and neighborhood experience. Two methods are most generally utilized; one includes definition of the person's minimum erythema dose (MED) by method for a different bank of TL-01 tubes^[10]. Another approach, as commonly practiced is the tight band skin sort convention. It involves standard initial dose according to Fitzpatrick skin

phototype (Table 1) with stepwise increments (typically 20%) contingent upon patient's erythema response. This plan has demonstrated colossally compelling and has been generally circulated and utilized as a part of an expansive choice of phototherapy practices^[8].

Minimum erythema dose determination includes uncovering little characterized ranges of sun-ensured, clinically unaffected skin to expanding dosages of UV light, the measurements to every zone normally being 1.4 times the past measurement. A layout of UV-hazy, glue plastic with eight 2.3 cm² gaps (ports), fastened to the lower back of the patient might be utilized, with every port presented to an alternate illumination dose from a board of TL-01 fluorescent tubes. Whatever remains of the patient's skin is secured amid these UV exposures^[11].

The dose for each port for NB-UVB photo-testing is reliant on the subject Fitzpatrick skin type. For skin types I -III, initial doses of 400, 600, 800, 1000, 1200, 1400 mJ/cm² are utilized while for skin sorts IV-VI, 800, 1000, 1200, 1400, 1600 and 1800 mJ/cm² are utilized. The patients are instructed not to receive any natural or artificial UV light to this region of the skin during the next 24 h and asked to return to the phototherapy center in 24 h. The area of the photo-testing should be identified by ink marking at the different dosage sites. A positive perusing is believed as recognizable erythema inside of the edges of the photo-testing port. If bright red erythema develops or blistering occurs at the site of any of the phototesting sites, topical corticosteroids can be used to treat the area^[12].

When MED has been detected, the treatment convention is typically "percent based". Regularly 70% of the MED worth is utilized for the first treatment; from there on treatment is given three times or all the more week by week with 40%, 20% or 10% increases relying upon neighborhood experience, erythema response and skin sort resistant^[13,14].

A semi-automated small hand-held MED tester (Durham MED tester) has gotten to be accessible which produces a settled arrangement of UV dosages, taking into account constricting foils. The Durham MED analyzer lessening arrangement approximates a geometric arrangement with a variable of 1.26. Beginning from the open gap (100%), each consequent gap is lessened by a variable of around 1.26^[15].

METHODS OF NB-UVB RESEARCH

NB-UVB as monotherapy

NB-UVB phototherapy has been observed to be powerful and alright for vitiligo^[16]. The consequences of monotherapy with NB-UVB have been exceptional in Asian skin. Roughly 75% of cases in a previous study accomplished more prominent than 75% to finish repigmentation after NB-UVB therapy for a greatest time of 12 mo^[17]. The average length of time of sickness was fundamentally shorter in the individuals who had stamped to finish pigmentation contrasted and the individuals

Table 1 Fitzpatrick's skin phototypes

Phototype	Sunburn and tanning history (defines the photo type)	Immediate pigment darkening	Delayed tanning	Constitutive color (unexposed) buttock skin	UVA MED (mJ/cm ²)	UVB MED (mJ/cm ²)
I	Burns easily, never tans	None	None	Ivory White	20-35	15-30
II	Burns easily, tans minimally with difficulty	Weak	Minimal to weak	White	30-45	35-40
III	Burns moderately, tans moderately and uniformly	Definite	Low	White	40-55	30-50
IV	Burns minimally, tans moderately and easily	Moderate	Moderate	Beige-olive, lightly tanned	50-80	40-60
V	Rarely burns, tans profusely	Intense brown	Strong, intense brown	Moderate brown or tanned	70-100	60-90
VI	Never burns, tans profusely	Intense (dark brown)	Strong, intense brown	Dark brown or black	100	90-150

UVA: Ultraviolet A; UVB: Ultraviolet B; MED: Minimum erythema dose.

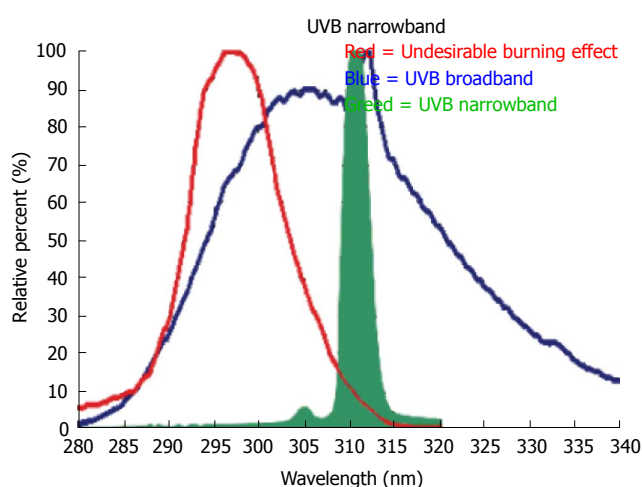


Figure 1 Narrowband ultraviolet B phototherapy (Bandow and Koo^[6]). UVB: Ultraviolet B.

who had weaker reaction. Likewise with any treatment methodology for vitiligo, the best results were seen in lesions on the face and neck, trailed by the proximal limbs and trunk. Pigmentation around the hair follicles was the more widely recognized kind of starting repigmentation that was seen in around seventy five percent of cases.

It was focused on impact of NB-UVB and the impact of influenced destinations, individual's age and duration of illness on the response^[18]. Full pigmentation was all the most ordinarily seen in facial sores and sores situated on the neck and trunk in diminishing request of recurrence (68, 57.9, half, individually). Age did not impact the reaction to treatment for facial sores, while in different extents aggregate pigmentation was significantly more ordinarily seen in more youthful patients (under a twenty years). Injuries over the neck and extremities (arms and legs) demonstrated a high percent of total pigmentation (83.3%, 33.3% and 28.5%, separately) in those with illness of late onset (less than two years).

Likewise as the time span of the lesion is prolonged, the sores over the face reacted better. Creators suggest early therapy, as the excellent outcomes were accomplished by youthful patients with late onset vitiligo.

In a randomized, controlled, side-to-side correlation

survey, the average change in the NB-UVB was 42.9% contrasted and 3.3% in the untreated side, with the seriousness of malady having been surveyed by VASI^[19]. The response changed extraordinarily between distinctive body areas, with the excellent reaction occurred over the lower furthest points and most exceedingly terrible reaction on the foot. While all cases did not get therapy for their face, 37.5% of the individuals who decided on therapy of this area had more than seventy five percent repigmentation.

In India, an extensive, open, forthcoming study, just around a quarter of patients could accomplish more than seventy-five percent repigmentation^[20]. This poor response can be credited to bring down initial estimation and twice-week after week therapy. In those patients who had huge pigmentation, it was ascribed to great consistence, a more prominent number of medicines and expanding total measurements. Albeit introductory repigmentation was darker, great shading coordinating could be accomplished with proceeded with treatment (Table 2).

NB-UVB vs psoralen and UVA

In a previous study contrasting twice-week after week, local psoralen and UVA (PUVA) against NB-UVB, authors reported return of pigmentation in 67% of cases in the NB-UVB bunch contrasted and 46% in the local PUVA bunch following four months of therapy^[21]. Following three months of NB-UVB therapy, 8% of cases indicated more than 75% repigmentation, though following 1 year of NB-UVB usage, 63% had such repigmentation. In another review, permanent pigmentation following 12 mo of therapy consummation was seen in 78.5% of patients in the NB-UVB bunch and 60% in the PUVA bunch^[22].

In the initially randomized, twofold visually impaired, fake treatment controlled study, change in body area territory influenced by vitiligo was more noteworthy with NB-UVB than fake treatment after 48 sittings^[23]. Following 1 year of end of treatment, predominance as far as adequacy for NB-UVB was kept up, in spite of the fact that it was not measurably huge. No relationship between length of time of malady and accomplishment

Table 2 Studies of narrowband ultraviolet B in treatment of vitiligo (monotherapy)

Ref.	Study component	Study design	Patient's No.	Mode of each treatment	Dosimetry	Degree of pigmentation	Incidence of side effects
Njoo <i>et al</i> ^[134]	NB-UVB	Prospective, open, uncontrolled	51	Twice a week	0.25 J/cm ² followed by 20% increments until minimal erythema	After a maximum of 1-yr treatment: > 75% repigmentation in 53%	Pruritus: 8% Xerosis: 4%
Scherschun <i>et al</i> ^[16]	NB-UVB	Retrospective	7	Three-times a week	280 mJ/cm ² ; followed by 15% increments until mild erythema or pruritus	70% patients achieved > 75% repigmentation after a mean 19 treatments	Mild asymptomatic erythema: 58% Pruritus: 14%
Hamzavi <i>et al</i> ^[19]	NB-UVB	Randomized, controlled side to side	22	Three-times a week	70% of MED on depigmented skin followed by 10% increments until onset of repigmentation	Mean improvement after 6 mo or 80 exposures: 42.9% (treatment side) vs 3.3% (control side)	
Kanwar <i>et al</i> ^[17]	NB-UVB	Open uncontrolled	14	Three-times a week	280 mJ/cm ² followed by 20% increments	After 1 yr: > 75% repigmentation in 71.4%	Burning and pruritus: 28.6% Xerosis 3 rd thickening of lesional skin: 21.4%
Kanwar and Dogra ^[27]	NB-UVB	Prospective, open, uncontrolled	20	Three-times a week	280 mJ/cm ² followed by 20% increments	After a maximum of 1 yr treatment: > 75% repigmentation in 75% patients	Lesional burning and pruritus: 20%. Xerosis 3 rd thickening of skin: 15%
Brazzelli <i>et al</i> ^[18]	NB-UVB	Open, uncontrolled	60	Twice or three times a week	180-200 mJ/cm ² followed by 50 mJ/cm ² increments until mild erythema	Complete repigmentation or up to maximum 2 yr: 68% (face) 57.9% (neck). 50% (trunk), limbs poorer results	
Kishan Kumar <i>et al</i> ^[20]	NB-UVB	Prospective, open, non-randomized	150	Twice a week	250 mJ/cm ² (150 mJ/cm ² for children) followed by 20% increments until perceptible erythema	> 75% repigmentation after maximum 1 yr treatment: 17.4%	Erythema, burning, pruritus: 7%. Xerosis: 6%

NB-UVB: Narrowband ultraviolet B.

of treatment was watched. Albeit some levels of repigmentations were seen in the total series of the NB-UVB bunch and 92% of those in the PUVA bunch, shading match was astounding in whole patients in NB-UVB, however it was so weaker with PUVA. The cosmetic prohibited shading planning had a tendency to bear notwithstanding taking after 12 mo of phototherapy discontinuance.

In a side-to-side examination work, a precisely break even with number of patients accomplished 0%-40%, 40%-60% and 60%-75% repigmentation following 60 sittings^[24]. The distinction in the frequency of symptoms, for example, erythema and rankling was not significant between the gatherings.

In a little review investigation, 70% of patients accomplished > 75% repigmentation following an average of 19 remedy sittings. Authors watched that more drawn out ailment length of time associated contrarily with reaction to therapy^[16]. In the same sitting, NB-UVB gave higher response contrasted and PUVA in bestowing strength in vitiligo and in pigmentation in both dynamic and permanent illness^[25].

Vitiligo for the most part starts in youth with half of the affected persons having ailment onset before the age of twenty years^[26]. Be that as it may, experience of NB-UVB in youth vitiligo is constrained. In a planned work, enlisted twenty six youngsters, of whom twenty finished the search. Following therapy for a most extreme of 12 mo, three quarters of the studied group had more than 75% repigmentation. After an average

introduction of 34 times, half repigmentation was accomplished. Median length of time of illness before treatment start was less for patients who had stamped to finish repigmentation contrasted and the individuals who had negligible or mild change. Excellent reaction was seen on the face and neck, trailed by the upper arms, thighs and trunk. In spite of the way that the makers assumed that NB-UVB is convincing and all around persevered in youngsters with vitiligo, the whole deal result for dermatologic issues when in doubt is unknown^[27].

NB-UVB offers significant points of interest over PUVA which might be essential in picking treatment for patient. It is less tedious, less demanding to perform, and does not require the associative organization of a photograph sensitizer that might bring about queasiness, waterfalls, phototoxic responses, and undesirable medication reactions^[25]. Different points of interest additionally incorporate the sheltered use in pregnant ladies and youngsters and truant medication expenses^[28,29].

However, short remission rate is one of the best disservices of NB-UVB contrasted and PUVA, regarding infirmities on palms and soles does not react to NB-UVB albeit such sickness can now and again react in youthful youngsters. In correlation, PUVA treatment is regularly viable at these locales as NB-UVB is less infiltrating than UVA radiation^[30,31].

NB-UVB vs broadband-UVB

NB-UVB has a moderately monochromatic range of

emission when contrasted and broadband-UVB (BB-UVB)^[32]. Erythema is more usually delivered by BB-UVB than NB-UVB, as NB-UVB is compelling at negligible erythema dosages considerably less than those utilized as a part of BB-UVB treatment^[33]. The TL01 light is around 5-10 overlay less strong than BB-UVB for erythema incitement, hyperplasia, edema, sunburn cell arrangement and langerhans cell exhaustion from the skin^[34].

NB-UVB is viewed as more powerful with fewer side effects contrasted and BB-UVB in treating a few ceaseless incendiary skin infections as psoriasis and vitiligo. Recently it has been ended up being better than BB-UVB in treatment of HIV-related eosinophilic pustular folliculitis with impressive achievement, particularly against the extreme tingle^[35].

Targeted NB-UVB treatment

Targeted phototherapy implies delivering light to localized diseased areas of skin involving less than 10% body surface area (BSA) and it can be combined with systemic treatments if needed^[36]. Since only the affected area is presented to radiation, more doses of radiation can be utilized to achieve better and faster results with lower total cumulative dose and hazards of phototoxicity. Also, it can be used to treat difficult to reach areas like skin folds.

Recent UV devices that discharge light successful for the improvement of vitiliginous patches in a targeted fashion are becoming popular. Among targeted phototherapy devices currently available, excimer laser has been shown to induce the most rapid onset of repigmentation in vitiligo. In addition to excimer laser a monochromatic excimer lamp has also been utilized in the treatment of vitiligo with almost comparable results^[37,38].

As far as the targeted UVB devices are concerned, the UV spectrum delivered varies from one machine to another. These devices include "BClear" that delivers BB-UVB, "multiclear" or "dualight" providing UVA and UVB combination and lastly "Bioskin", which gives a NB-UVB waveband peaking at 311 nm^[39].

Xenon chloride laser, popularly known as an excimer laser (EL), is a 308 nm laser that was initially used for treating psoriasis^[40]. Be that as it may, as its operational wavelength is near that utilized as a part of NB-UVB, it is utilized to regard vitiligo too. This laser offers the benefit of conveying high measurements of light to limited areas^[41,42].

It was initially utilized effectively in vitiligo by Baltás *et al*^[43] in 2001. In 2002 Spencer *et al*^[42] presumed that the level of repigmentation in a time of 2-4 wk is much higher than that accomplished with whatever other current vitiligo treatment. Taneja *et al*^[44] and Choi *et al*^[36] likewise demonstrated helpful results with excimer laser with non acral lesions reacting the best. Two reports contrasted the viability of excimer laser with NB-UVB, and found that the former brought about more huge and faster repigmentation^[45,46]. However, neither of these two

studies was controlled nor used a standardized scoring method.

The monochromatic excimer light (308 nm MEL) might introduce a few preferences over the laser. Firstly, it gives a bigger illumination field that empowers to treat bigger ranges at once. Secondly, bring down force thickness prompts diminished danger of mishaps because of overexposure, recommending a superior wellbeing profile. The excimer light was found to give proportional pigmentation as contrasted and an excimer laser. In 2003, Leone *et al*^[38] reported that 35/37 (95%) patients hinted at repigmentation inside of initial eight sittings of MEL and excellent and good repigmentation in 18 and 16 patients, respectively. They likewise demonstrated that 3 of their series who were resistant to NB-UVB phototherapy, indicated astounding repigmentation after 308 nm MEL treatment. They suggested this may be conceivable because of the distinction in the method of activity of these two sources, with 308 nm MEL gadget conveying higher vitality fluences to the objective tissue in less time when contrasted with NB-UVB devices.

The repigmentation rate was somewhere around 25% and half over the whole body, and somewhere around half and 75% for vitiligo injuries not situated at hard prominences or extremities^[47]. Interestingly, agents additionally noticed that MEL impelled more erythema than EL recommending that regardless of indistinguishable 308 nm crest wavelength, EL and MEL may have diverse photobiological properties.

Additionally, Shi *et al*^[48] likewise found that the repigmentation rates with excimer light were same as those with laser (79% vs 87.5%, $P > 0.05$). A review investigation of 80 patients with segmental vitiligo (SV) treated with EL demonstrated that 75%-99% repigmentation was accomplished in 23.8% of cases and 50%-74% repigmentation in 20% of cases^[49]. This report shows that other than surgical systems, EL may be a possibility for SV patients, with the level of repigmentation absolutely connecting with treatment span, combined measurements, and shorter malady duration^[49].

A recent study was conducted in 40 patients of "stable" vitiligo including under 5% BSA who were resistant to conventional oral/topical treatment options. They were treated with a focused on NB-UVB gadget twice-week by week for a most extreme of 30 sessions or until 100% repigmentation, whichever was come to first. Seventy-seven point five percent of cases accomplished pigmentation at a rate from half to hundred percent. Pigmentation started as ahead of schedule as the 3rd dosage now and again and by the 10th measurements in all responders. Best reaction was seen on the face and neck with 20 of the 31 injuries accomplishing 90%-100% repigmentation around there. There was not a correlation between the Length of time of the disease and the repigmentation accomplished. Focused on NB-UVB phototherapy is by all accounts a viable treatment choice in restricted lesion with a quick onset of repigmentation

appeared as right on time as 2nd week of therapy^[50].

Targeted BB-UVB vs targeted NB-UVB therapy

Very few studies utilizing broadband UVB exist. Asawanonda *et al*^[51] analyzed the repigmenting viability of targeted BB-UVB therapy with that of NB-UVB in an equi-erythemogenic manner. Twenty similar vitiliginous lesions from 10 patients were arbitrarily distributed to get either targeted BB-UVB or targeted NB-UVB treatment. Ultraviolet fluences were begun at half of the insignificant erythema measurements detected within the vitiliginous patches, then increased gradually, in the same manner, to ensure equi-erythemogenic comparison. Medicines were completed twice week after week for 12 wk. The outcomes demonstrate that review 1, *i.e.*, 15%-25% repigmentation, to review 2, 26%-50% repigmentation, happened in 6 of 10 subjects. Responses in terms of repigmentation, de-pigmentation, or lack thereof, were similar between lesions receiving broadband and NB-UVB phototherapy. Beginning of repigmentation happened as ahead of schedule as 4 wk of treatment in many subjects. Medicines were all around endured, with just negligible erythema and hyperpigmentation. They concluded that targeted BB-UVB produces comparable clinical reactions to targeted NB-UVB in the treatment of the non-segmental kind of vitiligo.

Combination therapy

The points of combination treatment are to lessen the reactions of phototherapy, by possibly encouraging a lower UVB combined measurements or number of medicines, and to enhance adequacy; this includes the simultaneous utilization of a specialists that might offer an added substance or synergistic effect^[52]. Similarity between medicines must be considered, as topical operators might have UVB blocking impacts; thus, it is for the most part exhorted that if topical specialists are utilized, they ought to be connected post-UVB presentation^[53].

Vitamin D analogs and NB-UVB

The blend of vitamin D simple and NB-UVB was utilized first by Dogra and Parsad^[54]. Decreased levels of vitamin D3 were observed in vitiligo patients and other co-morbid autoimmune conditions. A significant body of data suggests that vitamin D3 is strongly immunosuppressive and improves many Th1 triggered diseases, *i.e.*, it inhibits the Th1 phenotype and potentiates the Th2 phenotype; and that low levels are associated with autoimmune conditions including vitiligo. However, the cause of low vitamin D3 in patients with autoimmune conditions remains unknown^[55]. Some authors^[56] watched considerably better reaction with the blend contrasted and NB-UVB alone (in spite of the fact that not critical) in a side-to-side examination study. Likewise, others reported the adequacy of mix treatment of NB-UVB with calcipotriol in vitiligo and they recommended that phototherapy with NB-UVB in blend with topical

calcipotriol might prompt prior pigmentation with lower beginning aggregate NB-UVB radiation in subjects with vitiligo^[57,58].

On the other hand, some authors couldn't discover empowering contrasts in the rate of repigmentation^[59].

Topical calcineurin inhibitors and NB-UVB

Autoimmunity is most likely the major cause suggested for vitiligo. Its part in the disease is supported by discovery of organ-particular antibodies in the patients^[60]. Topical immunomodulators are discovered valuable in the treatment of vitiligo alone, and in addition in mix with NB-UVB. It was proposed that cooperation in the middle of pimecrolimus and keratinocytes, making a positive environment for melanocyte development and movement^[61].

Castanedo-Cazares *et al*^[62] and Nordal *et al*^[63] reported the viability of the combination in the treatment of vitiligo through the initiation of pathways impacting melanocyte movement and melanogenesis. They recommended that expansion of topical tacrolimus to NB-UVB ought to be further researched, considering its lower carcinogenic profile contrasted and systemic organization. Additionally, the utilization of tacrolimus might be valuable to counteract UVB-instigated erythema by restraining early-stage occasions of the provocative process^[64]. Most of the reports consolidating local calcineurin inhibitors with NB-UVB proved that the blend might expand the adequacy, and likely rush the reaction, just for facial sores.

Afamelanotide and NB-UVB

Afamelanotide, is a potent and longer-lasting synthetic analogue of naturally occurring α -MSH. Grimes *et al*^[65] showed in 4 vitiligo patients that combined treatment of NB-UVB and afamelanotide is likely to promote melanoblast differentiation, proliferation and eumelanogenesis leading to faster and deeper repigmentation (at least > 50%) in each case within 2 d to 4 wk.

In another recent study, patients with skin phototypes, III through VI and an affirmed conclusion of NSV that included fifteen percent to half of aggregate body area range were subjected to combination treatment ($n = 28$) vs NB-UVB monotherapy ($n = 27$). Following 30 d of NB-UVB therapy, 16 mg of afamelanotide was directed subcutaneously to the blend treatment amass month to month for 4 mo while NB-UVB therapy proceeded with; the second gathering kept on getting NB-UVB monotherapy. A blend of afamelanotide insert and NB-UVB phototherapy brought about clinically obvious, measurably critical predominant and speedier repigmentation contrasted and NB-UVB alone. Reaction was highly discernible in patients with skin types IV to VI^[66].

Fluorouracil and NB-UVB

In a recent study, various sessions of intradermal 5-fluorouracil have likewise appeared to enhance NB-UVB adequacy, with 48% of patients accomplishing > 75% repigmentation contrasted with 7% of patients

treated with NB-UVB alone^[67].

Oral or topical antioxidants and NB-UVB

The part of increased oxidative anxiety in the etiology of vitiligo has prompted the utilization of antioxidants orally and topically in the treatment of vitiligo^[68,69]. Topical preparations containing catalase and superoxide dismutase have been concentrated on with NB-UVB in a few case arrangement. Topical utilization of pseudocatalase (Mn/ethylenediaminetetraacetic acid-bicarbonate complex) and calcium in mix with decreased-measurements BB-UVB brought about total repigmentation on the face and dorsum of the hands in ninety percent of cases^[69]. Elgoweini and Nour El Din^[70] concluded that mean number of medicines required to accomplish > half percent repigmentation was diminished (sixteen vs twenty sessions) by adding oral antioxidants to NB-UVB. Dell'Anna *et al*^[71] found that a tablet containing vitamins E and C, alpha-lipoic corrosive, polyunsaturated unsaturated fats and cysteine monohydrate brought about more subjects accomplishing > 75% repigmentation contrasted with NB-UVB alone (47% vs 18%, $P < 0.05$). In another report, NB-UVB was joined with oral organization of polypodium leucotomus separate, which is known not anti-oxidative and immune-modulating characters. In the blend therapy bunch, a pattern towards an expanded repigmentation in the head and neck zone was watched, that almost came to measurable significance^[72].

Oral minipulse and NB-UVB

A previous study contrasted four different treatment gatherings of vitiligo patients with progressive course: Steroid oral minipulse (OMP) alone, betamethasone in a dose of 0.1 mg/kg body weight twice weekly on two continuous days for three months took after by decreasing of the dosage by 1 mg consistently over the accompanying three months, OMP with PUVA, OMP with NB-UVB, and OMP with BB-UVB. The outcomes demonstrated that OMP was not helpful all alone but rather had some quality as an enhancer treatment for PUVA and NB-UVB^[73].

Laser

Erbium laser dermabrasion has been speculated to bring about a more noteworthy profundity of radiation infiltration into the dermis, where it can animate melanocyte undifferentiated cells furthermore bring about conveyance of more prominent measurements of radiation^[74]. This standard was demonstrated successfully when generally UV-safe destinations on the hands, feet and hard protuberance were treated with NB-UVB with former Erbium laser dermabrasion. Measurably critical results were acquired with 46% of sores accomplishing > 50% repigmentation with going before 2940-nm erbium:YAG laser contrasted with 4.2% of control sores ($P < 0.0001$). Furthermore, unfavorable impacts like postponed recuperating (up to 21 d in 1 patient), edema going on for two through fifteen days when limits were dealt with, and hypertrophic scarring

hampered the general patient satisfaction^[74].

This study proposes a need to investigate the synergistic part of lasers with NB-UVB in the therapy of vitiligo, particularly on generally UV-safe locales.

Newer trends

Recently, home based NB-UVB regimens, using instruments like SS-01 UV phototherapy instrument, Dermfix 1000™ NB-UVB and Waldmann™ NB-UVB 109, have been attempted effortlessly of use at home, along these lines, maintaining a strategic distance from incessant visits to a healing facility based phototherapy unit more than a while. This modality makes phototherapy available to individuals who cannot afford this treatment because of logistical reasons; however, it may not be financially affordable by patients in resource poor developing countries. It is a useful option for localized lesions and can be used to target new lesions at the earliest. Shan *et al*^[75] reported excellent repigmentation in 27 of 36 cases with face and neck lesions, 16 of 43 cases with truncal vitiligo and 9 of 34 patients with limb lesions following treatment with SS-01 UV phototherapy. Lesions on the acral parts were, nonetheless, impervious to treatment.

Newer forms of unconventional phototherapy were endeavored in the management of vitiligo with changing outcomes. In a previous research, the authors^[76] looked at the response of skin taking after illumination with UVA1 (340–400 nm) and broadband noticeable light in typical people with skin sorts IV–VI. Utilizing diffuse reflectance accessories, the examiners demonstrated that melanin esteem expanded in a measurements subordinate way taking after UVA1 or noticeable light introduction. Be that as it may, in a late study, El-Zawahry *et al*^[77] contrasted UVA1 phototherapy and NB-UVB and reasoned that UVA1 was less effective than NB-UVB and along these lines had a constrained worth as a monotherapy in vitiligo.

A planned study utilizing a new multi-wavelength focused on Intense Pulse Light System UVA1-UVB in relationship with fluticasone cream was embraced. Eight of the ten patients who took an interest in the survey finished it. Four patients had grade 1 change (1%–25%); one had grade 3 (51%–75%); two had intensifying of the injuries after sun presentation; the last showed no response. The fundamental favorable circumstances of this strategy are that it is anything but difficult to do and it is focused to the skin lesions^[78].

It was demonstrated that unmistakable light created by a helium-neon laser (633 nm) could actuate melanocyte relocation and expansion^[79]. Few years later, Lan *et al*^[80] utilized the same laser light source to bring about repigmentation in SV. It is trusted that the dermatomal dispersion of SV suggests a neural dysregulation, forcing it somewhat diverse to cure than NSV. The helium-neon laser has been found to adjust the adrenergic dysregulation of cutaneous blood stream seen in SV^[81]. Taking after treatment with helium-neon laser, more than half repigmentation was noted in 60% of patients with

head and neck SV, repigmentation starting after 16-17 medications^[79,81].

Recently, Yu *et al*^[82] utilized 635 nm low-vitality laser for treating SV with the principle objective to distinguish components anticipating therapy result. In this study, 7 of 14 patients reacted to the treatment (reaction was characterized as accomplishing no less than 25% of repigmentation) accordingly affirming the effectiveness, albeit constrained, of noticeable light in SV remediation. Imperatively, the creators inferred that assessment of noninvasive cutaneous blood stream with and without earlier unmistakable light illumination on frosty focused on SV sores might serve as a treatment reaction indicator^[82].

Hartmann *et al*^[83] as of late attempted UVB extreme heartbeat light source with top outflow at 311 nm (Relume-Mode, Lumenis) in a right-left similar study where phototherapy was given once week by week on left side and tacrolimus was connected twice every day on right side. They reasoned that long haul treatment with both of the two modalities turned out to be equivalently compelling.

DISCUSSION

NB-UVB may exert its effects in vitiligo in a two-step process. Both may occur simultaneously. The first being the stabilization of depigmentation process and the second, the stimulation of residual follicular melanocytes^[84]. It is likely that NB-UVB, similar to PUVA therapy stimulates the dopa-negative, amelanotic melanocytes in the outer hair root sheaths, which are activated to proliferate, produce melanin, and migrates outward to adjacent depigmented skin resulting in perifollicular pigmentation^[85].

The helpful activity includes a mix of impacts in cell cycle energy, modifications in cytokine expression, impact on melanocytes and immunomodulation^[86,87].

MOLECULAR ASPECTS OF NB-UVB IRRADIATION

Urocanic acid

NB-UVB has been appeared to impel isomerization of urocanic corrosive (UCA), "a cutaneous photoreceptor", from trans to cis structure, which might be essential in the immunomodulatory impacts of TL-01^[86]. Cis-UCA has been appeared to stifle human natural killer cell action in a measurements subordinate manner^[56]. The safe concealment properties of cis-UCA might be because of tweak of cytokines, for example, tumor necrosis factor (TNF)- α , interleukin (IL)-10 and IL-12, and also LC depletion^[88]. A furthermore effort in the system of activity of cis-UCA incorporates the incitement of prostaglandins E2 (PGE2) generation^[89].

CELLULAR ASPECTS OF NB-UVB

NB-UVB induced apoptosis

The progress in using NB-UVB for treatment of numerous

provocative skin diseases is intellect to be through the inciting of apoptosis and incredible consumption of T cells. DNA harm is one of the real sub-atomic triggers for UVB-actuated apoptosis^[90]. Caspases, which are apoptosis related serine proteases inside of the cell, are enacted and give rise to a course of occasions which stimulate atomic buildup, DNA fracture, and breaking down of the cell^[87,91].

In caspase-dependent apoptosis, there are two primary pathways included: The natural pathway (mitochondrial/apoptosome pathway) in which cell passing happens through mitochondrial crumbling and the extraneous pathway (death-receptor pathway) in which coordinate enactment of death receptors by UVB is included in UV-prompted cell demise (Figure 2)^[92].

Demise receptors have a place with a super group of receptors communicated on any cell and are described *via* conveying an intracellular passing domain^[93]. This family involves CD95 (Fas), the TNF receptor and the TNF-related apoptosis-affecting ligand receptor^[94].

Impelling of apoptosis by UVB, in any case, is not particular for keratinocytes but rather influences different cells also including lymphocytes and macrophages^[95]. Little information has been created in regards to NB-UVB in keratinocytes. NB-UVB affects apoptosis in T lymphocytes more effectively than BB-UVB^[91].

It is conceivable that UVB-prompted lesional T cell apoptosis is interceded by implication by CD95L expression on neighboring keratinocytes or by direct cytotoxic effect of UVB^[96].

NB-UVB induced immunosuppression

Antigen presenting cells: Janssens *et al*^[97] showed that the impact of UVB on the capacity of epidermal langerhans cell (LCs) demonstrated a checked concealment of blended epidermal cell lymphocyte response (MECLR) which is utilized as a measure of insusceptible responsiveness. The decrease in MECLR was not paralleled by the progressions in LCs numbers or HLA class 2 expression. On the other hand, Aufiero *et al*^[91] affirmed that different exposures of NB-UVB diminished the thickness of LCs by 20% however on introduction to BB-UVB, LCs morphology was unaffected. Thus, NB-UVB decreases the quantity of both T lymphocytes and LCs.

Natural killer cells: NB-UVB radiation causes a measurement subordinate hindrance of natural killer cell action, in relationship with a lessening in NK-associated cytokines^[98-100].

Cytokine induction

Intense presentation to high measurements of NB-UVB appears to smother sort 1 (IFN- γ) and associatively incite sort 2 (IL-4) cytokine expression while incessant introduction to low dosages of NB-UVB comes about prevalently in the concealment of IFN- γ expression^[101]. Piskin *et al*^[102] also, confirmed that the declaration of IFN- γ actuating cytokines (IL-12, IL-18, IL-23 and IL-27) was diminished after chronic NB-UVB presentation.

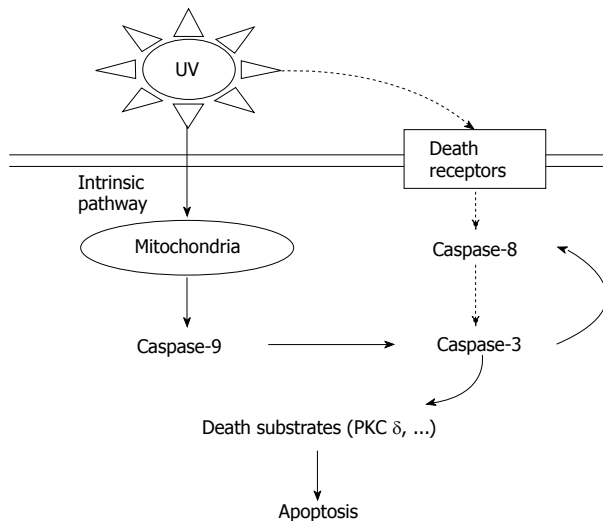


Figure 2 Proposed signaling pathway for ultraviolet-induced apoptosis in human keratinocytes (Sitailo *et al*^[92]). UV: Ultraviolet.

UVB also fortifies keratinocytes to discharge the immunosuppressive solvent cytokines including IL-10 which repeals the capacity of LCs to present antigens to Th1 clones and even tolerizes them. Therefore, IL-10 moves the resistant reaction from a Th1 into a Th2 reaction^[34].

Lebwohl and Ali^[103] suggested that UVB-prompt concealment of Th2 chemokine creation proposes that UVB introduction to the skin smothers invasion of Th2 cells to the epidermis, along these lines, both BB-UVB and NB-UVB are thought to be viable for the treatment of different Th2-interceded or Th2-penetrating skin illnesses. What's more, the impacts of NB-UVB on constituent cells of skin other than keratinocytes might take an interest in the aggregate restorative activity.

UVB radiation has been appeared to be an intense inducer of TNF- α quality expression which intervenes motioning by human keratinocytes^[104]. It is recommended that NB-UVB modifies the creation of cytokines and chemokines as a joined consequence of its immediate and aberrant TNF- α -interceded effects^[105].

NB-UVB phototherapy expands union of IL-1, TNF- α and LTC-4, which incite melanocyte proliferation and relocation and melanin formation^[16]. Furthermore, the parts of IL-1 and TNF- α in synthesis of melanin are disputable and opposing, as reported in a few researches^[104,106].

It was suggested that TNF- α hinders the appearance and movement of tyrosinase, the main chemical in melanin blend. It also provoke limitation of pigment formation which is optional to initiation of atomic variable κ B. IL-1 animates combination of endothelin-1, which is mitogenic and melanogenic^[107]. The disagreement is that IL-1 β has been found to lessening expansion of melanocytes and melanogenesis, while IL-1 β diminishes melanocyte tyrosinase movement with no impact on multiplication^[108]. Imokawa *et al*^[109] watched expanded articulation of endothelin-1, IL-1 and tyrosinase in human keratinocytes *in vivo* and *in vitro* after UVB

illumination, recommending the conceivable component of repigmentation. Arrival of PGE2 and PGF2 is other system of activity of phototherapy^[110]. PGE2 is incorporated in the skin and manages melanocyte and Langerhans cell work, and advances melanocyte proliferation^[111].

Skiba *et al*^[112] inspected the impact of UVB light on cytokines (TNF- α , IL-10, IL-1 β , FasL) by illuminating the unconstrained changed human epidermal cell line HaCaT to UVA (2000 and 8000 J/cm²) or UVB (200-2000 J/cm²) irradiation. RNA was removed from cells at 0, 4, 8, 12, 16, 24, 48 h post light for consequent ongoing PCR enhancement. They found that, TNF- α mRNA amount were promptly up managed (0 h) next light ,with highest incitement at 8 h post 2000 J/m² UVA and 200 J/m² UVB illumination.

Hino *et al*^[105] explored the impact of NB-UVB on creation of chemokines and proinflammatory cytokines by keratinocytes in examination with BB-UVB. They utilized the same method as that of Skiba *et al*^[112] and affirmed the past consequences of the expanded generation of TNF- α after UVB light however the increased impact of NB-UVB was not as much as that of BB-UVB.

Immuno-histochemical examination was done, to evaluate the TNF- α expression in lesional and perilesional skin when contrasted with ordinary control skin, prior and then afterward NB-UVB treatment. At standard, there was a critical increment of TNF- α in vitiligo injuries contrasted and perilesional and solid skin which proposes a conceivable inclusion of this substance in the loss of pigmentation in vitiligo. The expansion in TNF- α expression after NB-UVB phototherapy recommends another part in repigmentation^[106].

Effects on pigmentary system

Introduction to UV light results in expansion in the quantity of dynamic melanocytes, the rate of melanin combination, and the exchange of shade granules to encompassing keratinocytes^[113].

Sunlight exposure causes expanded levels of coursing MSH and ACTH with expanded skin darkening^[114]. It was watched that UVB and MSH act synergistically to build melanin content in the skin^[115].

UVB light causes lipid peroxidation took after by era of free radicals and consumption of the intracellular pool of diminished glutathione (GSH), bringing about oxidative anxiety. There is confirmation that the dynamic oxygen species created by UVB light might assume a part in melanogenesis and directs the epidermal melanin unit by expanded articulation of melanogenic α -MSH and ACTH peptides^[116].

NB-UVB might apply its belongings in vitiligo in a two-stage process. Both might happen all the while. The primary being the adjustment of depigmentation procedure and the second, the incitement of leftover follicular melanocytes^[84]. However, the molecular mechanisms of these processes remain unraveled^[117].

In ordinary melanocytes, the coupling of development

components, for example, bFGF HGF, and ET-1, to receptors on melanocyte results in the quick actuation of the mitogen-activated protein kinase (MAPK) and ribosomal S6 kinases^[118]. In melanocytes, a solitary development element is adequate to stimulate the MAPK course however is not ready to support melanocyte expansion or reasonability. No less than two distinctive development variables in mix are important to affect melanocyte expansion^[118].

Wu *et al*^[119] showed that NB-UVB irradiation stimulated the proliferation of melanocytes with a critical increment in the arrival of bFGF and ET-1 by keratinocytes. bFGF has been perceived as a characteristic mitogen for melanocytes, which improves the development and survival of them. ET-1 invigorates DNA union in melanocytes, and has a synergistically stimulatory impact on bFGF-activated DNA amalgamation of these cells.

Kawaguchi *et al*^[120] reported that NB-UVB is viable in stimulation of proliferation and differentiation of functioning melanocytes in epidermis. The precursor melanocytes seem to proliferate into mature pigmented melanocytes after UV exposure. They differentiate into TRP-2 positive melanocytes by the activation of c-kit receptor then become TRP-1 positive melanocytes.

NB-UVB animates expanded articulation of the POMC quality which is joined by creation and arrival of α -MSH^[119,121].

ADVERSE EFFECTS OF NB-UVB

Acute effects

Erythema: NB-UVB is moderately sheltered, and this is one of the fundamental purposes behind it being viewed as the first decision of treatment of summed up vitiligo in grown-ups, and also in youngsters. Erythema is the most critical intense symptom of NB-UVB, and the frequency differs somewhere around 10% and 94% according to the pharmaceutical style and meaning of erythema^[120]. Be that as it may, asymptomatic powerless redness is relied upon to be basic, as this is the final stage for NB-UVB in vitiligo. A more noteworthy extent of cases create erythema as contrasted and PUVA, yet they are less inclined to pulsate therapy because of a smaller span of NB-UVB-prompted redness.

Blistering: Lesional blistering following NB-UVB treatment is extraordinary, depicted for the most part in psoriatic plaques, and amid treatment of pityriasis rubra pilaris. The instrument of rankling is misty. George and Ferguson^[122] proposed that inside psoriatic plaques might be because of fast loss of scales, presenting lesional skin to a "phototoxic" measurements in connection to contiguous moderately photograph shielded skin causing rapid loss photoprotection from the lesions thus exposing them to a big dose of radiation.

Pruritus: Albeit additionally a typical symptoms of TL-01 treatment, it now and again mirrors the hidden infection forms^[123]. Wallengren^[124] explained this phenomenon

by the possibility of the role of prostaglandin E2 which induces itch and potentiates itch induced by histamine release.

Infection: Reactivation of herpes simplex infection can happen with NB-UVB therapy and safety oriented procedures ought to be brought in those with a background marked by this condition^[125]. The possible impacts of NB-UVB on the eyes, specifically presentation related conjunctivitis or keratitis; should be considered if treating patients with periocular skin inflammation, despite the fact that treatment can be performed deliberately with the eye close as opposed to with goggles in this circumstance^[126].

Chronic effects

Photoaging: Constant NB-UVB introduction is liable to increment photoaging. There is an expanded era of ROS in skin upon introduction to NB-UVB. These ROS are accepted to be basic go between of the photoaging process. ROS can adjust proteins in tissue to frame carbonyl subsidiaries, which aggregate in the papillary dermis of photodamaged skin^[127].

Carcinogenesis: Actuation of the decay brought on by UVB is settled. This light is a completed disease bringing about specialists and TL-01 has been seemed to provoke DNA hurt in individual's tissues and animal examples. In a final knockout mouse case, change of hurtful cutaneous neoplasms were essentially more noteworthy for NB-UVB than BB-UVB taking after similar dose presentation^[128]. The development of cyclobutane pyrimidine dimers (CPD) was basically ascending with NB-UVB, however those of radiation inducing and 8-oxoguanine were on a very basic level more after BB-UVB. These discoveries recommended the nearby connection in the middle of CPD and the higher cancer-causing capability of NB-UVB. In any event in the setting of psoriasis, it is suggested this hindrance of NB-UVB opposite BB-UVB could be offset the way which the aggregate measurements wanted for leeway of psoriasis is less than that for BB-UVB. The main accessible creature information required perception for a long time^[129].

However, there were conflicting data that NB-UVB has been appeared to be less^[5] just as^[130], and more cancer-causing than BB-UVB^[6]. Likewise NB-UVB related skin tumor danger might be not as much as that with PUVA^[22]. Rivard and Lim^[131] reported that the danger of improvement of nonmelanoma skin growth has been assessed to be under 2% every year which is not as much as that of PUVA. Black and Gavin^[132] have recommended that at present, NB-UVB has all the earmarks of being a moderately safe treatment methodology; in any case, consistent long haul follow-up is crucial.

The world writing was methodically explored to upgrade data on the skin tumor hazard with UVB phototherapy, and strategies suggested to reduce carcinogenicity during phototherapy^[133].

Skin sparing strategy: Parts of the body where no sores are available (particularly the face) ought to be protected amid medications. Likewise, parts that have repigmented palatable ought to, if conceivable, be protected amid consequent medications (for instance by wearing trousers when in doubt, don't react to phototherapy)^[134]. Privates ought to be likewise protected in light of the fact that these regions, when in doubt, don't react to phototherapy and genital tumors have been seen after PUVA treatment^[22].

Prevention of pointless presentation to characteristic daylight on both treatment and non treatment days and the utilization of UV-blocking specialists on sun uncovered ranges. Also, the use of combined treatments with other modalities to reduce the cumulative dose^[135].

Proper patient selection: And using protocols suitable to each patient with lower cumulative doses^[132].

Chemoprevention: This term is used to minimize the risk of carcinogenesis to UV therapy by using non toxic diet with antitumour properties. For example, black teas extract which contains dimeric faranols, and polymeric polyphenols. These are effective in reducing UVB and UVA mediated DNA damage and expression of early response genes^[136].

Light dose adjustment: This may be the best approach to obliging the carcinogenesis of NB-UVB. Close erythemogenic measurements of NB-UVB clear psoriasis quicker than lower dosages of NB-UVB, but the later regimen is similarly powerful with just somewhat more medicines^[6].

Less frequent doses: Dawe *et al*^[137] thought about thrice-weekly and five times week after week medications utilizing half body correlation study. Notwithstanding no critical contrast in extent of patients who indicated skin clearing and time to freedom were found between the two regimens. Besides, the five week by week bunches got higher aggregate measurements and had more scenes of very much delineated erythema.

ADVANTAGES OF NB-UVB PHOTOTHERAPY

From the advantages of NB-UVB phototherapy over other phototherapeutics: No topical or oral drug, tests, or unique glasses are needed^[34]. Quicker reaction than expansive band UVB and like PUVA^[138]. Number of medicines required for clearing is by and large not as much as wide band UVB and PUVA^[22]. Safe for youngsters, pregnant ladies and lactating mothers^[139]. Eliminating erythemogenic wavelengths underneath 311 nm grants higher intensities and more presentation times bringing about most extreme advantage from phototherapy and a shorter course of treatment^[22,32].

Longer reduction periods after treatment like those with PUVA treatment and particularly better than BB-UVB treatment^[33]. Studies show 38%-40% of NB-UVB

treated patients requires no extra treatment for no less than one year^[140].

DISADVANTAGES OF NB-UVB PHOTOTHERAPY

Because of the diminished force of tight band contrasted with expansive band, more lights are expected to give auspicious treatment. Standard wide band frameworks have 8 to 16 lights, though limit band frameworks need 24 to 48 lamps^[141]. Additionally NB-UVB lights seem to have a shorter future than expansive band and subsequently, require more continuous substitution. NB-UVB light lodges costs including the lights are a great deal more expensive^[34]. Erythema is less unsurprising than with expansive band UVB, however it might be more extraordinary and steady. Frequently lesional just^[8].

THE PERSONAL SATISFACTION AFTER NB-UVB TREATMENT

Vitiligo is an illness with significant restorative and ensuing psychological sway, instead of physical inability. Most of the researches carried out yet have evaluated the viability of NB-UVB in the change of restorative distortion - that is, a diminishing in the range of depigmentation. In spite of the fact that it is normal to trust that repigmentation taking after NB-UVB would enhance the personal satisfaction in vitiligo patients, there is insignificant target appraisal to such an impact. In an investigation of review configuration, Tjioe *et al*^[142] surveyed the personal satisfaction in vitiligo individuals after therapy with NB-UVB. Despite the fact that the patients evaluated their wellbeing to be by and large great to fantastic, phototherapy represented just a little change in a minority of patients as a rule prosperity. The principle issue of phototherapy in reasonable cleaned people is conspicuousness of the vitiligo injuries resulting in pigmentation of the encompassing typical skin demanding a more noteworthy level of disguising unto total repigmentation is accomplished in the sores. In a report in youngsters, personal satisfaction evaluated by the Children's Dermatology Life Quality Index (CDLQI) did not lessen altogether in kids having under 25% repigmentation, whereas the diminishment was noteworthy in the individuals who had more than 25% pigmentation with a corresponding abatement in CDLQI with change evaluation of repigmentation^[133].

CONCLUSION

Albeit various administration alternatives exist for vitiligo, UVB phototherapy is for the most part the treatment of decision as it is compelling as well as has a great danger to-advantage proportion. Ordinary BB- and NB-UVB is generally accessible and helpful especially in far reaching illness, despite the fact that NB-UVB has been all the

more broadly concentrated on with demonstrated viability. Combined treatments are likewise helpful and might give faster repigmentation and treat vitiligo with an added substance system of activity than UVB phototherapy. Progresses in innovation might prompt the proceeding with utilization of UVB phototherapy as a remedy for vitiligo through the improvement of complex gadgets and conveyance frameworks and in addition creative application strategies. These will give expanded helpful choices to all vitiligo patients, especially those with recalcitrant disease.

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Pediatric ocular rosacea, a misdiagnosed disease with high morbidity: Proposed diagnostic criteria

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Abstract

Ocular rosacea is an important and underdiagnosed

chronic inflammatory disorder observed in children. A clinical spectrum ranging from chronic eyelid inflammation, recurrent ocular redness, photophobia and/or hordeola/chalazions and conjunctival/corneal phlyctenules evolving to neovascularization and scarring may occur. Visual impairment and consequent amblyopia are frequent and corneal perforation although rare is the most feared complication. Ocular manifestations usually precede cutaneous lesions. Although few cases of pediatric ocular rosacea (POR) have been reported in the literature, many cases must have been underdiagnosed or misdiagnosed. The delay in diagnosis is greater than one year in the large majority of cases and may lead to serious ocular sequelae. This review aims to highlight the clinical features of POR, its epidemiology, easy diagnosis and effective treatment. We also propose new diagnostic criteria, in which at least three of the five clinical criteria must be present: (1) Chronic or recurrent keratoconjunctivitis and/or red eye and/or photophobia; (2) Chronic or recurrent blepharitis and/or chalazia/hordeola; (3) Eyelid telangiectasia documented by an ophthalmologist; (4) Primary periorificial dermatitis and/or primary features of rosacea; and (5) Positive familial history of cutaneous and/or ocular rosacea.

Key words: Ocular rosacea; Diagnostic criteria; Demodex folliculorum; Leukoma; Pediatric; Blepharoconjunctivitis; Chalazia

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Core tip: Ocular rosacea is a chronic inflammatory disorder with a clinical spectrum ranging from chronic eyelid inflammation, recurrent ocular redness, photophobia and/or hordeola/chalazions and conjunctival/corneal phlyctenules. Although few cases of pediatric ocular rosacea (POR) have been reported in the literature, many cases must have been underdiagnosed or misdiagnosed. This delay in diagnosis may lead to serious ocular sequelae. This review aims to highlight the clinical features

of POR, its epidemiology, new diagnostic criteria, treatment and outcomes.

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INTRODUCTION

Rosacea is a chronic condition affecting the facial and ocular surface tissues, particularly common in the fair-skinned population^[1-4]. The American National Rosacea Society developed a classification system that became the standard one. According to the patterns of signs and symptoms, four major clinical subtypes of rosacea are described: Erythematotelangiectatic, papulopustular, phymatous and ocular rosacea. In children, the phymatous type is not seen^[1-4]. These subtypes may be discrete variants or may be progressive from one to another, and they can also coexist. Ocular rosacea is one of the four described types of rosacea, characterized by involvement of eyelids, conjunctiva and corneal tissue^[1-4].

The prevalence of ophthalmic involvement in rosacea is probably higher than previously presumed and it varies considerably between ophthalmic and dermatological studies^[2,3,5]. In most adult cases, ocular manifestations are preceded by cutaneous signs, making the diagnosis easier. However, in pediatric ocular rosacea (POR) the ocular involvement may precede dermatologic manifestations in more than half of the patients^[5-8], delaying the diagnosis. The mean delay between disease onset and the diagnosis is greater than one year in most case series^[6,8-11], and greater than two years in more than half of cases^[6,8-10]. Before the established diagnosis, many patients are seen by multiple ophthalmologists and/or others clinicians and receive various types of therapy, including topical antibiotics, topical corticosteroids, lubricants and antiallergic drops, without success^[6,8,12,13]. In fact, the management must be multidisciplinary, including dermatologists, ophthalmologists and pediatricians.

The non-recognition of POR can also be a result of the varied names adopted in the literature and the lack of overall consensus: Chronic blepharokeratoconjunctivitis^[6,9-11,14-18], blepharokeratitis^[10], chronic phlyctenular keratoconjunctivitis^[8-10,18], phlyctenular blepharokeratoconjunctivitis^[10,14,18], and meibomitis-related keratoconjunctivitis^[19].

The main aim of this review is to make the children's health care providers aware of POR, by highlighting its clinical features, epidemiology, easy diagnosis and treatment. We also propose POR criteria.

EPIDEMIOLOGIC DATA

Few cases of POR have been reported in the literature.

In 13 published series^[5-17], a total of 259 patients were found and the number of patients in each varied between 3^[16] and 51^[15]. In another series, the largest ever published about POR, the sample included 615 cases, most of them described as mild, by Gupta *et al.*^[18] in 2010. In others studies, the number of cases was smaller probably because only severe cases were reported^[5-17].

POR is mostly diagnosed by ophthalmologists^[6,9,11,14,15], making this condition rare for other physicians and is underdiagnosed or misdiagnosed by them^[5-13,15,16]. In two tertiary centers of ophthalmology, in Philadelphia^[10] and in New Delhi^[18], chronic blepharokeratoconjunctivitis was the reason for referral in 15% and 12.3% of all children, respectively.

In the 259 patients of the 13 series^[5-17], 162 are girls (62.5%) and 97 are boys (37.5%), the opposite of what was found by Gupta *et al.*^[18] (37.5% vs 62.5%).

The median age of onset in five of the 13 series (122 patients) varied between 3.2 years and 7.0 years, with extremes of 1 mo and 17 years^[6,8,9,11,17]. There is a significant delay in diagnosis, often more than two years, justifying the median age at presentation in tertiary centers, between 4.6 years and 10.2 years^[6,7,11,18].

A positive family history for rosacea was found in nine of the 34 patients of two series (26.5%)^[5,8]. However, in most series family history wasn't reported. Since children with rosacea are more likely to have familial rosacea^[1,8], it is important to obtain this clinical data, which can help suggesting the diagnosis.

Bamford *et al.*^[20] demonstrated that having a hordeolum during childhood predisposes for rosacea in adulthood, underlying the close relationship between ocular and cutaneous inflammation. Ocular rosacea may occur without cutaneous manifestations and in individuals with any subtype of rosacea, although it is noteworthy that 50% of patients with erythematotelangiectatic and papulopustular types have eye inflammation^[1,5].

Fair-skinned children of European descent are more commonly affected, although any ethnic group can be afflicted^[1,4,5,8,12].

OUR EXPERIENCE IN POR

Since July of 2009, we have diagnosed and treated eight cases of POR: Three males and five females. They were referred to our tertiary Pediatric Rheumatology and Ophthalmology Units due to chronic red eye of unknown etiology, most of them after a medical peregrination and multiple ineffective topical treatments.

Their median age was 10 years (3-16 years) with an established diagnosis two years after the first symptoms (0-7 years); the mean previous medical consultations was eight (0-30 consultations), including at least one evaluation for an ophthalmologist in each (maximum of 13 different ophthalmologists). Two children have evolved to leukomas (Figure 1) and a decrease in visual acuity (7/10 and 8/10 respectively), what are persistent sequelae. We have already published the first two cases diagnosed at our unit^[21].

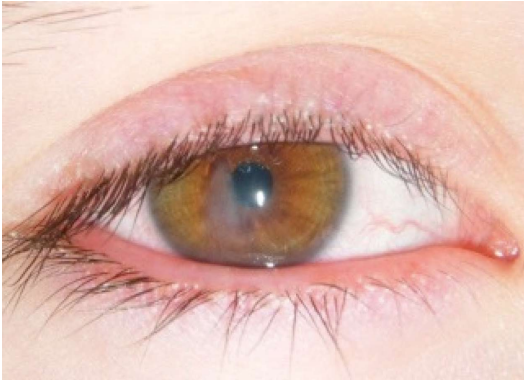


Figure 1 Sequelae of pediatric ocular rosacea: Leukoma.



Figure 3 Blepharitis in pediatric ocular rosacea.

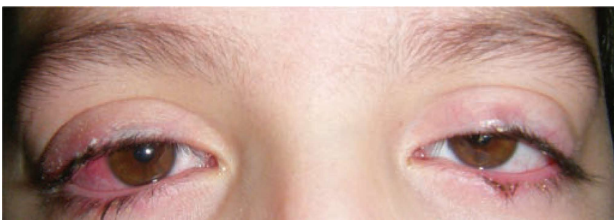


Figure 2 Chronic conjunctivitis and chalazia in pediatric ocular rosacea.

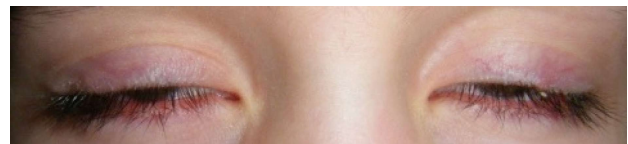


Figure 4 Telangiectasias and erythema of the lid margin in pediatric ocular rosacea.

ETIOLOGY, PATHOPHYSIOLOGY AND HISTOPATHOLOGY

The exact etiopathogenetic mechanism of rosacea and OR remains unknown. There are probably different regulatory systems involved^[3-5,22]. The infection by microbial organisms may have an important role. In OR, *Demodex folliculorum* mites, a common inhabitant of normal human skin, possibly represents a contributing cofactor to the inflammatory reaction seen in both cutaneous and ocular disease^[2-4,22,23].

Recently, bacterium *Bacillus oleronius* has been isolated from *Demodex folliculorum* mites and found to be responsible to trigger an immune system response. These seem to have a correlation with facial rosacea and OR^[1,24].

Gastric coinfection with *Helicobacter pylori* has also been implicated, since this bacteria has the ability to produce flush-inducing toxins^[3,4,7,22,23]. *Staphylococcus aureus* and *Staphylococcus epidermidis* are common organisms cultured from conjunctival or lid swabs, but their relationship with OR is questionable^[7,11,12].

Recent studies focus on the role of bacterial lipases and interleukin-1 alpha and elevated concentrations of promatrix metalloproteinases in the blepharitis and corneal epitheliopathy, respectively^[4]. Promatrix metalloproteinases are degrading enzymes responsible for the inferior corneal stromal thinning^[4].

Rosacea induces vasodilation with increased blood flow and vessel permeability leading to erythema, telangiectasias and lymphedema of the affected tissues, especially in the eyelids^[4]. The histopathological changes are unspecific, showing perifollicular infiltrates consisting

of lymphohistiocytes, epithelioid and giant cells^[16].

CLINICAL MANIFESTATIONS

The clinical spectrum and severity of POR is variable, depending on the involvement of eyelids, conjunctiva, cornea and other ocular findings^[3,4,6]. The first manifestations of POR can be chronic conjunctivitis, recurrent hordeola and/or chronic chalazia (Figure 2)^[5-8,11,16,20], which are quite frequent in childhood, explaining the common delay in the diagnosis of this condition. Nevertheless, POR is often silent, painless and has unspecific clinical manifestations^[2-6,12,16]. Table 1 shows the different ocular findings in POR.

The most common manifestations are blepharitis (Figure 3), recurrent hordeola/chalazia (Figure 2), telangiectasias of the lid margin (Figure 4), dry eye, conjunctivitis and keratitis, frequently in association (blepharoconjunctivitis, blepharokeratoconjunctivitis)^[2-6,8,10,15]. The typical clinical picture is a long history of hyperemic conjunctiva and intense photophobia associated with chronic blepharitis, explaining why POR is frequently called blepharoconjunctivitis^[6,11,19].

Combining 12 series, including 245 patients, 185 (75.5%) had bilateral involvement, generally asymmetrical^[5,6,8-17]. In the Gupta *et al*^[18] series only 47.5% had bilateral involvement.

Eyelid involvement may precede the other features in months to years, because it is primarily an eyelid margin inflammation, such as blepharitis or meibomitis^[4-6,8,11,13]. Corneal and conjunctival are secondarily involved.

The ocular symptoms include foreign body sensation, pain, burning, redness, photophobia and epiphora^[3-6,8,11,19]. As a consequence of the long diagnostic delay, more than a half of the children have already corneal injuries at diagnosis, such as punctate epithelial erosions,

Table 1 Different ocular findings in pediatric ocular rosacea^[1-8,10-19]

Eyelid: Telangiectasias and erythema of the lid margin, meibomian gland dysfunction, anterior blepharitis, recurrent chalazia/hordeola, madarosis (loss of eyelashes), trichiasis
Conjunctiva: Interpalpebral or diffuse hyperemia, papillary and/or follicular reaction, pinguecula, scarring
Cornea: Punctate erosions, pannus, superficial neovascularization, lipid deposition, spade-shaped infiltrate, scarring, thinning, ulceration, perforation, phlyctenula
Sclera: Episcleritis, scleritis
Insufficiency of tear film (dry eye) with abnormal Schirmer test
Uvea: Iritis (rare)

Table 2 Differential diagnosis of pediatric ocular rosacea^[2-4,8,17]

Chronic conjunctivitis (viral, allergic, atopic)	Medication toxicity
Keratoconjunctivitis sicca	Interstitial keratitis
Meibomitis	Infectious keratitis (herpes simplex)
Recurrent hordeola/chalazia	Sterile or bacterial corneal ulcers
Staphylococcal blepharoconjunctivitis	Auto-immune diseases
Seborrheic blepharoconjunctivitis	Sarcoidosis

subepithelial infiltrates, corneal phlyctenules, marginal keratitis, ulceration and corneal opacity^[8,11,13]. Pediatric corneal involvement tends to be central or paracentral^[6].

Depending on the severity, conjunctival and/or corneal phlyctenules may be present in 5.5%^[18] up to almost 40%^[8, 11,15].

The primary features of pediatric facial rosacea are chronic facial flushing, non-transient erythema, papules and pustules (limited to the cheeks, chin and nasolabial areas), telangiectasias, idiopathic periorificial dermatitis and the ocular and periocular signs previously described^[1,4,5,16]. Onset and severity of POR is not associated with the cutaneous signs^[2,3,13].

DIFFERENTIAL DIAGNOSIS

As previously mentioned, symptoms of POR aren't always specific and other ophthalmic disorders may present with similar findings, so the differential diagnosis includes a broad spectrum: Chronic conjunctivitis (viral, allergic, atopic), keratoconjunctivitis sicca, meibomitis, recurrent hordeola/chalazia, staphylococcal or seborrheic blepharoconjunctivitis, medication toxicity, interstitial or infectious (herpes simplex) keratitis, sterile or bacterial corneal ulcers, auto-immune diseases, sarcoidosis, among others (Table 2)^[2-4,8,17].

PROPOSED CRITERIA FOR POR

There are no specific clinical signs neither laboratory test nor histopathological markers for POR^[2-5,12]. Chamaillard *et al*^[5] and Hong *et al*^[16] have proposed "dermatologic and ophthalmologic criteria for childhood rosacea". However, in these clinical criteria four of five are cutaneous manifestations^[5,16]. Cetinkaya *et al*^[13] have also proposed the "pediatric acne rosacea diagnostic criteria" as a combination of meibomian disease, chronic blepharitis,

recurrent chalazia and chronic symptoms of photophobia, ocular irritation and redness, with or without corneal vascularization, that do not respond to routine medical treatment^[13]. For Léoni *et al*^[7], the diagnostic criteria of POR requires two ophthalmologic and/or two dermatologic criteria.

Considering the above mentioned publications^[5,7,13,16], in Table 3 we propose a new diagnostic criteria for POR. As in the previous proposed diagnostic criteria^[5,16], ocular redness may be absent. The diagnosis of POR should be multidisciplinary, with the contribution of dermatologists, ophthalmologists and pediatricians. The presence of lid margin telangiectasia and erythema, together with meibomian gland dysfunction (chronic chalazia) and a long history of ocular irritation should suggest the diagnosis of POR^[8,9,12-14], especially if there is no response to routine medical treatment^[13].

TREATMENT

The initial therapeutic approach should always include local measures, such as daily warm compresses, eyelid hygiene with neutral baby shampoo and liquefaction and removal of the thick meibomian gland secretions^[1-4,8,10,11,13,15]. Prolonged topical erythromycin ointment or, more recently, azithromycin 1.5% eye drops may be useful and effective in mild cases and in association with other treatments^[14]. Although very few publications support their efficacy and its administration in children is difficult, these eye drops are usually used^[16]. Doan *et al*^[14] described their experience with topical 1.5% azithromycin eye drops (monotherapy) being superior to systemic erythromycin and considered it as a first-line therapy.

Children that prove to be intolerant to prolonged topical treatment or with severe ocular involvement and/or both severe cutaneous and ocular rosacea must be treated with systemic antibiotics associated to topical care^[3,5-7,12,13]. Tetracycline and doxycycline, normally used in adults, are inadvisable in children younger than 7-8 years due to their potential bone toxicity and dental staining^[1,3-6,12]. Alternative safe and effective options are: Erythromycin (30-50 mg/kg per day, three times a day), clarithromycin (15 mg/kg per day divided in two doses) or azithromycin (10-12 mg/kg per day, one dose)^[1,6,10,11,13,17]. Treatment with oral metronidazole is another possibility, but its frequent neurologic adverse effects, particularly peripheral neuropathy, forbids prolonged therapies^[4,5,7,16]. Effective

Table 3 Proposed diagnostic criteria of Coimbra for pediatric ocular rosacea

Chronic or recurrent ¹ keratoconjunctivitis and/or red eye and/or photophobia
Chronic or recurrent ¹ blepharitis and/or hordeola/chalazia
Eyelid telangiectasia documented by an ophthalmologist
Primary features of pediatric rosacea (facial convex areas with chronic flushing and/or erythema and/or telangiectasia, and/or papule, pustules in cheeks, chin, nose or central forehead and/or primary periorificial dermatitis)
Positive familial history of cutaneous and/or ocular rosacea

Diagnosis: ≥ 3 criteria; ¹Chronic (≥ 2 mo); Recurrent (≥ 3 episodes lasting > 4 wk in 12 mo).

amoxicillin treatment has also been described^[15].

In children older than eight years old the cyclines can be used as first systemic therapy: Minocycline, doxycycline^[8,13,25]. After remission, prolonged treatment with doxycycline 40 to 100 mg once or twice daily is a good option^[4,8,12,13,25].

The recurrence rate is high, especially within the first three months of treatment if systemic therapy is tapered too quickly^[4,7,8,10,12]. Hence, therapeutic success is directly related to its duration, by reducing the number of recurrences. Prolonged treatments (over three months) may be required^[6,8,10,13-16], with some publications recommending systemic antibiotic for at least six months^[10] and others for a minimum of 12 mo^[13]. Some patients will need oral antibiotics during several years, but most children may be tapered off within six months of treatment^[6,10].

Intermittent treatments are necessary if shorter periods of systemic antibiotics are used^[5,7,11]. Since long-term use of oral antibiotics may be problematic, it has been suggested that after six to twelve months of treatment oral therapy should be tapered slowly^[4,8]. Some authors suggest that low maintenance dosages can be taken indefinitely^[4], but this is questioned by others given its subtherapeutic dosages^[16].

Topical (ocular) corticosteroids can prove useful for short-term exacerbations of eyelid disease and the management of inflammatory keratitis and episcleritis since they constrain eyelid and ocular inflammation^[3,4,8,11-15]. However, its long-term use should be avoided due to their well-known potential side effects, such as increased intraocular pressure, glaucoma and cataracts. They should be discontinued as soon as possible. Furthermore, their discontinuation can frequently lead to rosacea exacerbations (topical steroid dependency)^[1-4,7,13-15,17]. If indicated, topical corticosteroids must only be used during the initial weeks and the drops tapered by one drop per week^[7,11,13].

Cyclosporine A 0.5% to 2% eye drops (four-six times per day) is an interesting approach for children with steroid-dependent disease and in phlyctenular blepharokeratoconjunctivitis^[14,26]. Our experience shows that topic cyclosporine isn't well tolerated by children, probably due to the lack of a suitable preparation in Europe.

It was described the efficacy of ivermectin to the treatment of refractory cases of cutaneous ocular rosacea, as an antiparasitic drug effective against mites *Demodex*^[27]. The treatment consist in an oral single-

dose, and despite being proscribed to children under five years and under 7 kg, it has been used in pediatric age^[27]. This drug has primarily been reported in the treatment of immunosuppressed patients, but there are reports of its success in immunocompetent patients^[27,28].

Surgical care is needed in specific cases, like corneal perforation^[2,15,25]. Other options under investigation are laser and intense pulsed light therapy. Dietary intake of omega-3 has recently proven to be effective as an anti-inflammatory and in clearing meibomian gland secretions^[2,6]. Flaxseed oil (∞ -linoleic acid) 2.5 mL once a day for up to 12 mo, with gradual reduction to an alternate day administration, can be an option in children intolerant or non-compliant with the use of long-term systemic antibiotics^[7].

OUTCOMES/SEQUELAE

POR can wax and wane with a recurrence rate of 40%^[10]. Affected children suffer from chronic conjunctivitis, corneal pannus, corneal neovascularization, generalized keratitis and meibomian gland disease. Chronic symptoms and frequent exacerbations may lead to tissue hypertrophy, extensive neovascularization, scarring, corneal opacification, corneal perforation and complications from secondary infections^[1,4-8,11-13,15,18]. Some patients may develop raised intraocular pressure and cataract, possibly with relation to chronic topical steroid therapy^[15].

The duration of the disease and the corneal involvement are the determining factors of severity^[4,6,13]. Furthermore, a prolonged therapy regimen is required to minimize corneal scarring and visual loss. Gradual tapering is recommended to avoid relapses^[4,6,13]. Thus, POR can be a source of significant visual morbidity in children^[4,6,8,15,18].

In comparison to adults, children seem to be more susceptible to corneal damage imposed by the inflammatory and immune response to periocular bacteria. This may compromise vision development, which combined with the position of the opacities in the cornea may be complicated by secondary amblyopia^[1,4,6,8,10,12].

TAKE HOME MESSAGES

OR is a subtype of rosacea, which is a chronic inflammatory disease; POR is frequently under and misdiagnosed, so it is probably more common than we previously thought; POR may be associated with high morbidity, development of sequelae and it is a possible cause of loss of vision;

The diagnosis is facilitated by the proposed POR criteria; An ophthalmologist observation is mandatory for the diagnosis, but it should be suggested by pediatricians or dermatologists; Treatment requires a minimum of three months' antibiotic therapy and a subsequent gradual tapering.

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Actinic keratosis and field cancerization

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Abstract

While actinic keratoses (AKs) have been considered precancerous until recently for being able to turn into squamous cell carcinomas (SCCs), it is now agreed that it would be more appropriate to call them cancerous. Although not all AKs turn into SCC and some of them may even have a spontaneous regression, there is an obvious association between SCC and AK. Approximately 90% of SCs have been reported to develop from AKs and

AKs are the preinvasive form of SCCs. The presence of two or more AKs on a photodamaged skin is an indicator of field cancerization and represents an increased risk of invasive SCC. All lesions should be treated since it cannot be foreseen which of the lesions will regress and which will progress to SCC. AK can be a single lesion or it can involve multiple lesions in a field of cancerization; thus, AK treatment is grouped under two headings: (1) Lesion-specific treatment; and (2) Field-targeted treatment. Lesion-specific treatments are practicable in patients with a small number of clinically visible and isolated lesions. These treatments including cryotherapy, surgical excision, shave excision, curettage and laser are based on physical destruction of the visible lesions. Field-targeted treatments are effective in the treatment of visible lesions, subclinical lesions and keratinocyte changes in the areas surrounding the visible lesions. Field targeted treatment options are topical imiquimod cream, 5% 5-fluorouracil cream, ingenol mebutate, diclofenac gel, resiquimod and photodynamic therapy.

Key words: Actinic keratosis; Squamous cell carcinoma *in situ*; Field cancerization

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Core tip: While actinic keratoses (AKs) have been considered precancerous until recently for being able to turn into squamous cell carcinomas (SCCs), it is now agreed that it would be more appropriate to call them cancerous. The presence of two or more AKs on a photo-damaged skin is an indicator of field cancerization and represents an increased risk of invasive SCC. All lesions should be treated since it cannot be foreseen which of the lesions will regress and which will progress to SCC. In this review, epidemiology, etiopathogenesis, diagnostic approach and treatment options for AK and field cancerization have been evaluated in light of recent literature.

Emre S. Actinic keratosis and field cancerization. *World J*

INTRODUCTION

Actinic keratoses (AKs) are epidermal lesions characterized by skin-colored, red or red-brown crusty and squamous spots, patches or nodules with a potential to progress to squamous cell carcinoma (SCC). Being an indicator of cumulative ultraviolet (UV) exposure, AK lesions typically appear on the areas with chronic sun exposure such as the face, chest, hairless scalp, auricles, hands and dorsal regions of arms^[1]. It has been reported that one of every 10 AKs progresses to invasive SCC in time. People with more than five AKs have a relatively increased risk of SCC. While AKs have been considered precancerous until recently for being able to turn into SCCs, it is now agreed that it would be more appropriate to call them cancerous. The term keratinocyte intra-epithelial neoplasia (KIN) has been proposed for these lesions^[2].

Although not all AKs turn into SCC and some of them may even have a spontaneous regression, there is an obvious association between SCC and AK. Approximately 90% of SCs have been reported to develop from AKs and AKs are the preinvasive form of SCCs^[1]. About 20%-25% of the lesions regress in a year. In a similar period of time, 15% of the lesions will reemerge. It is very difficult to predict if any regression is permanent.

All lesions should be treated since it cannot be foreseen which of the lesions will regress and which will progress to SCC. It should be noted that subclinical lesions may also transform into SCC^[3]. The histopathology of subclinical lesions is the same as that of clinically observable AKs. The number of subclinical spots in an area is more than 10 times that of visible AKs^[1,3]. The risk factors of transformation from AK into SCC have been enumerated as endurance, bleeding, larger lesion diameter, fast growth, erythema and ulceration with minor risks including pain, palpability, hyperkeratosis, itching and pigmentation^[4].

EPIDEMIOLOGY

The real incidence of AK is not known. The risk of having AK in a lifetime is estimated to be 50%. The World Health Organization has reported that the prevalence of AK is clearly associated with the location of the place of living. In smaller latitudes, both the prevalence of AK is high and multiple AKs are seen more frequently^[5].

The rate of prevalence is reported to be 40%-60% on the average in Australia and between 11% and 25% in the northern hemisphere. They are seen more in males than females^[6]. A study has reported the prevalence as 15.4% in men and 5.9% in women in the United Kingdom. These rates go up to 34.1% in

men and 18.2% in women after 70 years of age^[7]. In Australia, the prevalence was found to be 22% in men and 8% in women and 83% and 64% between the ages 60 and 69, respectively^[8].

FIELD CANCERIZATION

Multiple AKs are usually seen in areas exposed to the sun and dysplastic keratinocytes or preclinical lesions can be seen histologically on the clinically lesion-free skin surrounding the AKs. Even if the keratinocytes on these areas appear to be normal histologically, they are candidates for a future tumor growth. This process is defined as field cancerization^[1,9]. The presence of two or more AKs on a photodamaged skin is an indicator of field cancerization and represents an increased risk of invasive SCC. Photodamage is the earliest finding of the process progressing from AK to finally SCC^[1]. The term field cancerization is defined as the presence of one or more areas created by genetically altered epithelial cells that lead to the prognosis of epithelial carcinogenesis. The effect of field cancerization is well-documented in squamous cell tumors^[10].

The definition of field cancerization was first used by Slaughter *et al*^[2] in 1953. Such areas are probably associated with exposure to carcinogens^[2]. Multiple cancers that are associated with gene aberrations induced by carcinogens, that do not occur due to metastasis of tumor cells and that appear as tumors independent of, and in different distances from, each other are associated with field cancerization^[11]. A cutaneous field cancerization refers to the histologically altered areas on the lesion-free skin tissues surrounding the non-melanocytic skin tumors on a chronically photodamaged skin^[3].

ETIOPATHOGENESIS

UV

UV radiation seems to be the major player responsible for the process starting from photodamaging of the skin and progressing to actinic keratosis and SCC. The leading risks are intensive or cumulative UV exposure, open area activities, tanning efforts and longevity. The DNA lesions induced by UV are either repaired or if the damage is severe the cell enters apoptosis to protect itself from mutation. In case the cell cannot be fully repaired but it remains alive, the damaged nucleotides result in permanent somatic mutations and accumulation of such mutations may end up in cancer^[6].

Gene mutations

In normal cellular growth, the p53 expression is suppressed. Its expression is activated during severe stresses in which the cell is caught between apoptosis and survival in the case of cytotoxic or mutagenic agents for instance. The gene that undergoes mutation most frequently in humans during AK is p53 (37%) and there is a strong relationship between TP53 mutations

and AK/SCC. Both the UVA and UVB wavelengths are among the causes of carcinogenesis in TP53 DNA mutations. The mutations of this gene appear at the early stages of carcinogenesis and also play a role in the progression of cancer^[12]. The UV radiation induced TP53 mutation has been found in more than 90% of SCCs developing from AKs^[7]. The clonal patches consisting of cells with TP53 mutations can also be found on normal skin. Jonason *et al*^[13] have reported that these cell clones are 10 times more in number and are larger on a skin exposed to the sun than on a skin not exposed to sun. Brennan *et al*^[14] have shown that tumor recurrence is significantly higher in the presence of mutations in peritumoral areas. No recurrence has been seen in the neighboring areas without any mutations^[14]. In CDKN2A mutation, the risk of progression from AK to SCC increases significantly^[6]. The other mutations associated with the progression of skin cancers are NOTCH1, NOTCH2 and SMO. Hu *et al*^[15] have shown that the Notch/CLS signal is suppressed in the stromal area neighboring premalignant AK lesions. They have also shown that tissue changes such as stromal atrophy and inflammation occur when the Notch/CLS signal is eliminated. This is a potent stimulus for epithelial tumors^[15].

Immune suppression

While the rate of progression from AKs to SCCs is 10% in immunocompetent persons, this rate is 50% in immunosuppressed people. Patients who underwent organ transplantations have 100-250 times increased risk of cutaneous SCC. UV and immunosuppressive drugs are effective in the occurrence of skin cancer. Because the immunosuppressive therapy used for transplant patients reduces peritumoral inflammation, the invasion of skin tumors can easily go unnoticed in clinical practice^[16]. Trans-urocanic acid (UCA), which is a UVB chromophore, is expressed in stratum corneum in ample amounts. It is rapidly isomerized into a cis form by the effect of UVB. CisUCA is a potent immunosuppressant^[6]. Another target of UV radiation is DNA. The keratinocyte and langerhans cells are also direct targets of UV for being located in the upper layers of the skin. Due to UV radiation, not only DNA is damaged but also the antigen presenting functions of LH are suppressed. At the same time, secretion of immunosuppressive inflammatory cytokines such as PG E2 and PAF becomes effective. In the end, UV acts in two ways in skin cancers, by causing genetic damage and by suppressing anti-tumor immunity. Both of these processes are important in the progression of preneoplastic AKs to SCCs^[17].

Others

The risk is higher especially in persons whose Fitzpatrick skin type is I or II (easily having sunburn and hardly having any tan). The presence of freckles on the face, even if only a few, increases the risk significantly^[1]. The HPV infections may play a role in the pathogenesis of non-

melanoma skin tumors. HPV 38 has been found more frequently in AK lesions than in SCC lesions^[18]. Chronic inflammation is an important indicator of tissue changes progressing to carcinogenesis. Cyclooxygenase-2 (COX-2) inhibiting anti-inflammatory drugs can reportedly prevent tumorigenesis, but cannot reverse tumorigenesis that has already started^[19].

Mucin 1 (MUC 1), a transmembrane glycoprotein plays a critical role in human cancer. MUC 1 is not expressed by the normal epidermis in human skin. It is expressed by keratinocytes in some premalignant and malign lesions such as epidermolysis bullosa, Paget's disease, Bowen's disease, and Merkel's carcinoma. Arciniegas *et al*^[20] found that MUC 1 was localised at the apical surface of some atypical keratinocytes of AKs, but was not detected in the epidermis of normal skin. This findings suggest that the expression of MUC 1 in AK may contribute to the progression of AK to SCC.

UVA in particular causes DNA mutations that are characterized by photo-oxidative stress. Longevity increases the risk due to factors such as increased cumulative UV exposure and decreased immune resistance. The prevalence of AK is higher in males. The rate of working in open areas being higher in men and AGA are risk factors for scalp AKs. The use of photosynthesizing medication and genetic diseases such as xeroderma pigmentosum are also risk increasing factors for AK development^[1,2].

HISTOPATHOLOGIC CHARACTERISTICS

AK is characterized by atypia and dysplasia of the keratinocytes in the basal layer of epidermis. The atypical and dysplastic clusters grow in time and advance to upper layers. Alternating areas of parakeratosis and hyperkeratosis are present in the corneum layer^[11]. The atypical changes in the epidermal keratinocytes may be in different sizes and shapes and involve nuclear pleomorphism. The neoplastic keratinocyte proliferation in AK is limited to the epidermis^[2]. There are signs of lymphocytic inflammatory infiltration and solar elastosis in dermis. From epidermal changes, AK and SCC cannot be distinguished histologically. Molecular changes associated with cancer are present in both AK and SCC. Padilla *et al*^[21] have shown that the genetic characteristics of AK and SCC lesions are closely associated with each other. This finding supports the fact that AK is of malign nature from the very beginning. Its lichenoid, hypertrophic, bowenoid, pagetoid and pigmented types have been defined histologically^[3,10].

CLINICAL SIGNS

It is most frequently seen in the areas which are mostly affected by DNA damage caused by UV radiation including the head, face, ears, lower lip, dorsal region of hands, lower legs, décolleté region, neck and upper back. AK is the most widely seen skin cancer on a sun-damaged skin^[1,22]. It appears as squamous, skin-

colored, pink or red-brown papules, macules or plaques with vague margins. It can be a single lesion, but more commonly there are multiple lesions on a photodamaged skin. A classical aspect of AK is the rough surfaces of lesions feeling like sandpaper^[1]. The size of lesions can range from a few millimeters to 3-4 cm and larger. When the lower lip is affected, it appears as a dry, scaled and atrophic lesion, which is called actinic cheilitis^[15]. Depending on its clinical appearance, AK may be of classical, hypertrophic, atrophic or pigmented type, or appear as cornu cutaneum or actinic cheilitis. The severity of AK was divided into 3 phases within itself: (1) Lesions not so visible, vaguely felt with palpation; (2) Lesions are of medium thickness, easily palpated and seen; and (3) Hyperkeratotic and thick lesions^[23].

DIAGNOSIS

A typical AK lesion does not require any histopathologic analysis. The clinical and subclinical changes of AK and field cancerization on the skin can be diagnosed by way of examination. Alongside multiple AK presence, those areas of the skin with a chronic UV damage such as solar lentigines, pigmentation disorders, altered skin tissue, deep and superficial lines, telangiectasias, xerosis and solar elastosis are considered as a field of cancerization^[3]. However, biopsies are required in patients suspected of having invasive SCC lesions including hyperkeratotic and hypertrophic lesions with a diameter larger than 1 cm, which involve induration, bleeding, inflammation, ulceration, fast growth, pain upon palpation, no response despite appropriate treatment or relapses in periods as short as 2-3 mo^[24].

DERMOSCOPY

Dermoscopy is a very useful method in diagnosing AK with 98.7% sensitivity and 95% specificity^[25]. The value of dermoscopy depends on the physician's experience and the AK's dermoscopic characteristics, of which superficial scurf/scales are the most common one. Sometimes, underlying structures cannot be discerned due to such scurf. The second most widely seen pattern is the red, artificial network structure, which is described by a strawberry appearance. The other dermoscopic signs include targetoid-like appearance, rosette sign, absent fissures/ridges, crypts and milia-like cysts^[26].

TREATMENT

The goal of AK treatment is to treat the field of cancerization and prevent formation of new lesions rather than to ameliorate the clinical appearance of AK lesions. Although the evidences showing that this approach is useful are very few, treatment is a requirement when the clinical and histological characteristics of AK are taken into consideration^[1]. The need for treatment also involves continuous monitoring of AKs with respect to patient complaints, AK's effect on quality of life and

transformation into SCC^[24].

AK can be a single lesion or it can involve multiple lesions in a field of cancerization; thus, AK treatment is grouped under two headings: (1) Lesion-specific treatment; and (2) Field-targeted treatment^[2].

Lesion-targeted treatments

These are practicable in patients with a small number of clinically visible and isolated lesions. They are based on physical destruction of the visible lesions.

Cryotherapy: This is the first-choice treatment method when the lesions are few or isolated. It is a fast and cheap method. There is no standard protocol about the application time, frequency or cycle intervals of cryotherapy. The success of treatment depends on the experience of the applying person. The correct application method is to create an ice ball that freezes the epidermis. Afterwards, a bulla should occur indicating that the basal membrane is separated from the dermis. This method has been shown to be successful in 90% of thin lesions^[2]. Applying it in two freeze-thaw cycles including an area of 1mm around the lesion is generally preferred. The rates of clearance with one or two applications have been reported to be between 68% and 75% at the end of a 3-mo period^[24].

Oliveira *et al*^[27] experimented the effect of cryotherapy on two lesions of similar character from 13 patients with multiple AKs. They applied a liquid nitrogen cryotherapy to one of the lesions in a single session for 10 s and 30 d later they compared the biopsies taken from the lesions that was and was not administered cryotherapy. They found distinct decreases in keratinocyte atypia, epithelial thickness, and lymphocyte infiltration in the corneum layer and dermis in the lesion which underwent cryotherapy. Thai *et al*^[28] administered their cryotherapy in a way to exceed the lesion margin by 1 mm using different freeze times. A full response was obtained in 39% of those that were administered less than 5 s of cryotherapy, in 69% of those that had longer than 5 s and in 83% of those that had longer than 20 s. They reported that they had full response in 94% of the lesions and the cosmetic results were good to excellent.

The side effects are pain during application, development of bullas and scars, hypopigmentation and hyperpigmentation. Hypopigmentation is seen in 29% of the cleared lesions and hyperpigmentation in 6% of them^[1,2].

Surgical excision, shave excision and curettage:

Surgical methods are not the first-choice in AK treatment. They should be preferred in hyperkeratotic, treatment-resistant and invasive SCC suspected lesions^[2]. Through curettage and shave excision, atypical cells are removed mechanically. Both of these two methods are usually completed with an electrodesiccation. In this way, both the remaining abnormal tissues are destroyed and bleeding is controlled. Their disadvantages include the necessity of local anesthesia and their applicability to

a few and only hyperkeratotic lesions. These methods are not useful in the treatment of subclinical lesions and broadly damaged areas. Their possible side effects are scars, wound site infections, dyspigmentation and anesthesia-related complications^[29].

Laser treatments: Ablative ultrapulse Er:YAG and CO₂ lasers are indicated in isolated and a limited number of lesions. However, their effects have not been evidenced with double-blind randomized studies. Sherry *et al*^[30] have reported that long-term efficacy continues in AK patients who were administered ablative CO₂ laser and the lesion-free period is 27.4 mo on the average. Their side effects include erythema, pain, irritation, itching, and secondary infection.

Non-ablative fractioned lasers (ER:YAG and CO₂) are able to improve skin quality, but they do not achieve a significant decrease in the number of AK lesions^[24]. Although a decrease has been achieved in the number of facial AK lesions that had been treated using the fractioned photothermolysis method, it has been reported that the histological aspects of AK and/or SCC continue to exist in histopathological examinations^[31]. Their disadvantages are higher cost than cryotherapy and the requirement for specially trained staff.

Field-targeted treatments

They are effective in the treatment of visible lesions, subclinical lesions and keratinocyte changes in the areas surrounding the visible lesions.

5-Fluorouracil cream: It is a pyrimidine analogue that was approved by the FDA in 1970. It impairs DNA formation by stopping conversion from deoxyuradilic acid to timidilic acid through inhibition of thymidilate synthetase. It disrupts cell proliferation, particularly in the fast reproducing cells of basal layer and AK, resulting in cell deaths. It is used in 5% cream form for 2-4 wk, applied once or twice daily^[3]. The area of application should not exceed 500 cm² at a time. Erythema, burning, itching, pain, hyperpigmentation, wound site infection, bullas and ulceration may occur for about 4-6 wk after the treatment. Its photosensitivity effect limits its use in summer.

The long-term effects of 5% 5-fluorouracil (5-FU) cream applied for 4 wk, twice a day have been explored in a large-scale study published recently. The rates of being cleaned from AK of the patients who were checked every 6 mo in 2.6 years were found higher than the placebo group. Moreover, their spot treatment needs were found significantly less than the placebo group^[32].

The 5-FU cream with a lower concentration of 0.5% is approved by FDA, but is not available in Europe. A 12-wk use applied once daily is recommended. The effect of 0.5% formulation has been found similar to that of 5% cream form, but the side effects were less and patient satisfaction was better^[33]. The penetration of 5-FU, the biological active substance, is increased by

combining low-dose 5-FU with salicylic acid (SA), taking advantage of the keratolytic effect of SA. The combined preparation is approved in Switzerland. Although the 0.5% FU and SA combination seems more effective with fewer side effects, there is a need for long-term studies^[3].

The effectiveness of the combination of low-dose 5-FU with 10% SA has been compared to that of diclofenac gel and carrier base. The 5-FU and SA combination was found significantly more effective than diclofenac gel and carrier base with 72% histological cleaning and 55.4% complete cleaning. The application area reactions were seen more in the 5-FU and SA combination and the side effects were found mild and moderate^[34]. In a prospective randomized study where it was compared to a two-session cryotherapy application, the 0.5% 5-FU and SA combination was found superior to cryotherapy^[35]. In a meta-analysis, the 5% and 0.5% 5-FU formulations were rated superior to other field-targeted treatments^[36].

Disadvantages of 5-FU cream include long treatment period, itching, prolonged erythema, pain, ulceration, erosion, secondary infection and depigmentation. It is teratogenic for impairing the DNA synthesis in fast dividing cells. It may have a systemic toxicity risk when used excessively and particularly when used for the areas with impaired barrier function^[22].

Imiquimod: Imiquimod is an immune response regulator from the imidazoquinolone group. It is a Toll-like receptor agonist showing its effect on cytokine-producing cells such as monocytes, macrophages and dendritic cells^[2,3,22]. It stimulates cytokine secretion by the TLR-7 induction, which improves cellular immunity. It is effective on both natural and acquired immune response, showing indirect antiviral and antineoplastic effect.

It was first approved by FDA in 2004 for the treatment of AK keratosis^[37]. Imiquimod 5% cream and 3.75% cream forms are available. The 5% cream form is approved to be used on a hairless scalp and on areas up to 25 cm² in the face twice a week for 4 wk followed by a 4-wk resting period. The purpose of such alternating treatment is to reduce local skin reactions. The 3.75% cream form was approved in 2010 to be used every night in a 2-wk period followed by a 2-wk resting period. It can be applied to larger areas on the face and scalp and has a shorter treatment period compared to the 5% cream^[2].

In both forms, subclinical lesions emerge together with inflammatory reactions at the beginning of the treatment, leading to an increase in the number of lesions. The rate of cleaning AKs is higher in people with severe local reactions. This supports the fact that inflammation is part of the action mechanism in AK^[38]. Pruritus, burning, erythema, edema, pain, dryness, desquamation, erosion and ulceration may be seen locally. Systemic reactions such as myalgia, nausea and weakness are less frequent. Fewer reactions are seen during the second treatment cycle. It should be used carefully if there is an ongoing immunosuppressive

therapy in immunodeficient patients who had organ transplantation^[24].

The effect of 3.75% imiquimod on the maximum number of lesions has been assessed in a placebo-controlled, double-blind study made with 319 patients and more than 90% decrease has been found in the number of lesions after 2 treatment cycles of 2 wk. The average and complete decrease in the number of lesions has been found significantly higher than placebo group^[39].

Resiquimod: Resiquimod is an immune modulator structured as an imidazoquinoline amin whose phase 3 studies still continue in Switzerland. It is a TLR-7 and 8 agonist and stimulates cytokine secretion (IL-12 and TNF- α) more strongly than imiquimod. Its total cure rates have been found as 74.2% with 0.01% gel and 90.3% with 0.03% gel in patients who were given one more cycle of treatment after the phase 2 study using it 3 d a week, once a day for 4 wk followed by a no treatment period of 8 wk. Most frequently seen side effects are irritation at the application site^[1,3].

Diclofenac: Diclofenac gel includes 3% diclofenac sodium in 2.5% hyaluronic acid carrier is a nonsteroidal anti-inflammatory drug which COX-2 inhibitor. UVB is known to induce COX-2 expression in human skin^[22]. The production of prostaglandins from arachidonic acid plays a role in the skin cancer induced by UVB. The COX-2 inhibition with diclofenac probably shows its effect in AK treatment by impairing this cascade^[2]. Diclofenac gel also plays a role in AK treatment by inducing apoptosis and inhibiting angiogenesis^[1]. It is recommended to use it twice a day for 90 d. Side effects include itching, erythema and dryness. Diclofenac gel may rarely lead to photosensitivity in some patients. It is suggested to use it in combination with cryotherapy in hypertrophic lesions.

It was reported at the end of an analysis of 17 studies made with 3% diclofenac gel that there was 58% complete clearing of lesions a month after a 3-mo treatment, its efficacy continued at the end of one year and its effect was comparable to those of 5% imiquimod and 5% 5-FU. It has also been evidenced that it is safe in immunosuppressive patients, suitable to be used following cryotherapy and FDT, and more tolerable than the other treatment agents^[40].

Ingenol mebutate (PEP005): Ingenol mebutate is a traditional treatment agent derived from the plant called *euphorbia peplus*. It was first approved by FDA in January 2012 for the treatment of AKs on the face, scalp, trunk and extremities in adult patients. It still has approvals in Europe, Australia and Canada^[1,41]. It is an effective option in the topical treatment of AKs that are not hyperkeratotic. Ingenol mebutate shows its effect through two mechanisms: (1) Causing death of keratinocytes that underwent transformation; and (2) Causing death of remaining cancerous cells by

increasing inflammatory reaction^[41].

The mechanism of action primarily involves cell necrosis as a result of impaired structures of cell plasma membranes and mitochondria. This action takes place in 1-2 h after its application. In the following days, the remaining tumor cells are eliminated through neutrophil-antibody dependent cellular cytotoxicity^[41].

It is recommended to apply its 0.015% gel formation on the face and scalp once a day for 3 consecutive days and its 0.05% gel formation on the trunk and extremities for 2 consecutive days. It can be washed away after keeping it at least 6 h on the application site^[42]. Its major side effect is that the local skin reaction makes a peak on the 4th day at the application site, but then dies away after the 8th day. Its other side effects, pain, itching and irritation, are less frequent and milder^[43].

The results obtained from the patient group that participated in the phase 3 study and received treatment with ingenol mebutate were assessed in terms of quality of life, patient satisfaction and clinical outcomes. Quality of life and treatment satisfaction were observed to improve significantly in the patients both in the face-scalp group and trunk-extremity group^[44]. The advantages of ingenol mebutate therapy are that it is cheaper than other topical treatments, it is used for a short period of time and it does not cause photosensitivity^[41,45].

The safety and tolerability of 5% 5-FU cream and 0.015% ingenol mebutate have been compared and the maximum local skin reactions have been found similar. Although the time of experiencing skin reactions has been found longer in the 5-FU group, both therapies have been found safe and tolerable in general^[46]. Ingenol mebutate gel applied after cryotherapy increases the effect of cryotherapy alone. A classical dose has been applied to the patients who had at least 10 recurrent and hyperkeratotic lesions 2 wk after cryotherapy and cleaning at a rate between 50% and 100% has been reported^[47].

Photodynamic therapy: Photodynamic therapy (PDT) is an effective treatment option for AKs, field cancerization and non-melanoma skin tumors. The most frequently used photosensitizing agents are 5-aminolevulinic acid (5-ALA) and its methyl ester methyl aminolevulinate (MAL), which are the precursors of protoporphyrin IX (Pp IX)^[1,2,41]. Pp IX increases mostly in hyperproliferative cells. It absorbs light and causes formation of cytotoxic free oxygen radicals as a result of a photochemical reaction. These radicals lead to cellular necrosis and apoptosis^[48]. Cleaning the sloughs and scales with curettage or keratolytic creams before the treatment increases the effect. The photosensitizing cream is applied with occlusion at least 3 h before the procedure. The incubation times, treatment protocols and light sources vary to a large extent. There are efforts to establish the optimal standards for treatment.

The treatment is administered once to thin AKs and AKs of medium thickness. If the effect is not satisfactory 3 mo later, the procedure is repeated once more. The

procedure is performed in 2 sessions with a 1-wk interval in hyperkeratotic AKs if severe atypia is present histopathologically, and in immunosuppressive patients. The most frequent side effects are local reactions in the application site and pain in the irradiation site. Rare side effects include nausea, weakness, paresthesia and headache. ALA-PDT is more effective in severe scalp lesions. MAL-PDT's disadvantage is that it is more expensive than ALA-PDT^[48].

PDT produces better cosmetic outcomes than cryosurgery and enables treatment of broader areas with a single session procedure, but cryotherapy has been found superior to PDT in the face and scalp, and in thicker lesions. Local side effects are also milder in cryotherapy^[1].

The effect of PDT applied in 3 sessions with monthly intervals was investigated in a study. The lesion biopsy values taken at baseline and at the end of the 3rd month were assessed and the rate of cleaning in AKs was found as 89.5%. The effect at the end of the 2nd treatment was found similar to that of the 3rd session. A significant decrease was found histologically in keratinocyte atypia and the extent of atypia, as well as significant improvements in collagen storage and healing of solar elastosis^[49]. Recently, a new nanoformulation of 5-ALA (nano-ALA) PDT was compared with MALT PDT in a pilot study. Passos *et al*^[50] found that the efficacy of nano-ALA is 10% higher than of MAL in treating skin field cancerization.

In a meta-analysis involving 25 studies on AK and field cancerization and including 5562 patients, all active treatment methods were found superior to placebo, and the most effective treatment method in terms of total cleaning obtained was found to be ALA-PDT (SUCRA score 90.8%), followed by 4-wk 5% imiquimod (71.7%) and 0.5% 5-FU cream (64.1%)^[51].

Piroxicam: Piroxicam (PXM), is a nonsteroidal anti-inflammatory drug which is nonspecific COX-1 and COX-2 inhibitor. Campione *et al*^[52] reported that local use of piroxicam was eligible, safe, effective, and well tolerated option for the treatment of AKs and field cancerization (PXM). It was used its 1% gel formation applied twice daily for 12 wk. But its use in AKs is still off-label.

COMBINATION TREATMENTS

Combination treatments are required in patients who have treatment-resistant, multiple lesions at different stages. Although there is no standard guideline on treatment combinations, lesion-targeted and field-targeted treatments may be combined to increase efficacy. Three point seven five percent imiquimod therapy following cryotherapy has been found useful and safe. The complete cleaning rates obtained from a 90-d diclofenac gel therapy following cryotherapy have been found twice as much compared to cryotherapy alone (64% vs 32%). Significant increases in the effect have also been achieved in post-cryotherapy 5-FU and post-cryotherapy ingenol mebutate

therapies. It has also been shown that more success can be achieved with PDT applied after 5% imiquimod cream, 5% 5-FU or diclofenac gel therapies compared to the success achieved in each therapy alone^[1,53].

AK TREATMENT IN ORGAN TRANSPLANT RECIPIENTS

Organ transplant recipients (OTR) are at high risk for NMSTs. Lesion-targeted treatments, cryotherapies, electrocautery, curettages and CO₂ lasers can be safely used in these patients. Diclofenac gel has been compared to placebo in 32 OTR patients in a 16-wk treatment. While the complete cleaning of AKs was 41% in the diclofenac group, it was found to be 0% in the placebo group. No patients were reported to develop invasive SCCs at the end of a 24-mo follow-up period^[54].

Ingham *et al*^[55] have been applied 5% 5-FU cream to AK lesions on eight renal transplant recipients face twice daily for 3 wk. They reported that 5-FU effective and safe treatment in renal transplant recipients. Imiquimod 5% cream has been found safe in heart, liver and kidney transplant patients if used 3 times a week not more than 2 sachets at a time on areas not exceeding 100 cm²^[56]. It was shown that PDT prevent new AKs formation in renal transplant recipients^[57]. But PDT is less effective in immunosuppressed patients compared to the immunocompetent people in the AKs treatment^[58].

PROTECTION

Childhood and adolescence are the really important periods for sun protection. The protection from the sun behavior acquired in these periods plays a key role in both prevention of excessive sun exposure and sunburns in childhood and acquisition of protection from the sun protection habit that will continue lifelong^[1]. Sunscreens may be useful in high-risk groups. Ulrich *et al*^[59] have investigated the effect of sunscreens on protection from NMST in OTR. They reported at the end of the 24-mo study that there was a decrease in the number of basal lesions in the group using sunscreens and they had fewer lesions than the control group. Therefore, protection from the sun is advisable for all patients with field cancerization. Patients should also be trained on the correct use of sunscreens.

It was shown that daily use of 30 mg acitretin for a period of 6 mo in renal transplant patients with multiple AKs resulted in a decrease in the number of AKs and it was effective in preventing the development of SCCs^[60].

The chemopreventive effect of nonsteroidal anti-inflammatory drugs such as diclofenac gel on nonmelanoma skin cancers has been demonstrated^[52].

FOLLOW-UP

If there are no special risk factors, patients are recommended to examine themselves every 3 mo. New

lesions are recorded, if any, and in the presence of suspicious lesions examination by a clinician is required^[1]. Through professional examinations and follow-up, formation of new lesions and occurrence of any changes can be detected at an early stage, other cancers such as melanoma can be identified and patients can be educated and informed about their diseases.

The oral mucosa, palmar regions, scalp and genital regions should also be assessed during examinations and in the presence of an invasive ca risk lymphatic glands should also be examined. Self-examination by the patients themselves is as important as clinical assessments and the patient should be trained for self-examination. Patients who have been subject to long-term immune suppression as in OTR require special monitoring for invasive NMSTs. Such patients should undergo annual dermatologic examinations and monthly self-examinations. OTR patients should be examined for NMSTs before the transplantation.

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**CASE REPORT**

- 125 Local hyperthermia cleared multiple cutaneous warts on a nephrotic syndrome patient

Zhang YJ, Qi RQ, Gao XH

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Local hyperthermia cleared multiple cutaneous warts on a nephrotic syndrome patient

Yu-Jing Zhang, Rui-Qun Qi, Xing-Hua Gao

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Abstract

Cutaneous warts are caused by human papillomavirus infection. Immunosuppressive state is one of the risk factors of human papillomavirus infection. A girl diagnosed of nephrotic syndrome and on immunosuppressive therapy developed multiple common warts. We treated her on a single lesion by local hyperthermia therapy at 44 °C for 3 consecutive days, each therapy lasted for 30 min. Ten days later, the patient received another 2 consecutive therapy. All lesions are completely resolved at the 9th week after the treatment. No recurrent sign was observed in a 3-mo follow-up. Side effects included burning sensation, stabbing pain at the target site during treatment.

Key words: Hyperthermia; Warts; Nephrotic syndrome; Immunosuppression

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Core tip: Common warts on immunosuppressive patients are characterized by multiple lesions, long duration and hard to treat. Current treatment method includes laser therapy, cryotherapy, topical salicylic acid, *etc.* Scar formation and high recurrence rate are the most common disadvantages of these treatments. In this case report, we provide a noninvasive treatment method called hyperthermia treatment. Using this method we succeed to cure multiple warts on a nephrotic syndrome patient who received immunosuppressive treatment for years without any scar formation. And we did not see recurrence 3 mo after the treatment.

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INTRODUCTION

Human papillomaviruses (HPVs) infection is associated with cutaneous warts and cervical cancer, depending on the virus subtypes. Smoking, a large number of lifetime sexual partners, and immunosuppressive state are the main factors that elevate the individual's rate of infection^[1]. The former two factors are more related to individual's unhealthy lifestyle than the latter one which is sometimes unpreventable, for instance, iatrogenic immunosuppressive agents for renal transplantation and autoimmune diseases^[2]. Multiple cutaneous lesions, long disease duration, and high recurrence rate - consequences of glucocorticoids and other immunosuppressive agents - are the challenges for the conventional treatment methods.

Controlled localized heating was proved successful to treat warts^[3]. Recently, we reported that the cure rate of cutaneous warts is over 50% using the intermittent local hyperthermia method. In these studies, we used a patented hyperthermia device (patent NO.: ZL 2007 2 01875403.3, Patent holder: The First Hospital of China Medical University, China). This device has an infrared emitting source. The heat generated by the device acted locally on skin surface without direct contact^[4,5]. Side effects were minimal except mild burning sensation and stabbing pain while receiving the treatment, and occasional heat-induced transit bullae. The recurrence rates were low. We treated an immunosuppressed patient with multiple warts by local hyperthermia at 44 °C for 30 min a day for 3 consecutive days plus 2 additional days 10 d later. The patient was followed-up weekly. The study was approved by the Ethics Committee of China Medical University (2009 No.22).

CASE REPORT

A 23-year-old girl presented with three slowly growing lesions on her left knee, and a similar one in the right nostril for 2 years. She did not receive any treatment. Months before developing the skin lesions, she experienced leg edema. Laboratory study revealed proteinuria (3+), occult urine blood (2+), serum albumin 19.9 g/L (normal range 40-55 g/L), serum total cholesterol 6.98 mmol/L (normal range 0-5.72 mmol/L), serum triglyceride 5.85 mmol/L (normal range 0-1.7 mmol/L), serum creatinine 48 µmol/L (normal range 59-104 µmol/L). She was clinically diagnosed with nephrotic syndrome, and membranous nephropathy by renal pathology. She received prednisone 50 mg/d and tacrolimus 3 mg/d. Her clinical symptoms disappeared

in 10 d and laboratory tests turned close to normal. In the following two years, her prednisone dose was tapered from 50 mg/d to 25 mg/d. Oral tacrolimus was replaced by tripterygium wilfordii (20 mg/d). Physical examination of the skin showed three flesh or gray-colored papules over or at side of her left knee. The largest papule was 0.5 cm × 0.5 cm in size, and had a hyperkeratotic appearance. There was a pink colored papule at her right nostril. General exam revealed nothing particular. We initiated local hyperthermia on a papule at the extensor side of her knee (circled in Figure 1). The target received local hyperthermia at 44 °C, once a day for 3 consecutive days, and each treatment lasted for 30 min. Ten days later, the patient received two more similar consecutive treatment. Then the patient was followed up once a week for next 3 mo. The lesions began to shrink at the 7th week after local hyperthermia therapy and completely resolved 9 wk after completion of the therapy (Figure 2). After the first treatment, the patient developed a tense blister adjacent to the target which resolved spontaneously within 3 d. It is noted that both treated and untreated sites over her knee had pigmentation left (Figure 2). The patient felt burning and stabbing pain at the targeted site while receiving treatment. We did not see any sign of recurrence during a 3 mo follow-up.

DISCUSSION

Chronic immunosuppression for various reasons can lead to persistent infection of human papillomavirus and HPV-associated diseases^[6]. This patient was diagnosed with nephrotic syndrome and she received glucocorticoids, tacrolimus, and tripterygium wilfordii (an immunosuppressive agent derived from plants). Glucocorticoids can interfere the function of both innate and adaptive immune system. Toll-like receptors are responsible for the microbial pathogen to elicit initial immune and inflammatory response. This reaction is normally limited by glucocorticoids to curb excess inflammation^[7]. Glucocorticoids-induced apoptosis in lymphocytes is mediated by the glucocorticoids receptor^[8]. Cell-mediated immunity is believed the main weapon against HPV virus. Antigen presenting cells, T helper cells, and cytotoxic lymphocytes may have the most significant role in clearing the critter. The use of glucocorticoids inhibits the effect of those cells, which is blamed to cause the long duration and multiple HPV induced lesions. Tacrolimus suppresses adaptive immune reaction through interfering the production of IL-2, which is an important cytokine for T cells development and proliferation. Besides, tripterygium wilfordii could reduce the cytokine secretion level of Th1 and Th2 cells^[9]. Common warts have a tendency to regress spontaneously: 23% cases within 2 mo, 30% within 3 mo and 65% to 78% within 2 years, however, warts are less likely to resolve in adults and in immunosuppressed

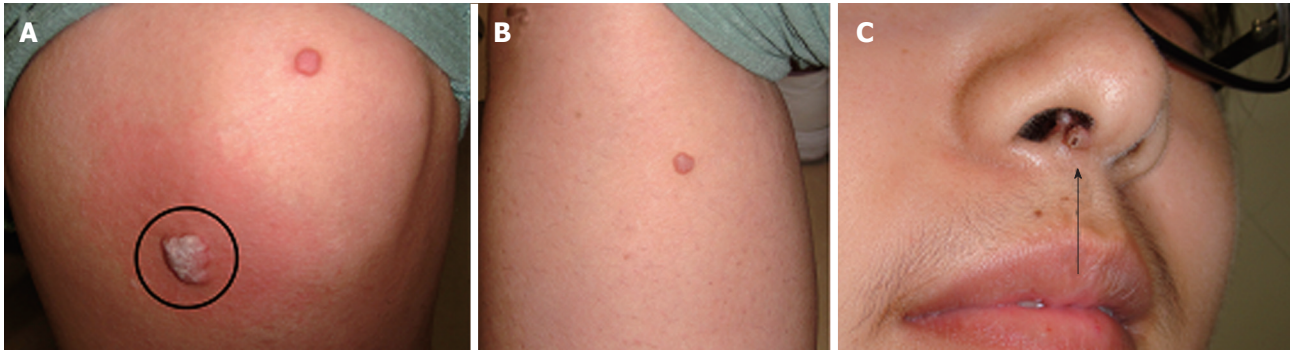


Figure 1 Local hyperthermia on a papule at the extensor side of knee. A: Lesion over left knee, target lesion is circled; B: Lateral side of left calf; C: Right nostril.

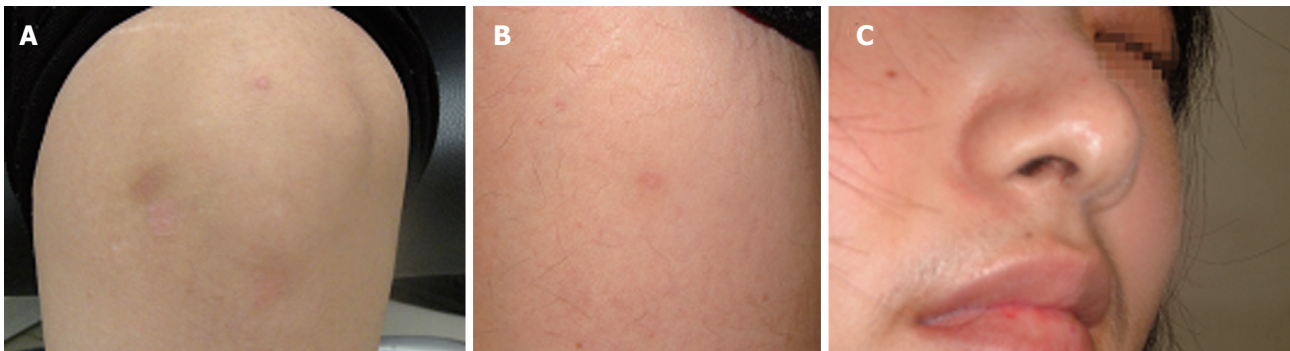


Figure 2 Ninth week after completion of five sessions of local hyperthermia treatment. A: Left knee; B: Lateral side of left calf; C: Right nostril.

patients^[10]. Topical salicylic acid therapy and cryotherapy are two first-line treatments for non-genital cutaneous warts^[11]. Both of the two treatments aim at eliminating signs and symptoms, and if the infectious areas are not removed thoroughly, the recurrence rate would be high. For this particular case, destructive options for the lesion over her nostril was not favored by the patient. We chose local hyperthermia therapy over a lesion on her knee, the resolution of which induced the spontaneous resolution of the untreated ones. The major advantages of the treatment include no scarring, high tolerability (especially for patients with multiple lesions as only one site is treated), easy accessibility and low recurrence rate^[4,5]. The full mechanism of local hyperthermia therapy is unclear. In our previous studies, we found that above fever range hyperthermia could increase influx of Langerhans cells to draining lymph node^[12] and could induce the IFN-induced antiviral activity and apoptosis of keratinocytes^[13,14]. These phenomenon suggest hyperthermia may help to setup an immune specific response against HPV infected keratinocytes, which could explain a single target treatment clears other untreated lesions.

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COMMENTS

Case characteristics

Hyperthermia-a new method succeed to treat multiple cutaneous warts in an immunosuppressive patient.

Clinical diagnosis

Verruca vulgaris and nephrotic syndrome.

Differential diagnosis

Molluscum contagiosum.

Treatment

Hyperthermia.

Experiences and lessons

Local hyperthermia provides with an effective, noninvasive, and low complication method to treat various warts.

Peer-review

It is an interesting case with a novel method and a good result.

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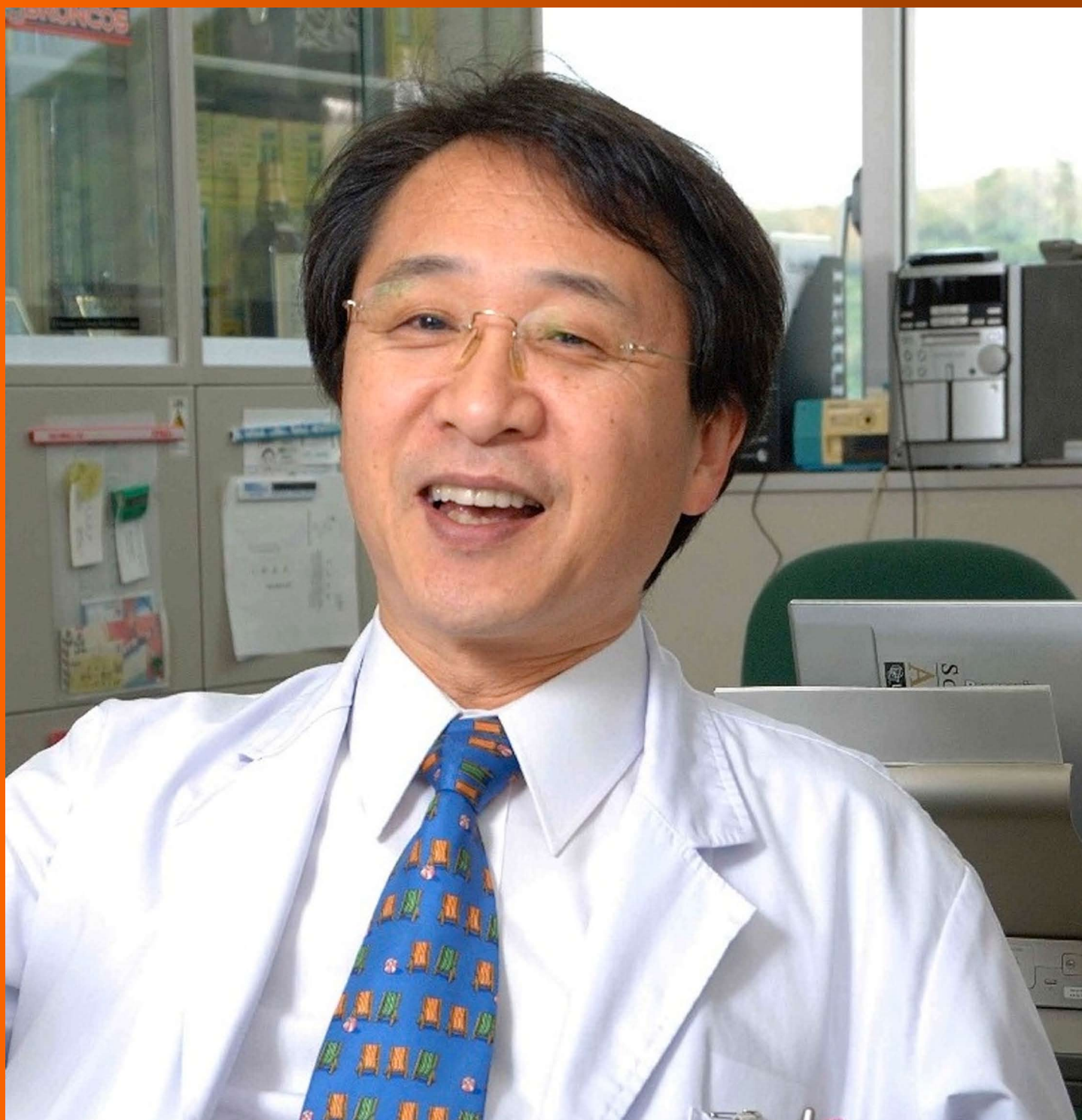
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Observational Study

- 129 Multi-channeling optimized radiofrequency energy: A new age in well-established radiofrequency technology
Tagger C, Belenky I

CASE REPORT

- 136 Papular mycosis fungoides: Six new cases and association with chronic lymphocytic leukemia
Vonderheid EC, Kadin ME, Telang GH

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Observational Study

Multi-channeling optimized radiofrequency energy: A new age in well-established radiofrequency technology

Cruzy Tagger, Inna Belenky

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Informed consent statement: All study participants provided informed written consent prior to study enrollment.

Conflict-of-interest statement: Both authors, both authors are employees in Viora Company that manufactures the RF system used in the study. However, both authors did not receive any additional financial or other benefit/interest due to this study or publication. All data provided in the study is original and not modified.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at inna@vioramed.com. Participants gave informed consent for data sharing.

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Abstract

AIM

To evaluate the safety and efficacy of Viora's new multi-polar radiofrequency (RF) handpiece.

METHODS

A group of twelve volunteers (11 females and 1 male) participated in the current study, ranging in age from 23-70 years with Fitzpatrick skin type II-V. The inclusion criteria for the enrollment were no contraindications for the treatment, body mass index (BMI) < 35 and local fat accumulation or cellulite formation. A total of 19 treatment areas were treated in the study: 9 abdomen, 2 abdomen plus flanks, 2 arms and 6 thighs. The treatment performed with new multi-polar RF handpiece (V-FORM) with 4 levels of RF power (up to 50 W), 4 levels of vacuum pressure intensity (up to 500 mbar) and 4 operational modes (0.8, 1.7 and 2.45 MHz). Circumferential reduction and cellulite reduction treatments were performed once a week (7 ± 1 d) for a treatment series of 3-8 sessions. The clinical assessment of the treatment outcomes included skin moisture level, skin impedance, body temperature, circumferential measurements, clinical photographic assessment and BMI.

RESULTS

Ten of twelve patients completed the treatment course. No side effects were recorded during the study. The skin responded with slight erythema and sometimes edema, which is considered a positive end-point. All patients maintained a stable weight during the

entire period of the study. No patient underwent any treatments or took medications for fat volume reduction during the study. A moderate positive correlation was found between the patient's age and BMI (correlation coefficient 0.54). The initial body temperature increased in average to 34.0 °C from 31.9 °C, the initial skin moisture level increased to an average 40.98% from 38.9% and the initial skin impedance decreased by 3.8%-35.9% by the end of the treatment course. The pre-heating time for all body areas ranged between 1-6 min with negative correlation to the body's end-point temperature (correlation coefficient -0.31). All patients responded to the treatment and showed some degree of circumferential reduction (up to 15 cm), on at least one of two-three measured points.

CONCLUSION

According to clinical data collected in this study, the new V-FORM handpiece represents an effective treatment with 100% response rate, with the safest treatment profile.

Key words: Radiofrequency; Vacuum; Body contouring; Circumferential reduction; Cellulite

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Core tip: The significant change in circumferential measurements post-V-FORM treatments can be contributed not only to volume reduction due to improved metabolic rate and enhanced natural lipolysis, but also to edema reduction due to vacuum pressure integrated in the handpiece. Moreover, this technology enables the control of radiofrequency depth penetration which allows finishing the treatments with a skin tightening effect using higher radiofrequency frequencies (1.7 and 2.45 MHz).

Tagger C, Belenky I. Multi-channeling optimized radiofrequency energy: A new age in well-established radiofrequency technology. *World J Dermatol* 2016; 5(4): 129-135 Available from: URL: <http://www.wjgnet.com/2218-6190/full/v5/i4/129.htm> DOI: <http://dx.doi.org/10.5314/wjd.v5.i4.129>

INTRODUCTION

Local fat accumulation and cellulite formulation are two main symptoms related to the reduced metabolic rate in the tissue and rigid connective tissue. Non-invasive procedures based on different modalities such as high intensity focused ultrasound energy (HIFU), radiofrequency (RF), infrared light (IR), cryolipolysis, low-level laser therapy (LLLT), cavitation ultrasound, *etc.*^[1-9], in their principle indicated to induce natural lipolysis and reduce fat volume. Technologies that aimed to heat the adipose tissue mainly focused on improving the blood microcirculation to improve the metabolic rate in the impact tissue. In several RF-based systems the thermal

heat is combined with vacuum to produce mechanical pressure^[3-7,10]. The addition of mechanical pressure enhances the improvement of blood microcirculation and stimulates lymphatic drainage.

The distribution of RF's electrical current mainly depends on the geometry of the device's electrodes. In the esthetic market, two typical configurations are used: Monopolar and bipolar. The major difference between these two configurations is in the way the RF current is controlled and directed at the target tissue^[11]. The main advantage of a bipolar configuration is the controlled distribution of RF current inside the tissue, which is limited by distance between the two electrodes. Recently in the esthetic market new terms have sprouted up, such as multi-polar, tri-polar, octi-polar, *etc.* In this concept, the multi-polar RF is an engineering modification of a bi-polar configuration, where more than one pair of bipolar electrodes exists in the handpiece^[10]. The main advantage of a multi-polar handpiece is the ability to cover a much larger treatment area in one pulse, which in most cases leads to faster heating of the treated tissue and its ability to deliver homogeneous distribution of the heat.

The aim of this clinical study was to evaluate the safety and efficacy of Viora's new multi-polar RF handpiece (V-FORM) based on channeling optimized RF energy (CORE), Viora's proprietary technology^[10].

MATERIALS AND METHODS

Case study group

A group of twelve volunteers (11 females and 1 male) participated in the current study, ranging in age from 23-70 years (average 43.7, SD \pm 14.1) with Fitzpatrick skin type II-V. The inclusion criteria for the enrollment were no contraindications for RF treatment, body mass index (BMI) < 35 and local fat accumulation or cellulite formation. A total of 19 treatment areas were treated in the study: 9 abdomen, 2 abdomen plus flanks, 2 arms and 6 thighs (Table 1).

The initial body weight range of the patients was 57.3-78.7 kg (average 67.64, SD \pm 7.56) with a height range between 150-180 cm (average 163.8 cm, SD \pm 7.88) and a calculated BMI of 22-31 kg/m² (average 25.4, SD \pm 2.2). Six patients were in the range of normal "healthy weight" (BMI 18.5-25 kg/m²), five patients were in the "overweight" category (BMI 25-30 kg/m²) and one patient was in the "obese class I" (moderately obese) category (BMI 30-35 kg/m²) (Table 1).

Handpiece description

The new multi-polar RF handpiece (V-FORM) utilizes Viora's proprietary CORE technology with vacuum^[10], which represents the Multi-CORE technology. V-FORM handpiece has 4 levels of RF power (up to 50W), 4 levels of vacuum pressure intensity (up to 500 mbar) and 4 operational modes (Mode I-IV) with three RF frequencies: 0.8, 1.7 and 2.45 MHz and additional

Table 1 Case study patient details

Patient ID	Treatment area	Age	BMI	Number of treatments
VF-001	Thighs, abdomen plus flanks	28	23	6
VF-002	Abdomen	33	22	7
VF-003	Abdomen	44	26	6
VF-004	Abdomen	56	26	8
VF-005	Abdomen	31	26	Dropped from the study
VF-006	Abdomen	40	26	3
VF-007	Abdomen and thighs	23	25	Dropped from the study
VF-008	Arms and abdomen	70	31	8
VF-009	Thighs	34	25	3
VF-010	Abdomen plus flanks	61	27	5
VF-011	Abdomen	47	24	2
VF-012	Thighs	57	23	3
Average		43.7	25.4	5.1
SD (\pm)		14.1	2.2	2.1

BMI: Body mass index.

operation mode which includes all three RF frequencies. The V-FORM handpiece incorporates integrated IR thermometer, continuous impedance measurement system and interchangeable applicators in different sizes.

Treatment regimen

Circumferential reduction and cellulite reduction treatments were performed once a week (7 ± 1 d) for a treatment series of 3-8 sessions. Each treatment area was treated for 15-20 min, according to the treatment area's size. The treatments were performed according to Viora's standard protocol.

Clinical assessment

The clinical assessment of the treatment outcomes included several measurements and tools: The skin moisture level measured with a digital moisture monitor (Skin Testing Checker, Hautpflege-Konzepte aus Erfahrung) before the treatment and immediately post treatment. The measurement was performed on the same spot of the body, after the glycerin was applied. According to the digital moisture monitor indicator, values < 30% indicate extremely dehydrated skin, values between 31%-36% indicate dehydrated skin, values of 34%-47% indicated normal skin and values > 48% indicated excellent hydration; a skin impedance measurement was conducted according to Ohm's law, in which the impedance was derived from the peak voltage detected during the "test pulse" of the V-FORM handpiece after the electrodes came in touch with the skin. This measurement was performed in a separate test, on 10 randomly chosen treatment areas before the treatment and immediately post treatment on the same spot of the body, after the glycerin is applied; body temperature was measured *via* an integrated IR thermometer, at three times points: Before, during and immediately post treatment; circumferential measurements were performed using the same tape measure tool at the same points on the treated area. Two-

three measurement points with 5 cm distance in between were taken for each treatment area at three times: before, middle of course and four weeks after the last treatment. The circumferential change (in cm) was calculated as the following: Circumference (cm) recorded in the baseline meeting, minus circumference (cm) recorded four weeks after the last session; BMI was calculated according to standard guidelines, where weight in kg (kilograms) is divided by height in square meter. The body height and weight were measured according to a standardized protocol where patients are requested to stand without shoes and heavy outer garments for the measurement^[12]. The calculation of BMI conducted during the enrollment meeting and four weeks after the last treatment; clinical photographic assessments were recorded twice: (1) during enrollment meeting-(before the first treatment); and (2) four weeks after the last treatment; finally, the treating personnel were asked to record and immediately report any adverse event or unexpected side-effect.

Statistical analysis

For statistical analysis all tests were performed using Microsoft Excel 2010. In total, ten patients were included in the statistical analysis since two patients didn't complete the treatment course. Descriptive analysis was performed on the treated group and the number of valid cases for each test, minimum and maximum values, mean and standard deviation (SD), correlations between two values (CORREL) and percentage were calculated.

RESULTS

Ten of twelve patients completed the treatment course. No side effects were recorded during the study. The skin responded with slight erythema and sometimes edema, which is considered a positive end-point.

All patients maintained a stable weight (weight fluctuations were limited to -0.4 and + 0.6 kg) during the entire period of the study. No patient underwent any treatments or took medications for fat volume reduction during the study.

A moderate positive correlation was found between the patient's age and BMI (correlation coefficient 0.54).

The pre-heating time for all body areas ranged between 1-6 min (average 2.26 min) with a low negative correlation to the body's end-point temperature (correlation coefficient -0.31).

The initial body temperature (temperature before the treatment) ranged between 31 °C-35 °C as the baseline (average 31.9 °C) and increased to 32 °C-36 °C (average 34.0 °C) by the end of the treatment course.

The initial skin moisture level (detected before the treatment) ranged between 28.5%-49.0% as the baseline (average 38.9%) and increased to 31%-50% (average 40.98%) by the end of the treatment course (these values are not related to the skin impedance test described in Table 2). The skin moisture level measured at the end of each treatment ranged between 28.6%-65.0% (average 47.2%) which represents a 0.4%-31.4% change in the

Table 2 Skin impedance change post treatment (correlated to skin moisture level)

Patient ID	Treatment area	Skin moisture level (%)			Impedance (Ω)		
		Initial	End	Change (%)	Initial	End	Change (%)
VF-001	Abdomen	38.9	48.4	20	156.4	123.5	21.0
VF-002	Abdomen	32.0	54.2	41	201.9	188.0	6.9
VF-003	Abdomen	39.6	46.1	14	139.1	114.6	17.6
VF-004	Abdomen	38.5	46.7	18	147.7	94.6	35.9
VF-005	Abdomen	38.9	48.4	20	143.9	97.0	32.6
VF-006	Abdomen	41.6	48.3	14	144.0	132.0	8.3
VF-007	Abdomen	38.9	48.4	20	144.2	104.2	27.7
VF-008	Abdomen	36.3	47.0	23	104.8	95.7	8.6
VF-009	Thigh	37.2	46.6	20	216.5	179.3	17.2
VF-010	Abdomen	40.0	56.3	29	114.3	110.0	3.8
Average		38.2	49.0	21.7	151.3	123.9	18.0
SD (\pm)		2.5	3.2	7.6	32.7	32.1	10.7

Table 3 All measurement points of circumferential reduction per treatment area, number of treatments and body mass index (each line represents a separate measurement point)

Area	Circumference measurement		Circumferential reduction (cm)	Circumferential reduction (%)	Number of treatments	BMI (kg/m ²)
	Baseline (cm)	4 wk post last treatment (cm)				
Thighs	63	62.5	0.5	0.8	6	23
	58	58	0	0		
	64	63.5	0.5	0.8		
	56	56	0	0		
	56.7	54.2	2.5	4.6		
Abdomen	52.5	51.4	1.1	2.1	3	25
	40.4	39	1.4	3.6		
	40	39.4	0.6	1.5		
	94	90	4	4.4	6	23
	71.5	71	0.5	0.7		
	92	90	2	2.2		
	96	94	2	2.1	4	27
	87	85	2	2.4		
	92	90.5	1.5	1.7		
	93	95	-2	-2.1	6	26
	87	86.5	0.5	0.6		
	83	82	1	1.2		
	91	87	4	4.6	8	26
	101	95	6	6.3		
	112	100	12	12		
Arms	104	104	0	0	5	31
	112	97	15	15.5		
	104	96	8	8.3		
	92	89	3	3.4	5	27
	96	92.5	3.5	3.8		
	87	84	3	3.6		
	38	37	1	2.7	4	31
	36	34	2	5.9		
	38	35	3	8.6		
	36	38	-2	-5.3	8	31
	35	34	1	2.9		
	35	36	-1	-2.8		
	35	33.2	1.8	5.4	8	31
	35	34	1	2.9		

BMI: Body mass index.

moisture level post-treatment (average 9.23% change).

A test that aimed to evaluate the change in skin impedance was performed separately on ten randomly chosen treatment areas (Table 2). The initial skin impedance (detected before treatment) ranged between

104.8-216.5 Ω in the baseline (average 151.3 Ω , SD \pm 32.7) and decreased by 3.8%-35.9% (average 18%) by the end of the treatment, which represents a 4.4-53.1 Ω change in the impedance post-treatment.

A moderate negative correlation was found between

the changes in the skin's moisture level and skin impedance (correlation coefficient -0.5) with similar coefficient between initial values of impedance and skin moisture level (Table 2). This finding was expected, since blood and parts of the body with high water concentration have lower electrical resistance^[10].

All patients (10 of 10) responded to the treatment and showed some degree of circumferential reduction, on at least one of two-three measured points. The measured circumferential reduction of all 36 measurement points ranged from -2 cm (gained circumference) to 15 cm, with an average reduction of 2.78 cm (SD \pm 3.38) (Table 3). From a total 36 measurement points, only three measurement points did not show any change in the circumference, (0 cm) and three showed an increase in circumference (negative values in Table 3). Thighs showed the lowest percentage of circumferential reduction (1.68%), followed by the abdomen (4.28%) and arms (4.74%). A negligible positive correlation was found between the percentage of circumferential reduction and number of treatments (correlation coefficient 0.21). However, a low positive correlation was found between a percentage of circumferential reduction and BMI (correlation coefficient 0.44).

DISCUSSION

In this study, 100 percent of patients responded to the V-FORM treatment with at least a 0.6% circumferential reduction on one of the measurement points, indicating that RF treatment has influence on all types of patients. No correlation between the circumferential reduction and the number of treatments (correlation coefficient 0.21) may indicate that treatment response is based on individual characteristics of the patient such as metabolic rate, age and BMI. The positive correlation between circumferential reduction and BMI (correlation coefficient 0.44) supports this conclusion. Interestingly, the high BMI values (above 30 kg/m²) were mostly considered as exclusion criteria for RF-based treatments. In this study, the positive value of correlation between circumferential reduction and BMI indicates that the higher the patient's initial BMI, the higher percentage of circumference reduction we can achieve. Moreover, the patient with the highest BMI in this study (BMI 31 kg/m²) was also the most responsive to the treatment, with the highest circumferential measurement values and percentages (15.5% and 8.3%, Figure 1). These findings may suggest the multi-polar RF together with CORE technology may represent a non-invasive solution for high BMI patients. However, in order to establish a more accurate recommendation, additional study with a bigger cohort size, with BMI 30-35 needs to be conducted. The moderate positive correlation between the patient's age and BMI was also expected due to the fact that the metabolic rate of the body reduces with age, which leads to higher values of BMI. The positive correlation between age and BMI was also showed in several unrelated studies^[13,14].

Since in this study, all patients had maintained a stable weight, the circumferential reduction can be directly related to the treatment itself. Contrary to fat destruction techniques, such as laser lipolysis, liposuction, cavitation ultrasound, etc., the RF-based treatment aimed to increase the metabolic rate and enhance natural lipolysis of the fat cells without hypodermal distraction^[10]. The assessment of improvement in blood circulation can be evaluated *via* the changes in initial body temperature, skin moisture level and skin's impedance. In this study, the increase in initial body temperature from an average of 31.9 °C to an average of 34.0 °C by the end of the treatment course indicates improvement in the local blood microcirculation. This data is further supported by an increase in the initial skin moisture level (from an average of 38.9%-40.98%) and even more by an 18% change in the skin impedance. The negative correlation between skin moisture level and skin impedance (correlation coefficient -0.5) indicates that low water concentration contributes to the skin resistance as showed by high values of impedance. This finding is expected, since blood, and parts of the body with high blood content, have the highest electrical conductivity. The 0.4%-31.4% change (average 9.23%) in the moisture level post-treatment is additional supporting point to prove improved blood circulation. The change in the skin's moisture level at the end of the treatment course compared to the initial level recorded in the first treatment (average change of 40.98%) indicates a long term influence on the extracellular matrix achieved *via* fibroblast stimulation. This finding stands together with previously published data on the influence of RF and, in particular, CORE technology, on the dermal tissue^[10].

In addition, the significant change in circumferential measurements post-V-FORM treatments can be contributed not only to fat volume reduction due to improved metabolic rate and enhanced natural lipolysis, but also to edema reduction due to vacuum pressure integrated in the handpiece. Moreover, the Multi-CORE technology enables the control of RF depth penetration which allows finishing the treatments with a skin tightening effect using higher RF frequencies, at 1.7 and 2.45 MHz.

Thighs showed the lowest percentage of circumferential reduction with only 1.68% (compared to abdomen and arms with 4.28% and 4.74%, respectively). This can be explained by the fact that patients who participated in the study for thigh treatments exhibited cellulite appearance and not local fat accumulation (Figure 2).

The design of the V-FORM handpiece includes multiple electrodes (multi-polar RF) enables the coverage of big treatment areas in a very short time (the time needed to increase the body temperature to 39 °C-42 °C measured an average 2.26 min pre-heating time). The negative correlation between pre-heating time and the body's end-point temperature related to the fact that patients with higher skin conductivity can be heated much faster and to higher end-point temperatures.

During the entire study no adverse effects were recorded. This can be attributed to the fact that the

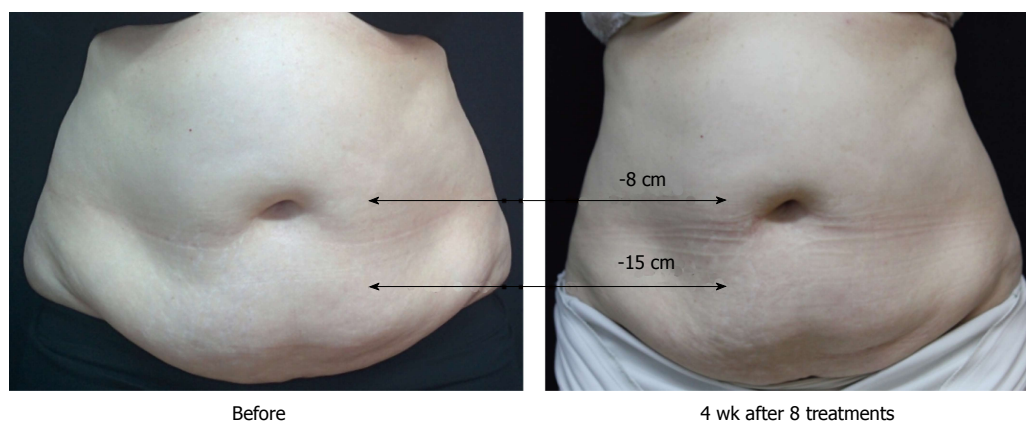


Figure 1 A 70-year-old female (body mass index 31) before and 4 wk after 8 treatment sessions (after), with 15 cm and 8 cm circumferential reduction (according to 2 measurement abdomen points).

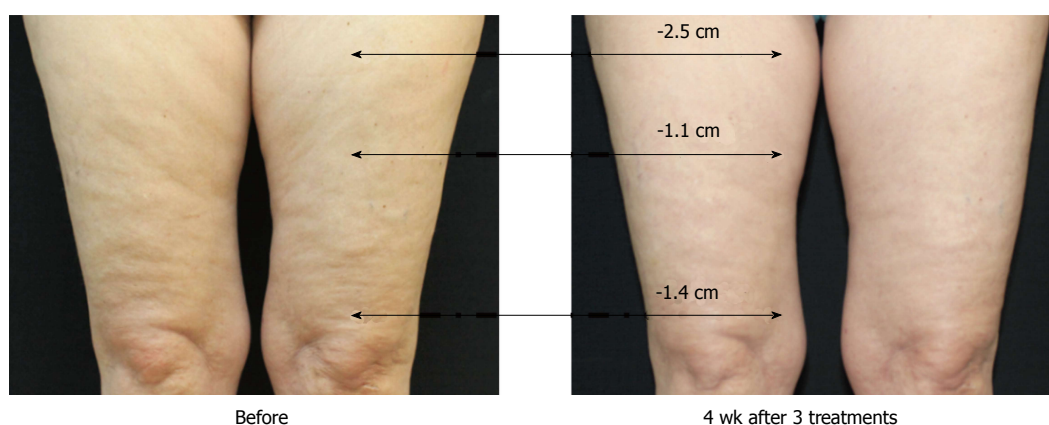


Figure 2 A 57-year-old female (body mass index 31) before and 4 wk after 3 treatment sessions with 2.5 cm, 1.1 cm and 1.4 cm circumferential reduction (according to 3 measurement points). Reduction of cellulite grade 3 to grade 2.

V-FORM handpiece monitors the skin impedance during the entire pulse and controls the RF energy current release accordingly. The design of the applicator itself contributes to an even vacuum spread over the tissue which dramatically reduces the chance to cause hematomas. Multiple electrodes contribute to the homogeneous heat spread over the tissue without hot-spots, which increase patients' tolerance to the treatments and also reduces the appearance of side effects. In addition, as expected, all skin types (I - V) that were included in the study reacted to the treatment regardless of the skin phototypes, as RF energy has similar behavior in all Fitzpatrick skin types.

In conclusion, according to clinical data collected in this study, the new V-FORM handpiece represents without any doubt an effective treatment with 100% response rate, with the safest treatment profile.

COMMENTS

Background

Local fat accumulation and cellulite formulation are two main symptoms related to the reduced metabolic rate in the tissue and rigid connective tissue. Invasive fat removal procedures are usually too expensive, with long downtime and complication. Therefore non-invasive procedure commonly used. Technologies that aimed to heat the adipose tissue mainly focused on improving the blood

microcirculation to improve the metabolic rate in the impact tissue. The main difference between these different technologies is the magnitude of change.

Research frontiers

In the recent years most of the studies in the field of non-invasive body contouring treatments concentrating on the ability to reduce fat volume with significant circumferential reduction achieved *via* several treatment without pain, complications and downtime.

Innovations and breakthroughs

This is a first published study conducted with multi-polar radiofrequency (RF) handpiece (V-FORM) which based on channeling optimized RF energy (CORE) technology. For the authors' knowledge, it was also the first study that examined the correlation between initial body temperature, moisture level, skin impedance and circumferential reduction.

Applications

The data in this study suggested that treatment with multi-polar RF based on CORE technology can achieve high percentage of circumferential reduction also among patient with BMI higher then 30, which was common limitation for most of RF based treatments.

Terminology

Multi-polar RF configuration is a system that has more than two typical bi-polar electrodes. In such configuration, each pair of electrodes acts as bi-polar RF, but more than one pair is available making the heating procedure faster and homogeneous.

Peer-review

This is an interesting paper regarding the use of radiofrequency technology, with regards to safety and efficacy. Overall, the study methodology was adequate, and the results were significant.

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Papular mycosis fungoides: Six new cases and association with chronic lymphocytic leukemia

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Institutional review board statement: The study was approved by the Johns Hopkins Institutional Review Board.

Informed consent statement: Information about patients was obtained from an approved Cutaneous Lymphoma Registry and informed consent for clinical photography was obtained from all patients.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Data sharing statement: No data were created no data are available.

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Abstract

Papular mycosis fungoides (MF) is a rare presentation of MF. Six illustrative cases of papular MF were retrospectively reviewed. Five of the cases studied by immunohistochemistry had variable numbers (range: 1%-20%) of CD30+ cells in the dermal infiltrate, a finding that is characteristic of lymphomatoid papulosis but may occasionally occur in typical early MF. Although none of our papular MF patients had progressive disease, lesions with relatively high numbers of CD30+ cells in 3 patients did not respond well to skin-directed treatments used for MF. Interestingly, these patients had evidence of co-existing clonal B cell populations in the blood (one with clonal B cell lymphocytosis and two with B-cell chronic lymphocytic leukemia). We conclude that: (1) papular MF may contain CD30+ cells, thereby causing confusion with lymphomatoid papulosis; and (2) papular MF, like more typical MF, may be associated with clonal B-cell proliferations including chronic lymphocytic leukemia.

Key words: Mycosis fungoides; Lymphocytosis; Chronic lymphocytic leukemia; Papule; Cutaneous lymphoma

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Core tip: Mycosis fungoides presenting with papules

as the only clinical manifestation is a rare variant of the disease. To date only 16 cases of papular mycosis fungoides have been described in the literature and none had CD30+ cells. We report 6 additional cases, 5 with 1%-20% CD30+ cells. Three cases had co-existing clonal B cell lymphoproliferation (2 with chronic lymphocytic leukemia). The possible pathogenic relationship between mycosis fungoides and chronic lymphocytic leukemia is discussed.

Vonderheid EC, Kadin ME, Telang GH. Papular mycosis fungoides: Six new cases and association with chronic lymphocytic leukemia. *World J Dermatol* 2016; 5(4): 136-143 Available from: URL: <http://www.wjgnet.com/2218-6190/full/v5/i4/136.htm> DOI: <http://dx.doi.org/10.5314/wjd.v5.i4.136>

INTRODUCTION

Mycosis fungoides (MF), a great masquerader of other skin diseases, can present with varied types of lesions that are confused with infectious and drug related eruptions among others^[1,2]. Recently, Kodama reported 6 cases of "papular MF" that presented with persistent papules that had the histopathologic features of MF but without typical patch/plaque MF lesions nor evidence of a lymphomatoid drug reaction^[3]. Lymphomatoid papulosis (LyP) was excluded by the absence of spontaneous regression of lesions and lack of CD30+ cells in the dermal infiltrate. With follow up, 2 cases subsequently developed typical skin manifestations of MF (one developed MF patches only 2 mo after the diagnosis of papular MF).

At the time of this report, 10 additional cases of papular MF have been published (Table 1)^[4-11]. Collectively, these papular MF cases (8 men, 8 women, ages, 27 to 83 years) are characterized by the following: (1) persistent papules, sometimes only a few millimeters in diameter, that did not enlarge into nodules, plaques or tumors; (2) Pautrier microabscesses in 8 of 14 cases; (3) a CD4+ immunophenotype in 8 cases and a CD8+ phenotype in 2 cases; (4) negative staining for CD30 in all 16 cases; (5) clonal T cells demonstrated in 7 of 8 cases; (6) subsequent appearance of typical patch or plaque lesions of MF in 3 cases including Kodama's 2 cases; and (7) an overall non-progressive clinical course.

Herein we report our experience with 6 additional cases of papular MF. Unlike reported cases, variable numbers of CD30+ cells were observed in the dermal infiltrate in 5 cases and 3 cases had evidence of co-existing clonal B-cell proliferations in the blood. The significance of these findings is discussed.

CASE REPORT

The registry of patients with cutaneous T cell lymphoma (1481 patients diagnosed with MF excluding its erythrodermic variant) that is maintained by one of us with



Figure 1 Patient 4 presented with a 6 mo history of persistent 2 to 8 mm papules of mycosis fungoides on the trunk and legs.

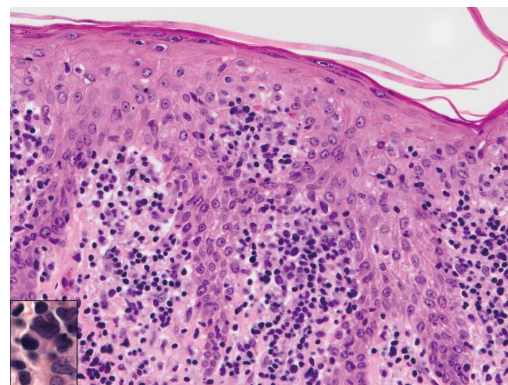


Figure 2 Skin specimen from patient 4 shows an acanthotic epidermis that contains atypical lymphocytes with hyperchromatic irregular nuclei (insert). The dermis has a superficial infiltrate composed of normal and atypical lymphocytes (H and E, × 400).

approval of the Institutional Review Board at Johns Hopkins University was reviewed for cases that fulfilled the clinical-pathological criteria for papular MF as defined by Kodama^[3]. Information obtained at the time of initial presentation, subsequent staging and follow up provide the basis of this report. This includes the results of histopathology, immunohistochemistry on corresponding frozen sections, and PCR amplification of T cell receptor gamma (TCR-γ) chain gene for T cell clonality on representative lesions.

The Surveillance, Epidemiology, and End Results (SEER)-9 registry, which captures data from 9.4% of the total United States population, was analyzed using SEER*Stat 8.2.1 software to determine the relative risk of developing chronic B-cell leukemia (ICD-O-3 Site C42.0, C42.1, C42.4 and ICD-O-3 code 9823/3) in patients initially diagnosed with MF (ICD-O-3 code 9700/3) and *vice versa* between 1973 and 2012. The statistical significance of the standardized incidence ratio (observed/expected) was determined using a Poisson distribution to calculate 95% confidence intervals.

Our retrospective review identified 6 patients who presented with persistent papules and/or small nodules with histopathologic features interpreted as diagnostic or consistent with MF (Table 2 and Figures 1-7). With follow-

Table 1 Mycosis fungoides presenting as persistent papules in the literature

Case ¹	ARG; Dur	Distribution	Dermal infiltrate	Epidermal lymphocytes	Immunophenotype	PCR	Progression (time) ²
Kodama1	57WM; NS	T	PV, F	Sm; PMAs	CD30-	ND	No
Kodama2	58WF; 2 yr	T, UE	Li, PV	Pleo Sm-med; No PMAs	CD4+30-	Pos	No
Kodama3	57F; Few mo	T, UE, LE	Li, PV	NS; No PMAs	CD30-	ND	Yes (3 yr)
Kodama4	41M; NS	LE	Li, PV	NS; No PMAs	CD30-	ND	Yes (2 mo)
Kodama5	59WM; 30 yr	T, UE, LE ³	Li	NS; PMAs	CD30-	ND	No
Kodama6	61M; NS	T	PV	NS; PMAs	CD4+8-30-	ND	No
Uddin	31WF; 2 yr	T, UE, LE	Li, PV, SC, VA	NS; No PMAs	Mostly CD30-	ND	No
Martorell- Calatayud1	50WF; 2 yr	T ³	A, P, Li, PV, F	Pleo Med-Ig; PMAs	CD4+30-	Pos	No
Martorell- Calatayud2	55WF; 1.5 yr	T, LE ³	NS	Sm-med; No PMAs	CD4+30-	Neg	No
Liu	27AM; NS	T ³	Li	NS; PMAs	CD4+8-30-	ND	No
Neri	47WF; 1 yr	UE, LE	PV	Sm-med CL; PMAs	CD4-8+7+30-	Pos	No
Noe1	83WF; 3 yr	T, UE, LE	PV	NS; PMAs	CD4+30-	Pos	No
Noe2	65WF; 1mo	T	Li, PV	NS	CD30-	ND	Yes (NS)
Brajon	63WM; 10 mo	T, UE, LE	Li, PV	CL; NS	CD4+8-30-	Pos	No
Santamarina- Albertos	55WM; 1 yr	LE	Li	Sm-med CL; NS	CD4+30-	Pos	No
Balta	35WM; 2 yr	T, UE, LE	A, PV	NS; PMAs	CD4-8+30-	Pos	No (10 mo)

¹References: [3-11]; ²Time to progression of disease; ³Some grouping or clustering of lesions. ARG: Age, race, gender; Dur: Duration to disease; PCR: Polymerase chain reaction for rearrangement of T cell receptor gamma chain; NS: Not stated; T: Trunk; UE: Upper extremities; LE: Lower extremities; Li: Lichenoid; PV: Perivascular; A: Acanthosis; P: Parakeratosis; F: Fibrosis; VA: Vacuolar alteration; SC: Subcutaneous; Sm: Small sized; Med: Medium sized; Lg: Large sized; Pleo: Pleomorphic; PMA: Pautrier microabscess; CL: Lymphocyte with cerebriform or infolded nuclei.



Figure 3 Persistent 2 to 14 mm papules of mycosis fungoides scattered on trunk and legs of patient 5.

up, none of these papular MF patients developed typical lesions of MF nor had disease progression. Pautrier microabscesses were described in skin specimens from 3 patients, and the immunophenotype of the neoplastic cells of 5 studied cases was CD4+CD8-. A dominant T cell clone was demonstrated by PCR in 3 cases.

Notably, all 5 patients evaluated for CD30 expression

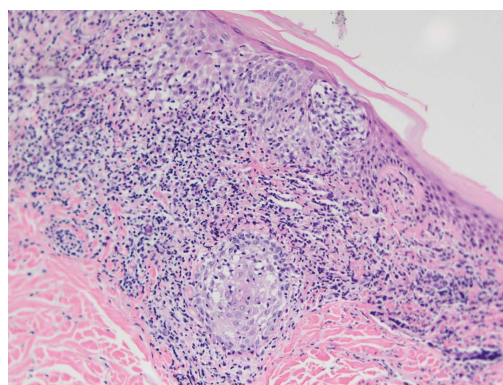


Figure 4 Skin specimen from patient 5 shows a moderately dense lichenoid infiltrate, wavy bundles of collagen in a thickened papillary dermis, and follicular mucinosis. Numerous atypical lymphocytes, some with large irregular nuclei, are located within the epidermis, both as solitary units and in aggregates, and dermal infiltrate (H and E, × 400).

had variable numbers of scattered atypical CD30+ cells in the dermal infiltrate (estimated range: 1%-20%), a finding that suggested the possibility of type A LyP with epidermotropic T cells or possibly type B LyP. This was particularly true for the specimen from patient 2 (Figure

Table 2 Six additional patients with papular mycosis fungoides

Pt	ARG; Dur ¹	Lesions and Size (mm)	Distribution	Dermal Infiltrate	Epidermal Lymphocytes	Immunophenotype ²	TCR- γ (method)	Course and Status (Duration FU)
1	68WM; 15 mo	Pa (1-2)	T, UE, UE	PA, VA, F, PC, Eos, LVC	Focal basilar Ep, Med CLs; No PMAs	ED: NS D: CD4 > CD8, CD30 10%	Pos Sk + Bd (SSCP) ³	Controlled on prednisone; developed pancytopenia; DwD (99 mo)
2	47 WM; 19 yr	Pa (3-5)	H/N, T	A, PV, F, Eos, PC, MtF, LVC	Focal basilar Ep, Med-Ig CLs; PMAs	ED: CD4+8-7-62L-30- D: CD4 90%, CD8 < 10%, CD7 < 10%, CD62L < 1%, CD30 5%-10%	Pos Sk + Bd (DGGE) ³	Poor or partial response to PUVA, MTX, isotretinoin, XRT, IFN α ; DwD (171 mo)
3	57 WF; 5 yr	Pa (2-5)	LE, UE	P, A, Li, PV, CLs	Basilar Ep, CLs; No PMAs	ED: CD4+8-7+62L+30+/- ⁴ D: CD4 80%, CD8 20%-30%, CD7 40%, CD62L 50%, CD30 1%-2%	Neg (DGGE)	PUVA/NBUVB: CR; breast CA; RA, HT; A, NED (156 mo)
4	68 WM; 6 mo	Pa (2-8)	T, LE	A, Li, F, EE, Neu (v), CLs	Diffuse Ep, Med CLs; No PMAs	ED: CD4+/-8-7+62L-30- D: CD4 60%-70%, CD8 20%, CD7 70%, CD62L 70%, CD30 1%-2%	Pos (DGGE)	PUVA: CR; no progression; AwD (210 mo)
5	58 WM; 2 mo	PaNd (2-14)	T, LE	Sp, Li, F, FM, CLs	Basilar Ep, Med-Ig CLs; PMAs	Not available	Neg (SSCP) ⁵	TopHN2: CR; No progression; A, NED (171 mo)
6	81 WM; 15 mo	PaNd (5-15)	T, LE	Li, F, CLs, MtF	Diffuse Ep, Med-Ig CLs; PMAs	ED: CD4+8-7-62L-30- D: CD4 99%, CD8 1%, CD7 10%, CD62L 99%, CD30 20%	Neg (DGGE) ^{3,5}	PUVA: PR; DwD/MI (12 mo)

¹Duration: Time from onset of disease to evaluation; ²Estimated percentage of positively labeled cells in dermal infiltrate (frozen sections). CD2, CD3, and CD5 expressed by all cases (data not shown); ³Clonal B-cell population detected by flow cytometry for patients 1, 2 and 6 and confirmed by PCR for patients 1 and 2 (see text for details); ⁴30% of epidermotropic T cells expressed CD30; ⁵Blood sample also negative for T cell clone. Pt: Patient; ARG: Age, race, gender; TCR- γ : T-cell receptor gamma chain rearrangement; FU: Follow up; Pa: Papule; Nd: Nodule; T: Trunk; UE: Upper extremity; LE: Lower extremity; A: Acanthosis; Sp: Spongiosis; P: Parakeratosis; VA: Vacuolar alteration; Ep: Epidermotropism; Li: Lichenoid (band-like); PV: Perivascular; PA: Periadenal; PDE: Papillary dermal edema; F: Fibrosis; FM: Follicular mucinosis; Neu (v): Neutrophils in vessels; PC: Plasma cells; Eos: Eosinophils; EE: Extravasated erythrocytes; CL: Lymphocytes with cerebriform or infolded nuclei (mycosis cells); MtF: Mitotic figures; LVC: Lymphocytes with vesiculated nuclei and prominent nucleoli; PMA: Pautrier microabscess; Sm-med: CLs with small-medium sized nuclei (5 to 7 μ m in diameter); Med-Ig: CLs with medium-large sized nuclei (7 to 9 μ m in diameter); ED: Epidermis; D: Dermis; >: Greater than; <: Less than; NS: Not stated; Sk: Skin; Bd: Blood; DGGE: Denaturing gradient gel electrophoresis; SSCP: Single-stranded conformation polymorphism; MTX: Methotrexate; XRT: Local field radiation therapy; IFN α : Interferon alpha; PUVA: Methoxsalen-ultraviolet A photochemotherapy; NBUVB: Narrow band ultraviolet B phototherapy; TopHN2: Topical mechlorethamine; CA: Carcinoma; RA: Rheumatoid arthritis; HT: Hashimoto's thyroiditis; MI: Myocardial infarction; AwD: Alive with active disease; DwD: Dead with active disease; A: NED, alive, no evidence disease; LTF: Lost to follow up.

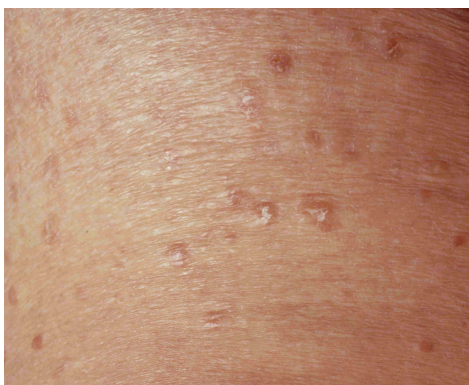


Figure 5 Patient 6 presented with a 15 mo history of persistent papules and small nodules, some with scaling, disseminated on the trunk and legs.

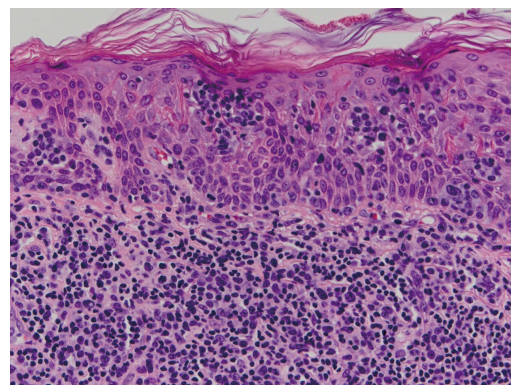


Figure 6 Skin specimen from patient 6 shows typical histopathologic features of mycosis fungoides. Nests of medium to large sized neoplastic lymphocytes with pleomorphic and cerebriform nuclei are observed within the epidermis (Pautrier microabscesses) and adjacent superficial dermis (H and E, \times 400).

7). However, his skin lesions did not spontaneously regress as expected in LyP. In addition, CD30 also was expressed by 30% of the epidermotropic CD4+T cells of patient 3 (discussed below). Therefore, other than

persistence of lesions, the histo-immunopathologic findings of papular MF overlap with those of LyP^[12,13].

Table 3 Frequency of B-cell chronic lymphocytic leukemia occurring after a diagnosis of cutaneous T cell lymphoma

Ref.	Cohort	No. patients (Dx)	No. secondary B-CLL (%)
Olsen <i>et al</i> ^[27]	One institution	63 (CTCL)	0 (0)
Kantor <i>et al</i> ^[28]	One institution	519 (MF)	2 (0.39)
Väkevää <i>et al</i> ^[29]	Finnish cancer registry	319 (MF/SS)	1 (0.3)
Barzilai <i>et al</i> ^[24]	Two institutions	398 (MF)	2 (0.50) ¹
Huang <i>et al</i> ^[30]	One institution	429 (MF/SS)	1 (0.23)
Huang <i>et al</i> ^[30]	SEER-9 registry	1798 (MF/SS)	0 or 4 (0 or 0.22) ²
Hallerman <i>et al</i> ^[31]	One institution	62 (CTCL)	0 (0)
Brownell <i>et al</i> ^[32]	One institution	672 (CTCL)	0 (0)
Hodak <i>et al</i> ^[33]	One institution	343 (MF)	2 (0.59)
Hodak <i>et al</i> ^[33]	Israeli population registry	683 (MF)	1 (0.15)
Lindahl <i>et al</i> ^[34]	Population-based	386 (MF)	0 (0) ³
Current study	SEER-9 registry	3,977 (MF)	10 (0.25)

¹One case with B-CLL preceding MF was excluded; ²Surveillance, Epidemiology, and End Results (SEER)-9 Cohort between 1984 through 2001 included 4 cases of leukemia, not defined; ³The 2 cases of hematologic cancer exclusive of non-Hodgkin lymphoma in this cohort were not B-CLL (Lindahl, personal communication, 2016). MF: Mycosis fungoides; SS: Sézary syndrome; CTCL: Cutaneous T cell lymphoma; B-CLL: B cell chronic lymphocytic leukemia; Dx: Diagnostic groups in cohort.

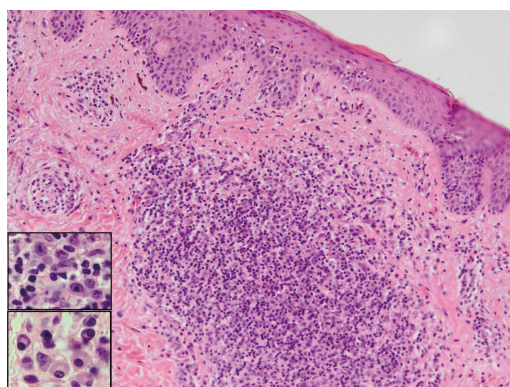


Figure 7 Skin specimen from patient 2 shows a perivascular and dense nodular infiltrate in the superficial and mid-dermis. A fibrotic papillary dermis and scattered epidermotropic lymphocytes aligned along the basal layer in the absence of spongiosis (H and E, $\times 400$). The dermal infiltrate is composed of lymphocytes, some with large hyperchromatic cerebriform nuclei, large immunoblast-like cells (top insert), small clusters of plasma cells (bottom insert), and occasional eosinophils.

A second observation is that 3 of the papular MF patients had evidence of an associated clonal B-cell lymphoproliferation. Patient 1 had a T cell clone in skin and blood plus 6% of blood lymphocytes with a CD5+CD19+CD23+ phenotype and B cell clone demonstrated by PCR of the IgH gene in the blood, but not the skin. The small B cell population remained unchanged with follow-up and is therefore classified as clonal B cell lymphocytosis. Patient 2 had a T cell clone in skin and blood plus 65% of his blood lymphocytes were CD19+CD20+ B cells (absolute lymphocyte count: 770 cells/mm³) and evidence of a B cell clone by PCR in the blood but not the skin. A subsequent bone marrow analysis revealed 20% B cells co-expressing CD5 and CD23 characteristic of chronic lymphocytic leukemia (B-CLL). Patient 6 also had a B cell clone in the blood by flow cytometry (21% of lymphocytes with a CD5+CD19+CD20+ phenotype; absolute lymphocyte

count: 2490 cells/mm³) but a negative PCR study when initially evaluated. However, a diagnosis of B-CLL was confirmed 6 mo later. These patients with clonal B cells tended to have higher percentages of CD30+ cells in their skin lesions and their response to treatment was partial or transitory compared to the other papular MF cases.

DISCUSSION

Papular MF is a very rare presentation of the disease, occurring in 0.4% of non-erythrodermic MF cases referred to our center. However, our patients differed from published cases with regard to the presence of atypical CD30+ cells in the dermal infiltrate in 5 studied specimens. Specimens from 3 patients had estimated numbers of dermal CD30+ cells that ranged from 5% to 20% such that LyP would be an alternative diagnosis. However, unlike LyP as currently defined, these lesions did not undergo spontaneous regression. Atypical CD30+ cells may also be encountered in clinically early lesions of MF so this finding does not exclude papular MF from the differential diagnosis^[14]. The clinical significance of CD30+ cells in this context is unclear. It has been reported that CD30 expression in non-transformed patch or plaque phase MF has an adverse prognostic significance^[14]. Although none of the patients in our small series developed more typical lesions of MF nor had disease progression, the 3 cases with 5% or more CD30+ cells in the dermal infiltrate did not respond adequately to various skin-directed therapies used to treat early MF.

An unexpected and previously unreported observation was that 3 patients with papular MF had an associated B-cell lymphoproliferative disorder (one with monoclonal B cell lymphocytosis and two with B-CLL). This raises the possibility that some of our papular MF cases might be examples of pseudo-MF reactions associated with B-CLL as described by Ingen-Housz-Oro^[15]. In that paper, the

authors reported 4 patients that presented with localized papules in concert with B-CLL. Three patients were diagnosed to have a pseudo-MF reaction and one had papular MF. All cases had evidence of folliculotropism by lymphocytes and 3 had follicular mucinosis including the papular MF case. Of note, a T cell clone could not be demonstrated by PCR of the TCR- γ chain gene in all cases, whereas clusters of neoplastic B cells were observed in 3 cases including the papular MF case. CD30 staining was not performed. Therefore our papular MF cases differ from Ingen-Housz-Oro's cases in several ways: (1) in our patients, lesions were more widespread; (2) folliculotropic T cells and a B cell component in the infiltrate were not present; and (3) T cell clonality was demonstrated in two cases. Of interest, mature appearing plasma cells were observed in the dermal infiltrate of skin specimens obtained from patients 1 and 2 who had evidence of clonal B cells in the blood but not the skin (Figure 7). In addition, a prior skin specimen from patient 6 and studied elsewhere also showed numerous plasma cells. This phenomenon may be the result of a homing process as suggested by Ingen-Housz-Oro^[15].

The association of MF and B-CLL may not be a fortuitous event. A review of the literature uncovered 23 cases of classic patch, plaque or tumor phase MF (erythrodermic MF excluded) co-existing with B-CLL^[15-26]. Of interest CD30 staining was performed on skin specimens from only 2 cases and both were reported to be negative. Nevertheless, it has not been established that the risk of developing secondary B-CLL in MF patients is significantly higher than for the general population (Table 3)^[27-34].

In the SEER-9 database, 1973 to 2012, there are 3977 cases coded as MF as the primary cancer for analysis. Of these, B-CLL was subsequently diagnosed in 10 cases compared to an expected frequency of 6.77 cases. Therefore, the relative risk (observed/expected) is 1.48 (95%CI: 0.71-2.71). Conversely, of 34160 cases with B-CLL as the primary cancer, 7 developed MF as a second cancer for a relative O/E of 7/4.02 or 1.74 (95%CI: 0.7-3.59). Although these relative risks are increased, they are not statistically significant. However, the possibility that the number of MF cases in the SEER registry might be under reported must be considered for several reasons: (1) some MF cases may be diagnosed as cutaneous T cell lymphoma and therefore coded by registrars as such (ICD-0-3 code 9709/3); (2) cases of MF and B-CLL that are diagnosed concurrently are coded separately as primary cancers; and (3) perhaps not all cases of MF are reported to the SEER registry by private dermatologists or dermatopathology laboratories^[35].

With regard to the first point, of 1304 patients coded initially as having cutaneous T cell lymphoma, 18 patients were subsequently coded as MF compared to an expected number of 0.15. The observed/expected ratio was 121.58 (95%CI: 72.06-192.15) was significantly high ($P < 0.05$). It is therefore conceivable but not proven that some patients with MF might be coded initially in the broader diagnostic category of cutaneous T

cell lymphoma.

Incidentally our review also uncovered a case reported in 1983 that was characterized by disseminated therapeutically resistant papules with histopathologic features of MF in a patient with B-CLL^[36]. We propose this case could represent the first example of papular MF associated with B-CLL.

The underlying basis for the uncommon but well documented association of MF and other forms of cutaneous T cell lymphoma with various B cell lymphoproliferations is unclear. Our hypothesis, which also has been suggested by others^[18,19], is that an inherited genetic attribute that predisposes a patient to lymphoma (such as a nucleotide polymorphism)^[37] or an acquired mutation is present at the level of the common lymphoid progenitor cell. If additional genetic alterations that promote lymphoma occur later in both the B and T cell developmental pathway, this would account for the observed associations of various T and B cell lymphoproliferations. It would also explain why B-CLL may precede, follow or present concurrently with cutaneous T cell lymphoma and the increased familial risk of lymphomas in family members of patients with cutaneous T cell lymphoma^[38]. The increased risk of non-hematologic cancers in patients with cutaneous T cell lymphoma could be explained by the immunosuppression related to the disease and/or use of oncogenic treatments^[27-30,33,34,39].

Alternatively, the interaction between stimulatory ligands such as CD30-CD30L and CD40-CD40L expressed by T and B cells may provide an explanation for the co-existence of T and B cell lymphoproliferative diseases in susceptible patients. For example, the interaction between CD40L, which is expressed by neoplastic T cells of MF^[40], and CD40, which is constitutively expressed by B cells, could result in up-regulation of genes involved in B cell survival and proliferation^[41,42]. The frequent expression of CD30 in some of our papular MF cases (and most LyP variants) with possible increased levels of soluble CD30 in the blood that we have observed in typical early MF patients could in theory contribute to the risk of developing B-CLL^[43-45].

We conclude that MF may rarely present with persistent papules, but that there is considerable clinical and histo-immunopathologic overlap with LyP including a favorable prognosis^[12,13]. Indeed the main difference is the persistence of lesions in papular MF and spontaneous regression of lesions in LyP. Considering that typical MF lesions may undergo partial or even complete regression^[46], we wonder if the differences between papular MF and LyP may be related to differences in factors that mediate lesion regression such as the host immune response. In addition, in this small series, there appears to be an association of papular MF with B-cell CLL that requires confirmation and further investigation.

ACKNOWLEDGMENTS

The authors thank Steve of the SEER*Stat Technical Support team, for his assistance in calculating the

relative risk of secondary B-CLL in patients with MF.

COMMENTS

Case characteristics

Mycosis fungoides (MF), a great masquerader of other skin diseases, can present with varied types of lesions that are confused with infectious and drug related eruptions among others.

Clinical diagnosis

Lymphomatoid papulosis (LyP) was excluded by the absence of spontaneous regression of lesions.

Differential diagnosis

The registry of patients with cutaneous T cell lymphoma (1481 patients diagnosed with MF excluding its erythrodermic variant) that is maintained by one of the authors with approval of the Institutional Review Board at Johns Hopkins University was reviewed for cases that fulfilled the clinical-pathological criteria for papular MF as defined by Kodama.

Imaging diagnosis

This retrospective review identified 6 patients who presented with persistent papules and/or small nodules with histopathologic features interpreted as diagnostic or consistent with MF

Experiences and lessons

Papular MF is a very rare presentation of the disease, occurring in 0.4% of non-erythrodermic MF cases referred to their center.

Peer-review

This is an interesting case series of papular mycosis fungoides. The authors described the clinical and histological features of this clinical entity, and its association with chronic lymphocytic leukemia. In general, the manuscript is well-written, and the content is clinically relevant and scientifically informative.

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