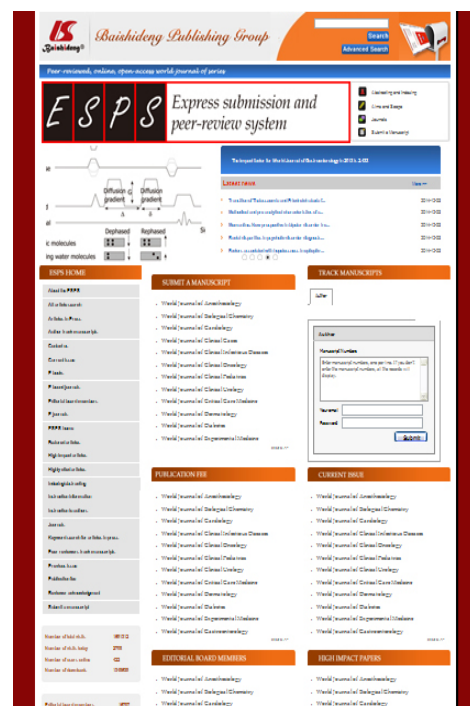
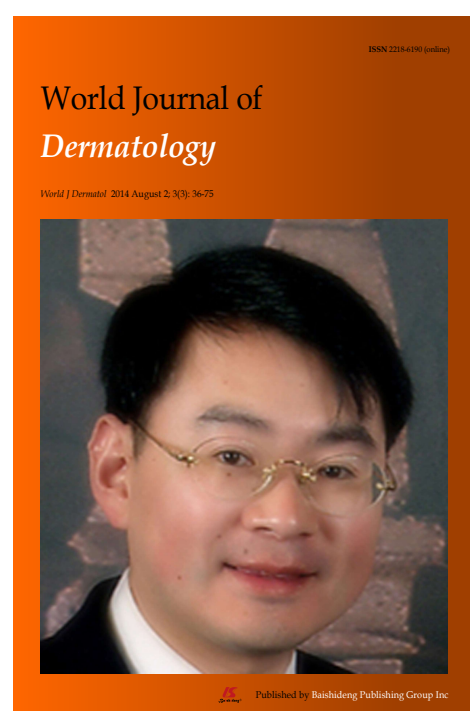
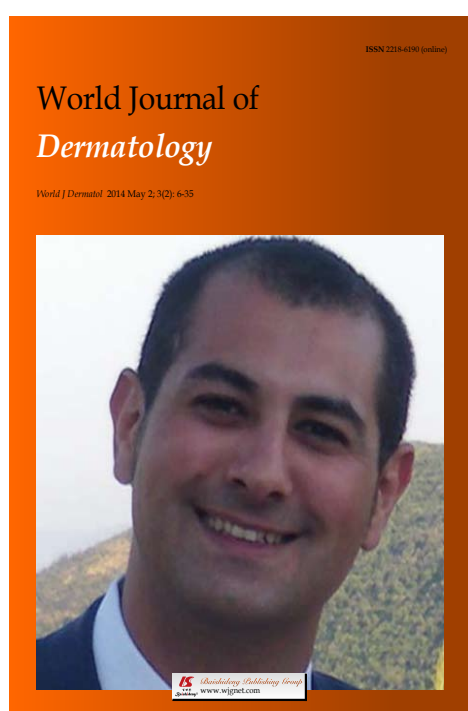
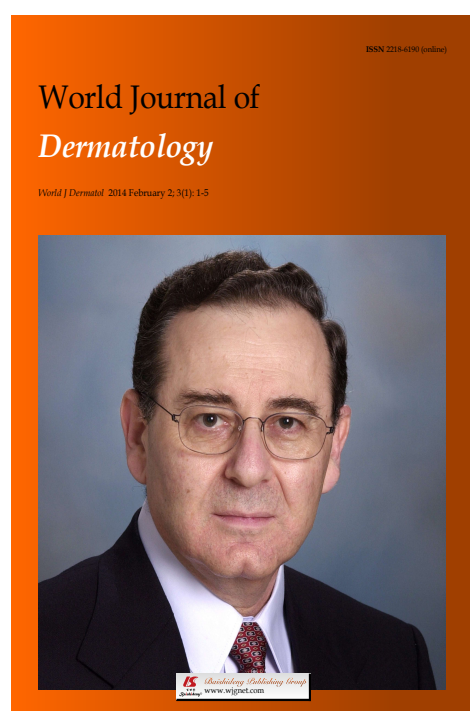


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Perianal verrucous epidermal nevus masquerading as warts

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Abstract

Verrucous epidermal naevus (VEN) is a rare form of epidermal naevus. We present a case of VEN occurring over the perianal region of a 7-year-old boy. The lesion was initially thought to be an area of chronic dermatitis; however it was refractory to treatment. Histopathology confirmed the diagnosis of VEN. VEN in the inguinogenital region may be misdiagnosed as flexural psoriasis, genital warts or sexual abuse. This is what precisely happened to our patient for a duration of more than 1 year.

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Key words: Perianal; Verrucous epidermal nevus; Warts

Core tip: The most interesting feature of this case is the difficulty of diagnosing verrucous epidermal naevus (VEN) of the genital region. It is expected that genital lesions are troublesome entities with respect to accurate diagnosis. It is essential for pediatricians as well as dermatologists to consider VEN as a possibility in warty genital or perianal lesions to avoid inappropriate accusations and irrelevant investigations of child abuse.

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INTRODUCTION

Epidermal naevi are hamartomas of the epidermis and papillary dermis. The histopathological appearance of verrucous epidermal naevus (VEN) is characteristic, with columns of hypergranulosis and orthokeratotic hyperkeratosis alternating with well-defined columns of agranulosis and parakeratotic hyperkeratosis^[1]. VEN affects the head neck region and the lower limbs; however, in a minority of patients, occur in the genital area.

CASE REPORT

A 7-year-old boy, hailing from an orphanage was referred to Dermatology for review of an intensely pruritic lesion in the perianal area, which had been present since 1 year. Previous treatment comprised of topical steroids and topical tar preparations, as per the advice of local physicians. After multiple visits to different medical professionals, the case was diagnosed as warts and he had received 2 cycles of cryotherapy before presenting to us. But, these only partially relieved his symptoms and the lesion remained unchanged. He was otherwise in good health, without regular medications or allergies. Since the child came from an orphanage, we took a multidisciplinary approach and meticulously enquired about history of sexual abuse. There was a definite history of multiple episodes of sodomy in the orphanage. On cutaneous examination, we found an extremely itchy, moist hyperpigmented and excoriated plaque over the perianal region. The surface of the plaque was verrucous in some places and atrophic and dyspigmented in other areas (Figure 1). There were no stigmata of eczema elsewhere on the skin. Hair, nail and mucosae did not reveal any abnormality. Even we kept perianal warts as our first differential diagnosis. Apart from that, other intertriginous dermatitis like

Das A, Gayen T, Das NK, Shome K. Perianal verrucous epidermal



Figure 1 Hyperpigmented and excoriated plaque over the perianal region.

candidiasis, zinc deficiency *etc.* were also kept in consideration. Routine blood investigations were within normal limits. Biopsy of the perianal region showed evidence of psoriasiform epidermal hyperplasia, with acanthosis, alternating parakeratosis and compact hyperkeratosis (Figure 2). Based on the clinical and histopathological findings, a diagnosis of verrucous epidermal nevus was done. The patient was prescribed topical antibiotic and steroid combination and surgical referral has been done for discussion of the viability of excision in this location. He was referred for psychiatric counseling as well in order to take care of the mental trauma which was much more than the physical issues.

DISCUSSION

The verrucous morphology and the occurrence in the genitalia may raise the question of sexually transmitted disease and sexual abuse. In a case report by Sarifakioglu *et al*^[2], a patient with scrotal verrucous epidermal naevus was treated with cryotherapy for genital warts prior to diagnosis. Sexual abuse is often suspected in children with genital dermatological conditions including dermatitis, vulval immunobullous conditions, infantile haemangioma, psoriasis *etc.*^[3]. Lichen sclerosus et atrophicus is often mistaken for child abuse with clinical findings of atrophic plaques, genital pruritus, erosions and bruising. A case of vulvitis circumscripta plasmacellularis mimicking child abuse has been reported by Albers *et al*^[4]. Porzionato *et al*^[5] reported a case where sexual abuse was suspected in a patient with perianal and vulval Crohn's disease presenting as perianal pruritus, fissuring and swelling of the labia majora.

VEN is resistant to topical therapies and symptomatic improvement usually requires ongoing therapy. Topical therapies include coal tar, corticosteroids under occlusion and retinoic acid. Topical calcipotriol has been used successfully. The long-term application of potent steroids on the genitalia is limited due to the possible adverse effects. Physical therapies used in the treatment include dermabrasion, cryotherapy and carbon dioxide laser therapy. Full-thickness excision with primary closure, use of adjunctive tissue expansion, skin flaps and split-thickness

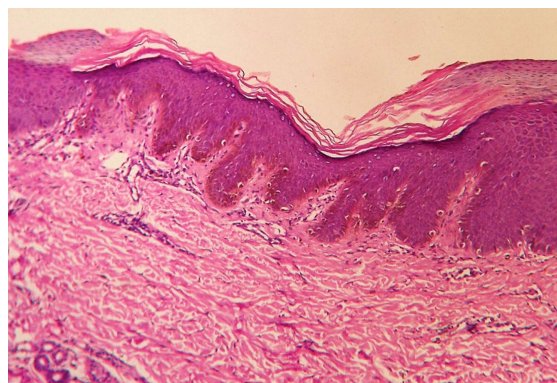


Figure 2 HPE showing foci of parakeratosis with depressed foci of orthokeratosis (HE, × 10).

skin graft has been reported by Lee *et al*^[6] in a case series of four patients (three children, one adult). Sarifakioglu *et al*^[2] described total excision of an epidermal naevus occurring on the scrotum.

The purpose behind reporting this case is to demonstrate the difficulty of diagnosing VEN of the genital region. It is quite common for genital lesions to evade accurate diagnosis and this is exemplified in our case. It is essential for pediatricians as well as dermatologists to consider VEN as a possibility in warty genital or perianal lesions to avoid inappropriate accusations and irrelevant investigations of child abuse. Diagnostic pointers include refractoriness to treatment, hyperkeratosis and the unilateral nature of the lesion. The diagnosis of verrucous epidermal naevus should be suspected in persistent genital eczematous or psoriasiform lesions in pediatric age group and any discordance in response to treatment for such lesions must be met with, seriously; and referral to a dermatologist is warranted.

COMMENTS

Case characteristics

A 7-year-old boy, hailing presented with an intensely pruritic lesion in the perianal area, which had been present since 1 year.

Clinical diagnosis

Cutaneous examination showed moist hyperpigmented and excoriated plaque over the perianal region, the surface being verrucous in some places and atrophic and dyspigmented in others. Clinically, it was probably a result of sexual abuse.

Differential diagnosis

Clinical differentials include warts, lichen sclerosus et atrophicus, verrucous epidermal nevus, flexural psoriasis, dermatitis, candidiasis, zinc deficiency, *etc.*

Laboratory diagnosis

Laboratory investigations were within normal limits.

Pathological diagnosis

Biopsy of the perianal region showed evidence of psoriasiform epidermal hyperplasia, with acanthosis, alternating parakeratosis and compact hyperkeratosis. It was consistent with Verrucous epidermal nevus.

Treatment

Patient has been prescribed topical antibiotic and steroid combination and surgical referral has been done for discussion of the viability of excision in this location.

Related reports

Sarifakioglu reported a patient with scrotal verrucous epidermal naevus who

was treated with cryotherapy for genital warts prior to diagnosis. A case of vulvitis circumscripita plasmacellularis mimicking child abuse has been reported by Albers. Porzionato reported a case where sexual abuse was suspected in a patient with perianal and vulvar Crohn's disease presenting as perianal pruritus, fissuring and swelling of the labia majora.

Experiences and lessons

The crux of this report is the difficulty of diagnosing VEN of the genital region. It is quite common for genital lesions to evade accurate diagnosis, consistent with the case. It is essential for pediatricians as well as dermatologists to consider VEN as a possibility in warty genital or perianal lesions to avoid inappropriate accusations and irrelevant investigations of child abuse. In any case of diagnostic dilemma, a histopathological examination is quintessential.

Peer review

The diagnosis of verrucous epidermal naevus should be suspected in persistent genital eczematous or psoriasiform lesions in pediatric age group and any discordance in response to treatment for such lesions must be met with, seriously; and a timely referral to a dermatologist is warranted. It is an interesting example to reflect on the implications of this disease and especially on the diagnostic difficulties. The manuscript emphasizes the special attention that was needed given that the boy lived in an orphanage.

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Actinic lichen planus: a presentation, deviant from the conventional

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INTRODUCTION

Actinic lichen planus is a variant form of lichen planus located on light-exposed areas, occurring in children or young adults (dark skinned individuals) living in tropical countries. The presentation of the entity can be diverse and hereby, we report an interesting presentation.

CASE REPORT

A middle-aged lady presented to us with asymptomatic multiple red-brown papules and plaques over the face and nose for a duration of 2 years. The course of evolution of the lesion involved a mild burning sensation on sun-exposure 2 years back and 1-2 mo after that, she developed a few papules which gradually increased in number and some of them also coalesced to form small plaques (1.0-2.5 cm) which were erythematous to brownish in color with a history of summer exacerbation (Figure 1). No history of regular drug intake or similar lesions in the past or in the family. Scalp, oral and genital mucosa and nails were absolutely normal. Cosmetic concern prompted her to seek medical treatment. On the basis of the clinical presentation of the patient, we considered syringoma and mucinosis as a differential diagnosis and one of the lesions was subjected to biopsy for confirmation of our diagnosis.

To our utter surprise, on histopathological examination we found epidermal atrophy, basal cell layer degeneration, melanin incontinence and band-like infiltration of lymphocytes at the dermoepidermal junction, which clinched the diagnosis of a variety of actinic lichen planus (Figure 2). Photoprotection and an intramuscular injection of triamcinolone were advised. Marked improvement was seen after a single dose (Figure 3).

Abstract

Actinic lichen planus, a variant of lichen planus usually in people living in the tropics, presents as annular or discoid patches over the sun-exposed regions. We present here a case of actinic lichen planus with papules and plaques over the malar region and dorsum of nose - a rare presentation of this entity.

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Key words: Actinic; Lichen; Planus; Unusual; Presentation

Core tip: This is an interesting case of a young lady who presented with brown and erythematous papules and plaques. Clinically, no one thought of lichen planus in the differential diagnosis. It exemplifies the fact that a dermatological entity can be so diverse in its presentation and become a mystery for the clinician to diagnose.

Ghosh A, Das A, Kumar D, Gharami RC. Actinic lichen planus: a presentation, deviant from the conventional. *World J Dermatol* 2014; 3(1): 4-5 Available from: URL: <http://www.wjgnet.com/2218-6190/full/v3/i1/4.htm> DOI: <http://dx.doi.org/10.5314/wjd.v3.i1.4>



Figure 1 Multiple erythematous to brownish in color papules, coalescing to form plaques over the malar regions and nose.

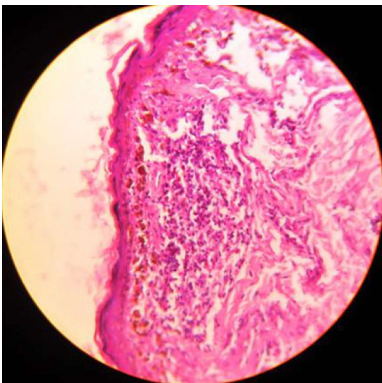


Figure 2 HPE showing epidermal atrophy, basal cell layer degeneration, pigment incontinence and band-like infiltration of lymphocytes at the dermoepidermal junction (HE, x 40).

DISCUSSION

Actinic lichen planus, also known as lichen planus subtropicus, lichenoid melanodermitis and lichen planus atrophicus annularis, mainly affects children and young adults of Middle-East, African or Indian origin. There are 3 clinical types: annular, pigmented and dyschromic^[1,2]. There is no sexual predilection and typical lesions are annular or discoid patches on sun exposed regions with a hyperpigmented center and a surrounding hypopigmented zone. Recurrent painful annular erythema on the face and hands in a 52 year old Japanese man have been reported, suggesting varied and atypical presentation of actinic lichen planus^[3]. It is treated with acitretin, topical corticosteroids^[4] and with cyclosporine^[5].

Uncommon morphology is the reason behind our purpose of reporting the case.

COMMENTS

Case characteristics

A middle-aged lady presented to us with asymptomatic multiple red-brown pap-



Figure 3 Showing pre-treatment photograph (A) and post-treatment photograph (B) following one intramuscular injection of triamcinolone.

ules and plaques over the face and nose for a duration of 2 years.

Clinical diagnosis

Syringoma and mucinosis.

Differential diagnosis

Syringoma, mucinosis, other deposition disorders, actinic lichen planus.

Peer review

This is an interesting case that has educative value.

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- 15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/eid/index.htm>

Patent (list all authors)

- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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Photodynamic therapy with topical aminolevulinic acid

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Key words: Photodynamic therapy; Aminolevulinic acid; Skin cancer

Core tip: Photodynamic therapy (PDT) with aminolevulinic acid is a relatively new therapy in dermatologic practice, and the indications for PDT are increasing continuously. PDT is based on the topical application of a porphyrin derivative followed by exposure of the treated area to a specific wavelength of light to selectively destroy a cutaneous target. A thorough knowledge of the mechanism of action of the treatment and its effects are necessary to provide the patient with an appropriate assessment and indication. In this paper we report the mechanism of action of PDT with aminolevulinic acid, the literature concerning the most common diseases treated with PDT and the subsequent level of evidence, according to the European Guidelines.

Abstract

Photodynamic therapy (PDT) is a relatively new therapy in dermatology that uses the topical application of a porphyrin derivative to selectively destroy a cutaneous target. The action is implemented by the application of a specific light frequency. The ability of porphyrin to selectively target tumor tissue has been known since the 1960s. In the late 1970s, the underlying mechanism was defined, and Dougherty's discovery of the first chromophore led to the production and commercialization of Photofrin®. Many other chromophores that can act as photosensitizers have been studied since then, with aminolevulinic acid currently the most commonly used chromophore in clinical practice. PDT is simple, minimally invasive and can be administered on an outpatient basis. The efficacy of PDT has been proven for actinic keratosis, Bowen's disease and basal cell carcinoma; another of its well-known applications is the treatment of photoaging. Indications for its use are continuously increasing, and promising results are reported for various skin diseases. In this paper we report the mechanism of action of PDT with aminolevulinic acid, the literature concerning the most common diseases treated with PDT and the subsequent level of evidence.

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INTRODUCTION

Photodynamic therapy (PDT) with aminolevulinic acid (ALA) is a relatively new therapy in dermatologic practice. PDT is based on the topical application of a porphyrin derivative followed by the exposure to a specific light wavelength to selectively destroy a cutaneous target. The indications for PDT are continuously increasing (Table 1). In this paper, we report the mechanism of action of ALA-PDT, the literature concerning the most common diseases treated with PDT and the subsequent level of evidence, according to the European Guidelines.

Table 1 Most common reported indications for photodynamic therapy in oncological and non-oncological skin diseases

Oncological skin disease
Actinic keratoses
Bowen's disease
Basal cell carcinoma
Squamous cell carcinoma
Cutaneous T-cell lymphoma
Cutaneous B-cell lymphoma
Extra-mammary paget's disease
Non oncological skin disease
Acne vulgaris
Warts
Photorejuvenation
Other indications:
Cutaneous leishmaniasis
Localized scleroderma
Lichen sclerosis
Perioral dermatitis
Cutaneous mycosis

Historical view

The use of light as a therapeutic tool was reported in 1900, when sunlight was used to activate eosin for tumor treatment^[1,2]. In 1960, Winkelman^[3] used a porphyrin to detect tumor tissue. In the same year, Schwartz isolated an impure hematoporphyrin derivative (HpD)^[4], and Lipson suggested that the derivate could be used as a photosensitizer to destroy neoplastic tissue^[4]. The mechanism of cellular destruction was recognized as singlet oxygen production in 1976^[5].

Dougherty discovered that the HpD had a high singlet oxygen quantum yield, a maximum absorption in the red spectrum and was selectively retained in tumor tissue^[6]. The active fraction of the HpD was then isolated and produced as Photofrin®. Dougherty can be considered the inventor of PDT.

Since the introduction of Photofrin® in medicine, many other photosensitizers have been studied, and ALA was recently introduced in PDT for the treatment of superficial skin lesions.

Photochemistry

The mechanism of action of PDT can be explained by analyzing the photochemical reaction that generates singlet oxygen^[1].

A chromophore exposed to a light with a specific wavelength is excited to a singlet state that is unstable. From the singlet state, the chromophore passes to the ground state, either emitting a fluorescent photon or transforming into the stable triple state (Figure 1). In an aerobic environment, the chromophore transfers energy to ground state oxygen, producing singlet oxygen ($^1\text{O}_2$). The ability to produce singlet oxygen is one of the most important factors in determining the activity of a chromophore.

Singlet oxygen in an aqueous environment has a lifetime of 2 μs , and its energy is dissipated as heat in a spherical volume of 10 nm in diameter.

In conclusion, PDT can induce oxidative damage

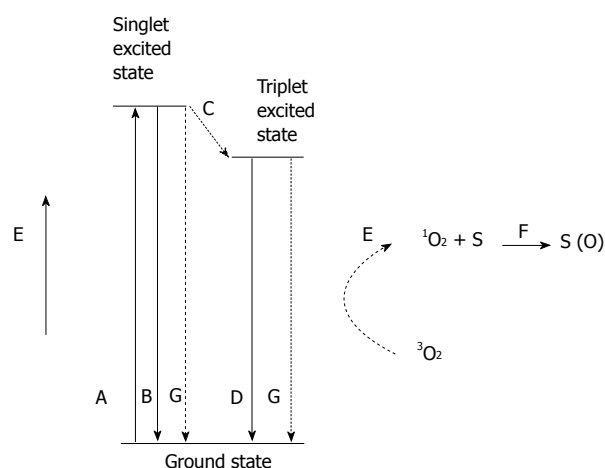


Figure 1 Jablonski diagram showing the various modes of excitation and relaxation in a chromophore. A: Excitation; B: Fluorescence; C: Intersystem crossing; D: Phosphorescence; E: Non-radiative transfer of energy to singlet oxygen; F: Substrate oxidation by singlet oxygen; G: Internal conversion (adapted from Macdonald *et al*^[1]).

that is localized near the point of production of singlet oxygen or in a region larger in diameter than a cell membrane; this induction can only occur in an oxygenated environment.

Aminolevulinic acid

Among the different chromophores studied as photosensitizers, Δ^5 -aminolevulinic acid (ALA) is the most commonly used to treat skin disease.

ALA is a precursor of heme^[7], and overloading a cell with ALA forces the cell to produce protoporphyrin-IX (PP), which acts as photosensitizer.

Neoplastic cells present a relative reduction of ferrochelatase activity, which is responsible for the conversion of PP into heme. Therefore, PP production is faster than its conversion to heme, and PP accumulates in cells that become photosensitive.

ALA selectively accumulates in tumor cells because of its high reproduction rate^[6,8]; the esterification of ALA alters its captation through the membrane from an active to passive mechanism, leading to high ALA penetration into cells.

The association with iron chelation appears to increase porphyrin loading and light action, while the entry of porphyrin into cells is limited by an intact corneal layer.

By illuminating PP with adequate light, we can induce the production of singlet oxygen, which leads to damage that is confined to membranes and subcellular organs.

The light used to activate PP requires a wavelength greater than 600 nm to reduce adsorption from melanin and hemoglobin. The absorption peak of PP is from 630-635 nm.

ALA is offered on the market as a cream with a concentration of 20%.

More recently, methyl aminolevulinate (MAL), a derivative of ALA, was introduced in clinical practice. MAL accumulates in tumor cells with a mechanism similar to

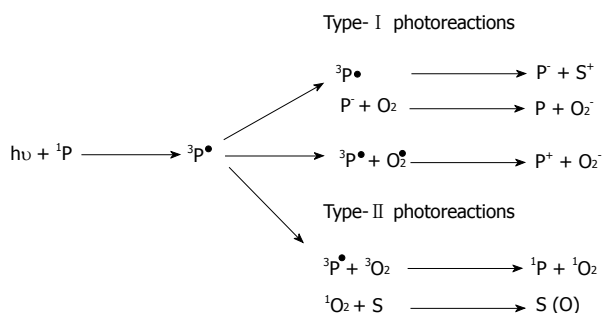


Figure 2 Cellular damage mechanism. Type-I and Type-II photoreactions, where 1P is a photosensitizer in a singlet ground state, ${}^3P^*$ is a photosensitizer in a triplet excited state, S is a substrate molecule, P^* is reduced photosensitizer molecule, S is an oxidized substrate molecule, O_2 is molecular oxygen (triplet ground state), O_2^- is the superoxide anion, O_2 is the superoxide radical, P is the oxidized photosensitizer, 3O_2 is triplet ground-state oxygen, 1O_2 is oxygen in a singlet excited state, and S(O) is an oxygen adduct of a substrate (adapted from Macdonald *et al*^[1]).

ALA and is hydrolyzed in the cytoplasm, releasing ALA into the cytosol. Unlike ALA, MAL is lipophilic.

Cellular damage mechanism

PP is excited by light with an adequate wavelength and, during the subsequent relaxation phase, PP transfers energy to oxygen producing singlet oxygen (type II reaction) and free radicals (type I reaction) (Figure 2). The type II reaction is predominant in PDT^[9,10].

The damage induced in the mitochondrial membrane leads to enzymatic inhibition and a subsequent breakdown of the electron transport chain and cytochrome C release, which is responsible for apoptosis induced by caspase pathway activation^[11,12] (Figure 3).

Oxygen free radicals also induce damage in endothelial cells, causing inflammation and platelet aggregation. The consequent thrombosis of intra-tumoral vessels starves neoplastic cells of oxygen and nutrients, promoting necrosis^[13,14].

Another effect induced by PDT is linked to indirect immune system activation against the tumor. The damage induced to tumoral tissues releases neoplastic antigens, which are captured by dendritic cells and presented to T lymphocytes, inducing a specific immune action against the tumor^[15].

All of the reported mechanisms are responsible for the damage induced by PDT to neoplastic tissues.

Technique

The lesion is adequately treated with a curette to selectively “modify” the corneal layer (Figure 4). No bleeding should be present and hemostasis must be obtained in cases where bleeding occurs (Figure 5).

ALA 20% cream is then applied to the lesion using approximately 50 mg/cm². The lesion is then occlusively dressed (Figure 6), and sun exposure must be avoided for at least 3 h^[16].

After 3 h, the dressing is removed, and the lesion is exposed to specific light for 12 min. The eyes must be protected during the exposure.

Pain during and/or after the treatment is the most common adverse effect and is most likely due to the direct stimulation of free nerve endings in the epidermis during irradiation and to the inflammatory environment induced by PDT^[17,18]. It is particularly noticeable in locations such as the scalp, face and hands and is related to the extension of the treated area. It has been proven that topical anesthesia is not effective in reducing this type of pain^[19,20], whereas good results were reported using devices that blow cold air^[21]. Erythema and edema are common after PDT; crust formation may also be observed, but complete healing is generally achieved in 2-6 wk (Figure 7).

Clinical applications

PDT is currently licensed for the treatment of actinic keratosis, Bowen's disease and basal cell carcinoma, but there are several studies on the use of PDT for other skin diseases^[22,23], and the possible indications are increasing continuously. The reported results of PDT in various skin diseases are summarized in Table 2. The strength of the recommendation and the level of the evidence for these different indications are reported in Table 3.

Actinic keratosis: Actinic keratosis is a very frequently reported skin disease that can lead to squamous cell carcinoma in 5% to 20% of cases in 10-25 years. Treatment with PDT reported good results, with high remission rates. In 1997, Jeffes *et al*^[24] reported a remission rate of 91% in the treatment of actinic keratosis of the face and scalp using ALA-PDT. Lower success rates (45%) were reported in trunk localizations, most likely due to less penetration of the photosensitizer. A comparison of different ALA concentrations led to Jeffes *et al*^[24] assessment that a 20% concentration is preferable for clinical applications. Tschen *et al*^[25] treated patients affected by actinic keratoses of the face and scalp with up to 2 sessions of ALA-PDT. He reported a clearance rate of 78% at 12 mo, with a recurrence rate of 19%; the cosmetic outcome was satisfactory in all cases, without any hyperpigmentation. Additionally, good results were reported for actinic cheilitis, with a complete clearance after 12 mo of follow up; the final aesthetic outcome was good, even if superficial peeling persisted for several months^[26].

ALA-PDT is an efficacious treatment for scalp and facial actinic keratosis, with high clearance rates and satisfactory cosmetic outcomes. The efficacy is higher using an ALA concentration of 20%. Actinic keratosis of the trunk and acral sites presents a lower remission rate in comparison to scalp and facial localization.

Bowen's disease: PDT is an effective treatment option for Bowen's disease. Remission rates of 89% were reported by Cairnduff *et al*^[27] in 1994, and in 1996, Morton *et al*^[28] reported higher clearance rates and better cosmetic outcomes with ALA-PDT compared with cryotherapy. More recently, in 2012, 29. López *et al*^[29] reported a complete clearance of 90% in 23 lesions treated by MAL-PDT, with a good aesthetic result. In another study conducted

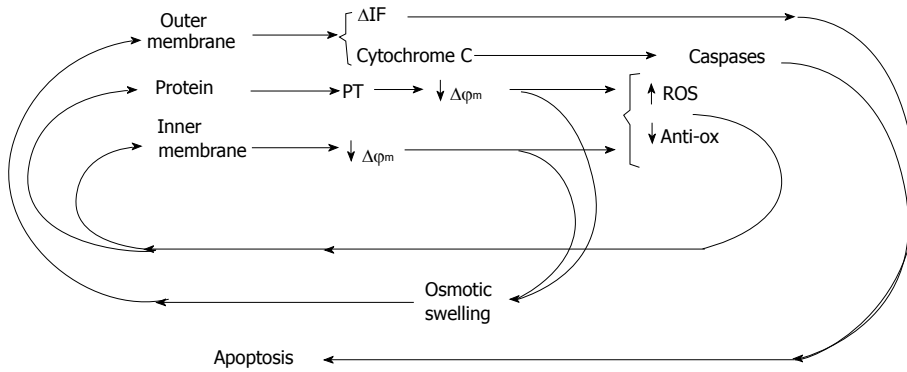


Figure 3 Summary of the pathways and feedback loops involved in mitochondrially controlled apoptosis. Star bursts represent possible points at which photodynamic therapy initiates mitochondrially controlled apoptosis (adapted from Macdonald *et al*^[41]).

Table 2 Reported results of photodynamic therapy in different skin diseases

Ref.	Disease	Remission rate	Follow up	n
Jeffes <i>et al</i> ^[24] , 1997	AK	91% scalp, face 45% trunk	16 wk	40
Tschen <i>et al</i> ^[25] , 2006	AK scalp, face	78%	12 mo	101
Stender <i>et al</i> ^[26] , 1996	AK lip	100%	12 mo	3
Cairnduff <i>et al</i> ^[27] , 1994	BD	89%	18 mo	36
López <i>et al</i> ^[29] , 2012	BD	90%	12 mo	18
Truchuelo <i>et al</i> ^[30] , 2012	BD	76%	17 mo	47
Calzavara-Pinton <i>et al</i> ^[31] , 2008	SCC	57% microinvasive 26% nodular invasive	2 yr	55
Christensen <i>et al</i> ^[32] , 2009	BCC	68% single session 91% two session	6 yr	60
Christensen <i>et al</i> ^[33] , 2012	BCC	60% single session 87% two session	10 yr	60
Souza <i>et al</i> ^[34] , 2009	BCC	> 90% 60%	3 mo 5 yr	34
Soler <i>et al</i> ^[35] , 2001	BCC	89%	3 yr	350
Svanberg <i>et al</i> ^[49] , 1994	TCL	100%	6-14 mo	4
Orenstein <i>et al</i> ^[50] , 2000	TCL	100%	24-27 mo	2
Mori <i>et al</i> ^[51] , 2006	BCL	100%	8-24 mo	3
Shieh <i>et al</i> ^[52] , 2002	PD	50% 31%	6 mo 10 mo	5
Raspagliesi <i>et al</i> ^[54] , 2006	PD	57%	1-5 mo	7
Stender <i>et al</i> ^[58] , 2000	Hand-foot W	76%	18 wk	45
Fabbrocini <i>et al</i> ^[59] , 2001	Plantar W	75%	2 mo	64
Fehr <i>et al</i> ^[63] , 2002	Vulvar W	66%	12 mo	16
Stefanaki <i>et al</i> ^[64] , 2003	Male genital W	73%	12 mo	12

AK: Actinic keratosis; BD: Bowen's disease; SCC: Squamous cell carcinoma; BCC: Basal cell carcinoma; TCL: Cutaneous T-cell lymphoma; BCL: Cutaneous B-cell lymphoma; PD: Extra-mammary Paget's disease; W: Warts.

on 47 patients affected by Bowen's disease, a complete clearance of 76% was reported after 17 mo from 2 sessions of MAL-PDT^[30].

Invasive squamous cell carcinoma: Squamous cell carcinoma presented a lower sensitivity to PDT in comparison with basal cell carcinoma. Clearance rates of 57% and 26% have been reported in microinvasive and nodular invasive squamous cell carcinoma, respectively, 2

Table 3 Strength of recommendation and the level of evidence of the different indications of photodynamic therapy^[24,25]

Disease	Strength of recommendation	Quality of evidence
Actinic keratoses	A	I
Bowen's disease	A	I
Invasive squamous cell carcinoma	D	II -iii
Superficial basal cell carcinoma	A	I
Nodular basal cell carcinoma	A	I
NMSC in organ transplant recipients	B	I
Prevention of NMSC in organ transplant recipients	B	I
Field cancerization	B	I
Cutaneous T-cell lymphoma	C	II -iii
Extra-mammary Paget's disease	D	III
Infectious and inflammatory dermatoses acne	A	I
Hand and foot warts	B	I
Genital warts	B	I
Cutaneous leishmaniasis	B	I
Photorejuvenation	B	I

Strength of recommendations: A: There is good evidence to support the use of the procedure; B: There is fair evidence to support the use of the procedure; C: There is fair evidence to support the rejection of the use of the procedure; D: There is good evidence to support the rejection of the use of the procedure. Quality of evidence: I: Evidence obtained from at least one properly designed, randomized control trial; II-i: Evidence obtained from well-designed control trials without randomization; II-ii: Evidence obtained from well-designed cohort or case control analytic studies preferably from more than one centre or research group; II-iii: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence; III: Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees; IV: Evidence inadequate, owing to problems of methodology (e.g., sample size, or length of comprehensiveness of follow-up or conflicts in evidence).

years after treatment with MAL-PDT^[31]. Considering the lower response rate and the metastatic potential, PDT is not the first choice for invasive squamous cell carcinoma treatment.

Basal cell carcinoma: PDT is particularly indicated for basal cell carcinoma treatment, especially in superficial carcinomas and in Gorlin Syndrome.

Several studies reported good results in the treatment



Figure 4 Lesion is treated with a curette to selectively remove the corneal layer.



Figure 5 After curettage no bleeding might be present.

of basal cell carcinoma with PDT^[32-35], with clearance rates up to 90% at 3 years and 87% at 10 years.

Similar results have been reported in studies comparing PDT to cryotherapy, with PDT obtaining a better aesthetic outcome^[36]. Good results were reported in patients affected by Gorlin Syndrome^[37], with a reduction in the need for surgical procedures.

Relatively poor results were obtained in invasive carcinoma and in morphoeic basal cell carcinoma^[38]; therefore, PDT must be considered not indicated in these cases.

Organ transplant recipients and field cancerization:

PDT has been studied for the treatment and prevention of non-melanoma skin cancer (NMSC) in organ transplant recipients. An important factor to emphasize is the reduced response rate in non-immunocompetent patients compared with immunocompetent patients, due to the role of the immune system in the action of PDT^[39]. PDT cannot be considered as a first choice in the treatment of skin cancer in organ transplant recipients, nor can it play a significant role in the prevention of NMSC in non-immunocompetent patients^[40].

However, in immunocompetent patients with multiple clinical or subclinical cancerous skin lesions, PDT can be used to prevent the lesions from evolving into invasive carcinomas^[41-43]. This preventive effect of PDT has been explained by the reduced expression of the proto-

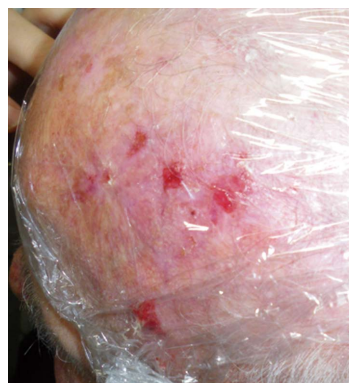


Figure 6 Cream is applied on the lesion and an occlusive dressing is then performed.

oncogene p53 in treated tissues^[44].

Cutaneous T-cell and B-cell lymphomas: Dougherty *et al.*^[45] and Forbes *et al.*^[46] demonstrated the efficacy of PDT in the treatment of cutaneous T-cell lymphoma. The selective uptake of ALA and MAL into CD71⁺ lymphocytes was observed^[47]. Small series with good results are reported in the literature^[48-50]. Satisfactory results were also reported by Mori *et al.*^[51] in 3 patients affected by cutaneous B-cell lymphoma. The effectiveness of PDT in the treatment of cutaneous lymphomas has not been proven; therefore, PDT should not be considered an indication. Further studies are necessary to verify the application of PDT in this field.

Extra-mammary Paget's disease: Few reports have shown promising results in the treatment of Paget's disease^[52-55]. A more appropriate role for PDT may be as an adjuvant therapy in association with radiotherapy or surgery^[56], as PDT not only induces tissue destruction but also causes a reduction in tumor cells' adhesive and metastatic capacities.

Acne vulgaris: PDT has been used with good results in the treatment of acne vulgaris.

It was noted that ALA accumulates in sebocytes, which are then destroyed by the photoreaction, reducing sebum excretion. Another positive effect is linked to production of porphyrins by *Propionibacterium acnes*, which became a target for PDT^[57].

Warts: Several studies have reported good results concerning the application of ALA-PDT for the treatment of warts^[58-60]. Many comparative studies reported higher clearance rates in patients treated with ALA-PDT versus patients treated with a placebo^[58,59] or cryotherapy^[60]. Similar results were reported in hand and foot warts and in genital warts^[61-64]. In the treatment of genital warts, PDT was reported to have clearance rates similar to other therapies, such as laser CO₂, but lower recurrence rates.

It should be noted that studies regarding MAL-PDT in the treatment of warts are limited.



Figure 7 Patient affected by multiple actinic keratosis of the scalp treated with photodynamic therapy with aminolevulinic acid; result after 3 wk from the 1st application.

Accurate curettage of lesions is mandatory to reduce typical hyperkeratosis, which limits the penetration of the photosensitizer.

Other indications: Some other indications for PDT are currently under study.

A review of patients affected by cutaneous leishmaniasis reported complete healing in 94%-100% of cases treated with PDT^[65]. These results were confirmed by randomized trials^[66]. The mechanism was studied in vivo by Kosaka *et al*^[67], who suggested that the clinical outcomes observed with ALA-PDT are the result of unspecific tissue destruction accompanied by the depopulation of macrophages rather than by the direct destruction of parasites, as observed by previous in vitro studies^[68].

Several series have reported improvements in PDT-treated patients diagnosed with localized scleroderma^[69,70], lichen sclerosus^[71], perioral dermatitis^[72] and cutaneous mycosis^[73,74].

These preliminary results appear to be promising, but further research is necessary to demonstrate the actual efficacy of PDT in the reported diseases.

Photorejuvenation: Many studies have reported good results for skin rejuvenation after the application of PDT^[75-77]. PDT is useful for improving dyspigmentation, depigmentation, fine lines and roughness, skin smoothness and for reducing actinic elastosis^[78]. Other techniques can be combined with PDT to improve results, acting synergistically to induce self-stimulated collagen biosynthesis (microneedling, ablative fractional lasers) or to improve photosensitizer penetration (curettage, peeling, lasers, microneedling). All of these treatments must be performed before PDT; chemical peeling can be applied immediately before PDT or up to 3 d (maximum) prior to PDT; curettage can be performed 2 wk prior to PDT; and lasers, microneedling and mechanical peeling can be applied immediately before PDT. Other aesthetic procedures can be associated with PDT; fillers can be used 2 wk after PDT, and botulinum toxin can be used 2 wk prior (at the earliest) to PDT. Pre-treatment can increase phototoxic effects, prolonging the downtime of

the patient. The expected aesthetic results are usually observed after 3-6 mo, and 2 or 3 sessions conducted every 4 wk are usually necessary. The scalp is more painful than other sites, whereas the hands are usually reported as minimally painful. The neck and décolleté present fewer skin appendages, thereby leading to more prolonged re-epithelization and erythema^[79].

ALA-PDT induces the deposition of collagen in the dermis, normalizes elastotic materials induced by photoaging and may even have a direct effect on the normalization of fibroblast morphology^[80]. Marmur *et al*^[81] observed a series of ultrastructural changes leading to clinical improvement. In the epidermis, ALA-PDT induces reorganization because of keratinocyte adhesion recovery. In the dermis, there is a recovery of the dermal extracellular matrix, which is demonstrated by the reappearance of anchoring fibrils, the displacement of elastosis and the superficial remodeling of dermal collagen.

CONCLUSION

PDT is very useful in dermatology; PDT is minimally invasive, especially compared with surgery, and allows better results than non-surgical treatments, such as lasers and cryotherapy. In our experience, PDT was widely applied in over 250 patients affected by actinic keratoses, basal cell carcinomas and Bowen's disease, with excellent results. In our opinion, assessing the depth of a lesion to determine the appropriate indication for PDT compared with surgical treatment is important. In deeper lesions, or in particularly sensitive areas such as the face, PDT can be a useful treatment in association with surgery, as described by other authors. Skin cancers, especially if arising on actinic keratosis, often present ill-defined margins. In these cases, PDT may be useful to better define the edges of a lesion before surgical treatment. We have used this method in 14 patients diagnosed with basal cell carcinoma of the face with surrounding photodamaged skin; after 3 PDT sessions, the patients underwent surgery, and the excision margins were found to be free from disease in all of the cases. Additionally, we used PDT for the treatment of photoaging in 57 patients, with excellent

results after an average of 3-4 sessions. We believe that the other proposed indications require further research to verify the effectiveness of PDT.

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Biomarkers of psoriasis severity and therapy monitoring

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Abstract

Psoriasis is a chronic, recurrent inflammatory cutaneous disease. Psoriasis patients alternate between periods of remission and periods of exacerbation of the disease. Usually, psoriasis severity is clinically evaluated using tools like Psoriasis Area and Severity Index that present some limitations and subjectivity. Clinicians select the therapy according to psoriasis severity, aiming that patients achieve longer remission periods and improve their quality of life. Biological markers for diagnosis and prognosis of psoriasis help to establish its severity and to monitor the therapeutic response; moreover, biomarkers of psoriasis assist clinicians in their therapeutic decision to treat psoriasis and to choose earlier and more adequate therapeutic strategies, avoiding or minimising worsening of psoriasis. With these markers, they would be able to monitor therapeutics, avoiding unnecessary therapeutic surcharge or changes to a more aggressive therapy. As any attempt to identify these biomarkers should be encouraged, in this review,

we will debate published data concerning the proposal of biomarkers to evaluate severity and response to treatment of psoriasis vulgaris.

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Key words: Psoriasis; Severity; Monitorization; Markers; Inflammation

Core tip: Severity of psoriasis, a chronic, recurrent inflammatory disease, is clinically evaluated by Psoriasis Area and Severity Index that present some limitations and subjectivity. Biological markers for diagnosis and prognosis of psoriasis help to establish its severity and to monitor the therapeutic response; moreover, psoriasis biomarkers assist clinicians in their therapeutic decision to treat psoriasis and to choose earlier and more adequate therapeutic strategies, avoiding or minimizing psoriasis worsening. As any attempt to identify these biomarkers should be encouraged, in this review, we will debate published data concerning the proposal of biomarkers to evaluate severity and response to treatment of psoriasis.

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INTRODUCTION

Psoriasis affects about 2%-3% of the World population, and is characterized by epidermal hyperplasia, dilated and prominent blood vessels in the dermis, and by an inflammatory infiltrate of leukocytes, predominantly in the dermis. It is a chronic, recurrent, immune-mediated inflammatory disease, with a recognised genetic predisposition. Several acute phase reactants, cytokines and growth

factors are known to play an important role in the pathogenesis of psoriasis. Indeed, it is accepted that different cells are crucial in psoriasis at different stages^[1], and that the interleukin (IL)-23/T-helper (Th)17 axis is decisive in psoriasis pathogenesis, and its inhibition appears to be crucial for therapeutic achievement^[2,3].

Psoriasis patients alternate between periods of remission and periods of exacerbation of the disease. This chronic, unpredictable course of the disease and the need of periodical alternation of drugs or classes of drugs, makes difficult to treat psoriasis. Psoriasis patients require an individual management and long-term planning of therapeutic strategies. The risks vs benefits ratio and the cost-effectiveness of the different treatments should be carefully evaluated. A variety of approaches are available for its treatment, ranging from topical agents, for milder and limited forms of psoriasis, to phototherapy, photochemotherapy, systemic and biologic agents, for moderate and severe psoriasis. The main goal of psoriatic therapies is to control the disease and its clinical manifestations, contributing to improve the quality of life of the patient. The therapy is chosen in accordance with skin type, clinical history, patient's age, the effect on the patient's quality of life, the response to previous treatments and, obviously, the severity of psoriasis.

The psoriasis area and severity index (PASI) is the prototype to measure psoriasis severity, being the most widely used tool to assess the severity of the disease in clinical trials and in clinical practice. This system has two major advantages: it is sensitive to changes in the affected skin area and in the severity of the lesions, and, therefore, the changes in PASI score reflect improvement or worsening of the disease. However, it presents some subjectivity and limitations^[4-6], such as a poor sensitivity to changes in small areas of involvement; thus, it may not be the best tool to be used in patients with mild disease. There are other approaches to assess psoriasis severity, such as the percentage of involved body surface area, the Physician's Global Assessment, the Lattice System Physician's Global Assessment, and the National Psoriasis Foundation Psoriasis Score. There are also more specific instruments, focusing on aspects of quality of life that are affected by skin disease, such as the Dermatology Life Quality Index^[7], but they are all clinical tools.

Biological markers for diagnosis and prognosis of psoriasis help to establish its severity and to monitor the therapeutic response. The identification in blood of predictive biologic markers of worsening of the disease could be useful for clinical evaluation of psoriasis and to monitor the treatment of the disease. Indeed, biomarkers of psoriasis severity are useful to clinicians in their therapeutic decision to treat psoriasis and to choose earlier and more adequate therapeutic strategies, avoiding or minimising worsening of psoriasis. With these markers, they would be able to monitor therapeutics, avoiding unnecessary therapeutic surcharge or changes to a more aggressive therapy.

Considering that any attempt to identify these bio-

markers should be encouraged, we intend to review and debate published data concerning the proposal of biomarkers to evaluate the severity and the response to treatment of psoriasis vulgaris. To avoid a length and complex manuscript, we will only consider biomarker evaluation in psoriasis vulgaris without arthritis.

INTERLEUKINS AND GROWTH FACTORS

Nowadays, it is proposed that psoriasis development depends on skin infiltration of Th1/Th17 cells that stimulate macrophages and dermal dendritic cells to release mediators that sustain inflammation and cause abnormal keratinocyte proliferation. The mediators of the Th17 immune system include IL-1, IL-6, IL-23 and transforming growth factor (TGF)- β ^[8,9]. Additionally, IL-23 and related interleukins seem to be crucial for psoriasis pathogenesis^[10,11].

Tumour necrosis factor (TNF)- α , a cytokine of the Th1 pathway, influences the proliferation, activation and differentiation of several cell types, stimulates apoptosis, enhances the synthesis of several cytokines and the expression of some adhesion molecules^[12]. The neutralization of TNF- α , the basis of some psoriasis therapies, strengthens the important role of this cytokine in the disease. High concentration of TNF- α ^[13-22] and significant and positive correlations with PASI scores^[3,17-19,23] were found in active psoriasis. However, some authors did not find this significant increase^[3,24,25]. Bevelacqua *et al*^[26] observed that the correlation of TNF- α with psoriasis severity was only found for the severer forms and Nakajima *et al*^[20] found a negative correlation of TNF- α with PASI^[20]. These controversial results suggested that TNF- α is essentially produced and act locally, and, therefore, its circulating levels might be lower than at the inflammatory area. Its activity was found to decrease after effective treatments, including narrow-band ultraviolet light B (NB-UVB), psoralen plus UVA (PUVA) and topical therapy^[3,19,22]. However, Emerit *et al*^[27] found a significant decrease in its levels only after infliximab and etanercept therapies; no changes were found after PUVA and NB-UVB treatments. Borska *et al*^[25] did not find a decrease in its levels after Goeckerman's therapy. The levels of soluble TNF- α receptor type 1 (sTNF-R1) were found to be increased in active psoriasis and to correlate with PASI^[28,29]. TNF- α -converting enzyme from peripheral blood mononuclear cells may contribute to the up-regulation of sTNF-R1 in psoriasis. The raised concentrations of sTNF-R1 in psoriasis were correlated with PASI and were diminished after NB-UVB therapy, suggesting that it may be a marker of the disease severity^[30].

Interferon (IFN)- γ is important in the early stages of psoriasis, increasing the migration of immune cells into the skin and the activation of monocytes/macrophages, dendritic cells and endothelial cells^[1]. IFN- γ inhibits apoptosis of keratinocytes, contributing to the hyperproliferation of keratinocytes, and to stimulate epidermal cell proliferation^[31,32]. The levels of IFN- γ are elevated in ac-

tive psoriasis^[15,17,18,21,24,33] and correlate with PASI^[15,18,24,33]. The improvement of psoriasis, with a significant decrease in PASI, has been associated with a significant decrease in its concentrations^[33]; moreover, patients with high levels of IFN- γ that did not decrease significantly after treatment show shorter remission periods^[33]. Yet, Abdel-Hamid *et al*^[17] reported that TNF- α was a more efficient predictor for disease severity than IFN- γ , and Tigalónowa *et al*^[34] did not find any alterations in INF- γ levels after treatment with cyclosporine.

IL-12 is a key cytokine responsible for the induction of Th1 response, leading to the secretion of IFN- γ and homing of T cells in the skin, and the maintenance of the Th1 response. IL-12 shares with IL-23 a common p40 subunit, an attractive therapeutic target in psoriasis, as the ustekinumab efficacy has demonstrated^[35]. IL-12 concentrations were reported to be increased in patients with psoriasis^[15,18,36], to be correlated with PASI^[15,18] and to decrease after psoriasis treatment^[18,36]. However, Jacob *et al*^[24] observed that IL-12 levels were decreased in sera from active untreated psoriasis patients compared with normal controls, and, as Borska *et al*^[36], they did not find a significant correlation with PASI. These controversial findings compromise its value as a possible biomarker for psoriasis.

In psoriasis, IL-18 is important for cellular adhesion^[37] and synergizes the stimulation of IFN- γ release^[38]. Its levels seem to be enhanced in psoriatic patients^[15,18,39-42], to be correlated with PASI^[15,18,39-42] and to decrease after treatment^[39]. Flisiak *et al*^[42] reported that the combined measurement of plasma IL-18, TGF- β 1, tissue inhibitors of metalloproteinases (TIMP)-1 and matrix metalloproteinase (MMP)-1 has a superior value as a biomarker of psoriasis activity in comparison with IL-18, or with any of the others individually.

Neutrophils are recognized as a component of the leukocyte infiltrate in psoriasis lesions. Its mobilization and degranulation is induced by IL-8, which is produced by keratinocytes. A rise in IL-8 levels has been reported in psoriasis vulgaris patients^[3,14,15,17,24,25], although Deeva *et al*^[43] did not find it. A study in our lab showed a significant correlation between IL-8 and PASI^[3]; still, Jacob *et al*^[24] referred a positive correlation only with the degree of erythema^[24] and others did not find any significant correlation^[15,17]. We also found a significant decrease in its levels after PUVA and after NB-UVB treatment^[3]. However, Borska *et al*^[25] reported a significant increase in IL-8 serum concentrations after Goeckerman's therapy.

IL-6, known to be increased in psoriasis^[14,15,20-22,43-45], mediates T cell activation, stimulates proliferation of keratinocytes and mediates the acute phase response^[15]. It has been reported that an enhancement in its levels is associated with an increase in psoriasis severity, as defined by PASI^[21,22,44]. Nonetheless, Bevelacqua *et al.* reported that the mean value of IL-6 was higher in severe than in mild psoriasis patients and in healthy controls, but there were no differences between mild psoriasis patients and healthy controls, and IL-6 correlated with PASI only for the severer forms of psoriasis^[26]. Elango *et al*^[45] observed

that only 2 indices of PASI, infiltration and desquamation, showed a positive correlation with IL-6, before and after treatment, and Deeva *et al*^[43] reported that no correlation was found between psoriasis severity, assessed by PASI, and IL-6. A few successful treatments, such as PUVA^[22,46], methotrexate^[45], etanercept^[47], were associated with a significant decrease in IL-6 levels. No significant reduction in IL-6 concentrations was found after NB-UVB and topical therapy^[22]. These studies suggest that IL-6 may not be the best tool, if not combined with other(s) marker(s), to monitor all options of psoriasis treatments.

As referred, the IL-23/Th17 axis is believed to be crucial in psoriasis pathogenesis^[48]. IL-23 sets in motion several pathways leading to neutrophil recruitment, and stimulates the production of other cytokines, which may directly act on keratinocytes in a TNF-regulated way, resulting in epidermal hyperplasia and/or altered regulation of keratinocyte differentiation. It seems, therefore, that IL-23 is a causative independent factor in psoriasis pathogenesis. Therapies directed to IL-23, such as ustekinumab, that targets the p40 subunit of IL-12 and IL-23, has been used successfully for the treatment of moderate to severe psoriasis^[35]. In a 12-wk NB-UVB or PUVA therapy, its levels decreased after 3 weeks of treatment, which figured to be crucial to reverse several of the analytical changes found in psoriasis, and to achieve resolution of the lesions^[3]. As far as we know, there is no data showing a correlation between psoriasis severity and IL-23. The expression of CC chemokine ligand 20 (CCL20) and its receptor CC chemokine receptor 6 (CCR6) is up-regulated in psoriasis^[49,50], which may be related to the disease pathogenesis. Indeed, Hedrick *et al.* found that CCR6 has an important role in IL-23-related responses and identified CCR6 as a potential therapeutic target in psoriasis^[51]. In opposition to the therapy with calcipotriol, camptothecin or tazarotene, clobetasol treatment inhibited the CCR6 expression in a imiquimod-induced psoriasis-like mouse model^[52].

IL-22 is the linkage between the infiltrating Th17 cells, driven by IL-23, and keratinocyte hyperplasia and activation. This cytokine is the downstream effector cytokine of IL-23, and can induce many of the pathological features seen in psoriatic skin lesions. The production of IL-22 is up-regulated in psoriatic skin^[53]; their levels are high in the peripheral blood^[3,20,46,54-57], and are correlated with the severity of the disease^[20,46,54,55], suggesting an important role for IL-22 in the pathogenesis of psoriasis. Moreover, a 12-wk successful PUVA or NB-UVB treatment induced a significant decrease in its levels after 6 weeks of therapy^[3]; treatments with calcipotriol alone or combined with NB-UVB, with NB-UVB, and with etanercept were also associated with a decrease in IL-22 concentrations^[56,57]; no changes were found after treatment with acitretin^[57]. However, some studies did not find significant correlations between IL-22 and psoriasis severity^[3,57]. Shimauchi *et al*^[55] reported that IL-22 can be used as useful biomarker of psoriasis severity, however, it

is not a good predictor of the biologic response for biologic therapies.

IL-17, produced by Th17 cells, is a critical component in the establishment and perpetuation of inflammation. It induces the production of pro-inflammatory cytokines, mainly by endothelial cells and macrophages^[58], and activates keratinocytes to produce interleukins, such as IL-8^[12]. Increased levels of IL-17 were found in blood of psoriatic patients^[3,18,56,57], and they seem to correlate with psoriasis severity^[18,57]. Romaní *et al*^[59] and our group^[3] did not find this correlation. Romaní *et al*^[59] and Arican *et al*^[15] found that IL-17 levels in patients were similar to controls. IL-17 concentrations decreased significantly after treatment with calcipotriol, PUVA, NB-UVB, and NB-UVB combined with calcipotriol^[3,56]. As observed for IL-22, etanercept reduced IL-17, but acitretin therapy did not change its levels^[57]. Some of these findings suggest a limited applicability of IL-22 and IL-17 levels as monitors of psoriasis therapy.

IL-21 seems to play an important role in a variety of inflammatory diseases, such as psoriasis. It is highly expressed in psoriatic plaques and promotes the proliferation of epidermal cells in mice^[60]. Serum IL-21 levels were reported to be enhanced in psoriasis^[20,61] and to correlate with PASI^[61]; this correlation was not found by Nakajima *et al*^[20].

Vascular endothelial growth factor (VEGF) contributes to improve the vascularization of the lesions^[62], to stimulate epidermal hyperplasia, vascular growth and leukocyte infiltration in the skin^[63]; through its receptors, it appears to play an important role in regulating psoriatic keratinocyte activity^[64], to increase the permeability of the endothelium and to induce vasodilatation^[65]. Several authors reported that its levels are significantly high in plasma in the active stage of the disease^[3,43,66-71]. Nonetheless, Shimauchi *et al*^[55] did not find significant differences in VEGF levels between psoriasis patients and controls. Flisiak *et al*^[72] reported that the increase of serum VEGF becomes significant only in patients with medium and severe activity of the disease, and that soluble VEGF receptor 1 (sVEGFR1) was higher than VEGF in serum of patients with low psoriasis activity. A significant positive correlation has been reported between PASI and VEGF^[18,55,67-70,72] and sVEGFR1^[72]; yet, according to Deeva *et al*^[43] severity of skin symptoms do not correlate with plasma VEGF concentrations. VEGF levels appear to be reduced by standard topical therapy^[68], PUVA therapy^[3,71] and acitretin combined with PUVA^[67]; the effect of UVB irradiation in VEGF levels is more controversial^[3,70,71] and the effect of retinoids combined with NB-UVB was associated with an increase in VEGF circulating values^[71]. Besides, VEGF levels were reported to serve as sensitive biomarkers, but not as predictors of therapeutic response to biological therapies in patients with psoriasis^[55].

According to Nockowski *et al*^[73] serum concentrations of TGF- β 1, an inhibitor of keratinocyte hyperproliferation, were significantly increased in psoriasis; the circulating levels are higher in patients with more severe

disease than in those with mild psoriasis, and, actually, TGF- β 1 concentrations seem to correlate with disease severity^[39,42,73,74]. Zaher *et al*^[75] found correlations between TGF- β 1 and extent of the disease and PASI and, as Flisiak *et al*^[42] they did not observe significantly higher levels of TGF- β 1 in active psoriasis^[42,74,75]. Enhanced levels of TGF- β 1 for patients with a PASI lower than 15 were not found^[76]. As referred previously, the combination of plasma TGF- β 1, IL-18, TIMP-1 and MMP-1 has a superior value as a biomarker of psoriasis activity than each one separately^[42]. Increased TGF- β 1 levels in patients with mild psoriasis decreased after biological drug treatment, which was accompanied by a reduction in PASI^[77], and after treatment with salicylic acid and/or sulphur followed by dithranol ointment^[76].

The levels of the anti-inflammatory cytokine IL-10 were reported to be decreased^[18] or below detection levels in psoriatic patients^[24], and negatively correlated with PASI^[18]. Another study, by Borska *et al*^[36] reported that IL-10 concentrations were significantly higher in psoriatic patients, and decreased after treatment. Deeva *et al*^[43] reported that mild-to-moderate psoriasis vulgaris patients showed higher levels of IL-10, and did not find any correlation between PASI and IL-10. The controversial data do not confirm IL-10 as a reliable biomarker for psoriasis.

Fibroblast growth factor levels correlated to PASI before psoriasis treatment^[70], and its values were diminished by Goeckerman's therapy^[70], but as far as we know, no more published data concerning its relationship with psoriasis activity and/or severity exists.

PENTRAXINS

C-reactive protein (CRP), a short-chain pentraxin produced in the liver, is a positive acute phase protein that increases rapidly in the presence of inflammation, a hallmark of psoriasis. Elevated CRP levels result from the interaction between pro-inflammatory cytokines, namely IL-6, TNF- α and IL-1, their receptors and inhibitory factors^[78]. TNF- α induces secretion of IL-6, which stimulates hepatic production of CRP, an effect that can be enhanced by IL-1 β . The development of high-resolution CRP assays, has allowed clinicians to explore the potential role of these assays to detect low-grade inflammation, in diagnosing and predicting pathologic conditions.

Increasing concentrations of CRP have been widely reported in mild, moderate and severe forms of active psoriasis^[69,78-95]. Only a few reports did not observe significantly increased values^[96,97], probably because high-resolution assays were not used, included different clinical forms of psoriasis, or patients that were not at the active stage of psoriasis, or were under treatment with anti-psoriatic regimens. The majority of data reveals CRP as a potential marker of psoriasis severity, since its levels correlate with disease severity, as defined by PASI^[69,79,84,87,90,93-95,98], few studies did not report these findings^[81,99], and Kanelleas *et al*^[82] only found significant correlations after treatment. CRP levels decreased significantly after successful treatments with

several types of psoriasis therapies^[88], such as phototherapy, alone or combined with coal tar^[79,81,83,97], photochemotherapy^[78,79], systemic^[78] and biologic agents^[82,91,92,98]. Moreover, our group has recently proposed the CRP value after treatment, as an important determinant of the length of remission of psoriasis, at least for patients treated with phototherapy or topical therapy^[100]. Thus, CRP concentration is a potential marker to access the severity of psoriasis, to monitor the treatment and to predict the length of remission of psoriasis, especially if combined with PASI.

Pentraxin 3 (PTX3), a long chain pentraxin, is produced in response to inflammatory signals by macrophages, dendritic cells and endothelial cells. PTX3 and CRP reflect different sides of the inflammatory process^[101]. Enhanced PTX3 levels are found in active psoriasis^[26,81,102]; Czirad *et al.*^[81] did not find increased values of PTX3. Significant correlations between PTX3 concentrations and psoriasis severity have been reported^[26,102]. After effective Goeckerman's, NB-UVB and PUVA therapies, PTX3 values decreased significantly^[81,102]. PTX3, combined with PASI and CRP, seems to be important for the clinical evaluation and monitoring of psoriasis.

We must emphasize that CRP and PTX3 evaluation, although sensitive, lacks specificity, as they are also increased in different types of inflammatory diseases. Therefore, the presence of inflammatory comorbidities should be considered when using these biomarkers to assess psoriasis.

MARKERS OF OXIDATIVE STRESS

It has been suggested that increased reactive oxygen species, such as nitric oxide (NO) and malondialdehyde (MDA), may play a part in the pathogenesis of psoriasis. The balance between oxidant and antioxidant agents seems to be altered in psoriasis. In psoriasis patients, a significant increase in NO and MDA and a decrease in superoxide dismutase (SOD) levels was reported^[103,104]. Some authors did not find a significant correlation between PASI and NO, MDA, SOD and total antioxidant status^[103,105], while others reported a significant correlation between PASI and MDA, NO, SOD, catalase and total antioxidant status^[104,106]. MDA levels decreased after treatment with PUVA, NB-UVB, infliximab and etanercept, yet without reaching baseline levels^[27].

Methylglyoxal serum level, that reflects oxidative and carbonyl stress status, increases in psoriasis patients and is associated with psoriasis severity, assessed by PASI^[107]. Considering the controversial data, it seems that although oxidative stress has a crucial role in psoriasis pathogenesis, markers of redox status/oxidative stress may not be the best translators of psoriasis severity.

Increased lipid oxidation is also associated with psoriasis. One of the major and early lipid peroxidation product is oxidized low-density lipoprotein (oxLDL)^[108]. The levels of autoantibodies against oxLDL (auAb-oxLDL), an indirect evidence of LDL oxidation, seem to be increased

in psoriasis^[109,110], and, according to Orem *et al.*^[110] the levels of auAb-oxLDL are correlated with PASI score. There is no data concerning the effect of psoriasis therapies in auAb-oxLDL concentrations.

ADIPOKINES

The adipokine adiponectin, which is adipose-tissue specific, is known to inhibit the inflammatory response and to protect against metabolic and cardiovascular diseases^[111,112], as it plays an important role in lipid metabolism and atherogenesis^[113]. Moreover, adiponectin reduces the production of TNF- α , IL-6, IFN- γ , the expression of monocyte cell adhesion molecules, the phagocytic activity of macrophages and, therefore, its transformation to foam cells; adiponectin also increases insulin sensitivity and the repair of damaged vasculature^[114,115]. The high molecular weight (HMW) form is considered the active fraction, and, therefore, it is considered a better marker of metabolic disturbances than total adiponectin. Data concerning adiponectin in psoriasis are controversial. Reduced adiponectin levels have been associated with psoriasis, at least in overweight/obese patients^[22,116-118], and were correlated inversely with PASI^[69]. Yet, increased concentrations of total adiponectin that correlate positively with PASI were reported^[20]; HMW adiponectin levels were described to be decreased and negatively correlated with PASI^[20]. However, according to the meta-analysis performed by Zhu *et al.*^[119] adiponectin and HMW adiponectin levels are not significantly different in patients with psoriasis, compared with controls. These authors suggested that the levels of total adiponectin and HMW adiponectin may not be associated with psoriasis *per se* and that the relationship between psoriasis and adiponectin needs to be clarified^[119].

Resistin is expressed by cells from the stromal compartment of the adipose tissue, particularly by macrophages and by peripheral monocytes that are up-regulated during their differentiation to macrophages. High resistin levels are reported to be associated with the atherosclerotic process, and insulin resistance; resistin has been shown to increase the expression of several pro-inflammatory cytokines, including TNF- α and IL-6, suggesting an involvement in inflammation^[120]. Psoriasis patients seem to present enhanced levels of resistin^[22,121]. A study performed by our team found that the severer psoriasis forms presented significantly higher values when compared to moderate forms and controls^[22]. The PASI score was found to correlate with serum resistin concentrations^[69,121,122].

High levels of leptin, another adipokine adipose-tissue specific, seem to enhance Th1 immune responses, and increase macrophage activity, with production of different cytokines. Serum leptin levels were reported to be significantly higher in psoriasis patients^[22,59,116,117,123,124], particularly in those with severe psoriasis^[125] and/or with higher body mass index^[22], and to positively correlate with PASI^[125]. Nonetheless, others authors did not find

these significant results^[126].

Data concerning the more recent discovered adipokines and its relationship with psoriasis is limited. Ghrelin seems to take part in the development of metabolic syndrome and its concentrations are decreased in some pathologic conditions, such as obesity and type 2 diabetes^[127]. A strong negative correlation between PASI and ghrelin was reported, yet, ghrelin concentrations were not different from controls and did not suffer a significant alteration after cyclosporine treatment of psoriasis^[126]. Patients with psoriasis also showed considerably enhanced serum levels of visfatin^[128,129], an inflammatory adipokine, with significant positive correlation with disease severity and duration^[128]; however, this increase in its levels was not always found^[91]. According to Takahashi *et al.*^[56] the levels of omentin were decreased in psoriasis patients and negatively correlated with PASI scores. However, Romani *et al.* did not find these significant differences for omentin; instead, they observed higher baseline serum concentrations of retinol binding protein (RBP)-4 and lipocalin-2, that correlated both with PASI^[59]. Although Ismail *et al.*^[128] described lower omentin concentrations in psoriasis, the correlation with disease severity was not found. Concerning RBP-4, and oppositely to the previously referred results by Romani *et al.*^[59], Gerdes *et al.*^[129] observed that RBP-4 is independently decreased in psoriasis, and Karadag *et al.*^[130] did not find significant differences in its basal concentrations compared to controls, although a decrease was found after treatment with anti-TNF- α agents.

In what concerns the changes in adipokine levels following different types of psoriasis treatments, data is controversial. In summary, therapies, such as topics, NB-UVB, TNF- α inhibitors, did not induce significant alterations in the levels of adiponectin, visfatin, leptin, ghrelin, resistin and apelin^[22,131,132]. However, an increase in adiponectin concentrations was reported after PUVA^[22] and cyclosporine^[126] therapies. Corbetta *et al.*^[133] did not observe any alteration in adiponectin circulating values after retinoid therapy, but reported a decrease in resistin levels; in opposition, Ozdemir *et al.*^[126] observed an increase in resistin concentrations after cyclosporine treatment. Phototherapy induced no remarkable change in the levels of leptin, but decreased resistin levels^[134]. Therefore, adipokines may not be the best tools to monitor psoriasis activity.

OTHER POTENTIAL BIOMARKERS

Elastase, released at inflammatory sites, when neutrophils are stimulated by a variety of compounds, mediates inflammation and tissue damage, by inducing activation of other inflammatory cells and by inducing degradation of matrix proteins and clotting factors^[135]. Its levels are known to be increased in active psoriasis^[79,80] and seem to be crucial for the formation and enlargement of psoriatic plaques. Orem *et al.*^[136] reported that elastase correlates with PASI, but only in the active period of the disease;

accordingly, we also found a trend towards a correlation between elastase and PASI^[79]. We also found a significant decrease in elastase levels after PUVA and NB-UVB therapy, but not after topical therapy (calcipotriol and betamethasone dipropionate, combined or alternatively)^[79].

TNF- α and IFN- γ increase the expression of intercellular adhesion molecule-1 (ICAM-1), promoting skin infiltration of T cells and other inflammatory cells, such as monocytes. The levels of the soluble form of ICAM-1 (sICAM-1) were reported to be higher in psoriasis patients than in controls, to correlate with disease severity^[25,29,41,137-140], and to decrease after NB-UVB therapy^[137], but not after dithranol combined with UVB therapy^[141]. In opposition, Takahashi *et al.*^[18] reported that in psoriasis patients, sICAM-1 concentrations were not significantly different from those of controls and were not associated with PASI. Krasowska *et al.*^[142] also observed that its levels are not related with psoriasis severity.

The levels of E-selectin, another classical marker of endothelial dysfunction, are significantly elevated in psoriatic patients and positively correlated with disease severity^[140,143]. Long *et al.*^[137] found that serum levels of soluble E-selectin decreased significantly after NB-UVB treatment, but were not correlated with PASI score before therapy, which is in accordance with Borska *et al.*^[25] data.

The levels of adenosine deaminase, a nonspecific marker of T cell activation, are increased in psoriasis, and decreased after cyclosporine, etanercept, and PUVA therapies, suggesting that it may be a good marker of psoriasis activity, but it did not correlate with PASI^[144,145], thus, it is not a good marker for psoriasis severity.

Soluble IL-2 receptor (sIL-2R) seems to correlate with disease activity in psoriasis^[146,147]. The levels of sIL-2R decreased after treatment with PUVA and cyclosporine^[146,147], but did not change with NB-UVB treatment^[148].

In psoriasis patients, a rise in serum levels of neopterin, a non-specific marker of the activation of cell-mediated immunity, that correlates with PASI was reported^[149]. Urine neopterin levels are also elevated in psoriatic patients and reduced significantly after etanercept treatment, however, no correlation with PASI was found^[150].

Other analytical parameters were occasionally reported to be related with psoriasis severity. For instance, hydrogen sulfide [H(2)S], that seems to be a signalling molecule with both pro- or anti-inflammatory effects, was significantly decreased and negatively correlated with clinical psoriasis severity^[151]. Nonetheless, its relationship with psoriasis has not been clearly elucidated. Procollagen III peptide levels were found to relate with psoriasis severity^[138]. Higher platelet factor 4 levels were found in psoriasis and correlated with PASI scores^[152]. Additionally, endothelin-1 seems to be increased in sera of psoriatic patients, to associate with PASI^[153,154] and to decrease after PUVA therapy^[154]. Plasma platelet-derived microparticles were higher in psoriasis, presented a significant correlation with PASI, and reduced after clinical improvement^[152]. Prolactin levels were increased in psoriatic

Table 1 Potential inflammatory biomarkers and its relation with psoriasis activity, severity and therapy

Biomarker	Studies reports about its levels			
	In active psoriasis	Correlation with severity	After therapy	Relation (after therapy) with length of psoriasis remission
TNF- α	Increased levels ^[13-22] Mild psoriasis with higher levels than controls, lower than severe psoriasis ^[26] Not altered ^[3,24,25]	Correlated positively ^[3,17-19,23] Only for severe psoriasis ^[24] Correlated negatively ^[20]	Improved ^[3,19,22] Only for infliximab and etanercept ^[27] Not improved for PUVA and NB-UVB ^[27] ; and for Goeckerman's therapy ^[25]	No report
IFN- γ	Increased ^[15,17,18,21,24,33]	Correlated positively ^[15,18,24,33] Not correlated ^[21] Not the best predictor ^[17]	Improved ^[33] Not improved ^[34]	Longer length of remission if decreased ^[33]
IL-12	Increased levels ^[15,18,36] Decreased levels ^[24]	Correlated positively ^[15,18] Not correlated ^[24,36]	Improved ^[18,36]	No report
IL-18	Increased levels ^[15,18,39-42]	Correlated positively ^[15,18,39-42] Combined with TGF- β 1, TIMP-1 and MMP-1 - superior value as predictor ^[42]	Improved ^[39]	No report
IL-8	Increased levels ^[3,14,15,17,24,25] Not increased ^[43]	Correlated positively ^[3] Correlation only with erythema ^[24] Not correlated ^[15,17]	Improved ^[3] Increased significantly ^[25]	No report
IL-6	Increased levels ^[14,15,20-22,43-45] Higher levels in severer forms than in mild and in controls; no differences between mild forms and controls ^[26]	Correlated positively ^[21,22,44] , for severe psoriasis only ^[26] Correlation only with desquamation and infiltration ^[45] Not correlated ^[43,46]	Improved ^[45-47] , for PUVA ^[22] Not improved for NB-UVB and topical therapy ^[22]	No report
IL-22	Increased levels ^[3,20,46,54-56]	Correlated positively ^[20,46,54,55] Not correlated ^[3,57]	Improved ^[3,56] Only for etanercept ^[57] Not improved for acitretin ^[57] Only in high-responders; not predictor of biologic therapeutic response ^[55]	No report
IL-17	Increased levels ^[3,18,56,57] Not altered ^[15,59]	Correlated positively ^[18,57] Not correlated ^[3,59]	Improved ^[3,56] Only for etanercept ^[57] Not improved for acitretin ^[57]	No report
VEGF	Increased levels ^[3,43,66-71] Only in medium and severe psoriasis ^[72] Not increased ^[55]	Correlated positively ^[18,55,67-70,72] Not correlated ^[43]	Improved ^[3,67,68] Only for PUVA ^[71] Discordant results with NB-UVB ^[3,70,71] Increased values with retinoids combined with NB-UVB ^[71] Only in high-responders; not predictor of biologic therapeutic response ^[55]	No report
IL-21	Increased levels ^[20,61]	Correlated positively ^[61] Not correlated ^[20]	No report	No report
TGF- β 1	Increased levels ^[73] Not increased ^[74,75]	Correlated positively ^[39,42,73-75] Combined with IL-18, TIMP-1 and MMP-1 - superior value as predictor ^[42]	Improved ^[77] The decrease was not significantly ^[76]	No report
IL-10	At least for patients with a PASI < 15 ^[76] Decreased ^[18] Below detection levels ^[24] Increased ^[36,43]	Correlated negatively ^[18] Not correlated ^[43]	Decreased ^[36]	No report
CRP	Increased levels ^[69,78-95] Not increased ^[96,97]	Correlated positively ^[69,79,84,87,90,93-95,98] Correlated after treatment ^[82] Not correlated ^[81,99]	Improved ^[78,79,81-83,88,91,92,97,98]	Longer length of remission if decreased; predictor of length of remission ^[100]
PTX3	Increased levels ^[26,81,102]	Correlated positively ^[26,102] Not correlated ^[81]	Improved ^[81,102]	No report

CRP: C-reactive protein; IL: Interleukin; IFN: Interferon; MMP: Matrix metalloproteinase; NB-UVB: Narrow-band ultraviolet light B; PTX3: Pentraxin 3; PUVA: Psoralen plus ultraviolet light A; TGF: Transforming growth factor; TIMP: Tissue inhibitors of metalloproteinases; TNF: Tumor necrosis factor; VEGF: Vascular endothelial growth factor.

patients and reduced after tacalcitol ointment; moreover, there was a correlation between the baseline levels and PASI^[155]. Finally, the levels of the microRNA (miR)-1266, apparently one of the regulators of IL-17, were considerably higher in psoriasis patients than in control subjects and showed an inverse association, although weak, with PASI and body surface areas of involved skin, which lead the authors to propose it as a marker of disease activity^[156]; however, further studies are warranted to clarify the role of miR-1266 in psoriasis pathogenesis.

CONCLUDING REMARKS

For most of the potential biomarkers there are studies with divergent results, compromising their definition as markers of psoriasis severity and/or monitors of therapy. In several cases, their levels are altered in active psoriasis, but may or may not be correlated with PASI, and may or may not be reversed by different therapies. Differences in the study design, characteristics of patients and controls enrolled in the study, psoriasis severity and its assessment, among other factors, may account for these discrepancies. Nonetheless, in most cases the alterations seem to reflect more the involvement of the biomarker in psoriasis pathogenesis, rather than to reflect directly psoriasis severity and/or activity. Moreover, the use of some of these biomarkers must consider other inflammatory comorbidities that may be misleading, as they are not specific for psoriasis.

Considering adipokines, although several studies referred a possible association between their levels and disease severity, this correlation seems to be dependent of the body weight of the patient and/or to be more pronounced in the severer forms, that are usually associated with higher adiposity. This raises the question: patients with severe psoriasis forms and with low adipose mass present also alterations in these adipokines levels? And do they relate with psoriasis activity?

Considering that psoriasis is an immunologic, inflammatory chronic disease, it is not surprising that most of the potential biomarkers of psoriasis are inflammatory/immunologic markers or are somehow related with the inflammatory process. In spite of some controversial data, it appears that a bio-panel by combining the most promising inflammatory biomarkers may become a reliable alternative to assess psoriasis severity and to monitor the response to therapy. A summary of the reported data about these biomarkers and its relation with psoriasis activity, severity and therapy is presented at Table 1.

With several and more consistent data, we might propose CRP, one of the most sensitive markers of inflammation, as the most promising biomarker to evaluate psoriasis severity and to monitor the response to different types of treatment of psoriasis. However, since there is no consistent data for mild psoriasis forms, it seems that the combination of CRP values with other analytical or clinical markers would be valuable. Thus, the need to search for an accurate marker or a combination of clinical and/or analytical markers, to support therapeutic

decisions, needs further studies. We believe, considering the current data, that the association between CRP levels and PASI score, provides a valuable bio-panel to evaluate psoriasis severity and to monitor its treatments. Moreover, as CRP and PASI are both predictors of the length of psoriasis remission^[100], their evaluation at end of the treatment may help to decide if the treatment should be continued to achieve lower CRP values and longer periods of remission.

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Looking within the lesion: Large scale transcriptional profiling of psoriatic plaques

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Abstract

Psoriasis is a lifelong, chronic, recurring and highly variable skin disease. Psoriatic plaques are formed through induction of inflammation in the epidermis and deregulation of keratinocyte proliferation and differentiation. This results in red or silvery scaly patches on the surface of the epidermis. To look within the lesions and define the changes in gene expression in psoriasis, investigators compared the transcriptomes of psoriatic plaques, of uninvolved skin of patients and of skin from healthy individuals. In several large studies with many patients, the genes expressed at much higher level in psoriatic plaques included those responsible for the cell cycle, keratinocyte differentiation, and response to wounding; conversely, lipid and fatty acid metabolism enzymes were expressed at reduced levels. The nonlesional and healthy skin appeared fairly similar. The largest study included paired biopsies from 85 individual patients. The same group used transcription profiling to follow the course of treatment in a set of patients, and correlated changes in the transcriptome of blood samples of psoriatic patients. Importantly, a noninvasive technique involving tape-stripping of skin, has been shown effective in transcriptional studies of

psoriasis. Current efforts are focused on deconvoluting the contributions of various cell types in psoriasis, keratinocytes, lymphocytes, fibroblasts etc. Taken as a whole, these efforts will lead to personalized medicine, *i.e.*, to specific, individualized treatments of patients with psoriasis.

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Key words: Cytokines; Inflammation; Metaanalysis; Microarrays; Skinomics

Core tip: Dermatology was among the first medical specialties to adopt bioinformatics methodology, and Psoriasis, with its high prevalence, among the first diseases. Genome-wide association studies identified close to 50 genetic predisposition loci, to date. Recently, large-scale transcriptome analysis using DNA microarrays identified the important signaling pathways and regulators of gene expression in psoriasis. These efforts, and the fundamental knowledge they provide will lead to personalized medicine, *i.e.*, to specific, individualized treatments of psoriatic patients in the near future.

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INTRODUCTION

According to the National Psoriasis Foundation, psoriasis affects 7.5 million Americans and 125 million people worldwide. It is a chronic autoimmune disease with a multifactorial (genetic and environmental) etiology^[1].

Table 1 Psoriasis susceptibility loci identified using genome-wide association studies

Psoriasis	Chromosome	Gene	Locus	Ref.
1	1p31.3	IL-23R		Nair <i>et al</i> ^[11]
1	1p31.3	IL-23R		Liu <i>et al</i> ^[48]
1	1p31.3	IL-23R	rs9988642	Tsoi <i>et al</i> ^[8]
2	1p36	RUNX3	rs7536201	Tsoi <i>et al</i> ^[8]
3	1p36.11	IL28RA	rs7552167	Tsoi <i>et al</i> ^[8]
4	1p36.23	SLC45A1, TNFRSF9	rs11121129	Tsoi <i>et al</i> ^[8]
5	1q21	PSORS4		Julia <i>et al</i> ^[49]
6	1q21	LCE3D	rs6701216	Liu <i>et al</i> ^[48]
7	1q21.3	LCE3B	rs4112788	de Cid <i>et al</i> ^[1]
8	20q12-q13.12	NCOA5	rs2903908	Zervou <i>et al</i> ^[50]
9	20q12-q13.2	CD40	rs4810485	Zervou <i>et al</i> ^[50]
10	20q13.13	RNF114	rs1056198	Tsoi <i>et al</i> ^[8]
11	22q11.21	UBE2L3	rs4821124	Tsoi <i>et al</i> ^[8]
12	2p15	B3GNT2	rs10865331	Tsoi <i>et al</i> ^[8]
13	2p16.1	FLJ16341, REL	rs62149416	Tsoi <i>et al</i> ^[8]
14	2q14.2	IL1RN		Julia <i>et al</i> ^[49]
15	2q24.2	KCNH7, IFIH1	rs17716942	Tsoi <i>et al</i> ^[8]
16	3p12.1	CADM2		Hiruma <i>et al</i> ^[51]
17	4q27			Liu <i>et al</i> ^[48]
18	5q15	ERAP1	rs27432	Tsoi <i>et al</i> ^[8]
19	5q31	IL-13, IL-4	rs1295685	Tsoi <i>et al</i> ^[8]
20	5q31.1-q33.1	IL-12B	rs12188300	Tsoi <i>et al</i> ^[8]
21	5q32-q33.1	TNIP1	rs17728338	Bowes <i>et al</i> ^[52]
22	6p21.3	HLA-C		Knight <i>et al</i> ^[53]
23	6p25.3	EXOC2, IRF4	rs9504361	Tsoi <i>et al</i> ^[8]
24	6q21	TRAF3IP2	rs33980500	Ellinghaus <i>et al</i> ^[10]
25	6q23	TNFAIP3	rs582757	Tsoi <i>et al</i> ^[8]
26	6q25.3	TAGAP	rs2451258	Tsoi <i>et al</i> ^[8]
27	7p14.1	ELMO1	rs2700987	Tsoi <i>et al</i> ^[8]
28	9p12	DDX58	rs11795343	Tsoi <i>et al</i> ^[8]
29	9q31	KLF4	rs10979182	Tsoi <i>et al</i> ^[8]
30	9q34	TSC1	rs1076160	Bowes <i>et al</i> ^[52]
31	10q22.3	ZMIZ1	rs1250546	Tsoi <i>et al</i> ^[8]
32	11q11-q13	RPS6KA4, PRDX5	rs645078	Tsoi <i>et al</i> ^[8]
33	11q22.3	ZC3H12C	rs4561177	Tsoi <i>et al</i> ^[8]
34	11q23.3	ETS1	rs3802826	Tsoi <i>et al</i> ^[8]
35	12q13.3	STAT2, IL23A	rs2066819	Tsoi <i>et al</i> ^[8]
36	13q12	LHFP		Liu <i>et al</i> ^[48]
37	13q14.11	COG6	rs7993214	Liu <i>et al</i> ^[48]
38	14q13	NFKBIA	rs8016947	Tsoi <i>et al</i> ^[8]
39	15q21		rs3803369	Liu <i>et al</i> ^[48]
40	16p11.2	PRSS53, FBXL19	rs12445568	Tsoi <i>et al</i> ^[8]
41	16p13.13	PRM3, SOCS1	rs367569	Tsoi <i>et al</i> ^[8]
42	17q11.2-q12	NOS2	rs28998802	Tsoi <i>et al</i> ^[8]
43	17q21.31	PTRF, STAT3, STAT5A/B	rs963986	Tsoi <i>et al</i> ^[8]
44	17q25	CARD14	rs11652075	Tsoi <i>et al</i> ^[8]
45	18q21.2	POL1, STARD6, MBD2	rs545979	Tsoi <i>et al</i> ^[8]
46	18q22.1	SERPINB8		Julia <i>et al</i> ^[49]
47	19p13.2	TYK2	rs34536443	Tsoi <i>et al</i> ^[8]
48	19p13.2	ILF3, CARM1	rs892085	Tsoi <i>et al</i> ^[8]

Note that many of the loci were identified in multiple studies (*e.g.*, shaded).

Past research suggests that external, internal and/or environmental triggers, such as stress, systemic illnesses and environmental allergens, combined with the genetic predisposition, may result in an altered immunity and an in-

creased risk for the development of psoriasis^[2]. However, the initial trigger for psoriasis and development of psoriatic lesions remains unknown^[3-5]. While the exact causes are unknown, in psoriasis the immune system sends out incorrect signals that speed up the proliferation of epidermal keratinocytes. While normal keratinocytes mature and desquamate in about a month, psoriatic skin ones reach the surface in only 3-4 d and, instead of sloughing off individually, they accumulate to form large flaking scraps of skin^[2].

Psoriasis is typically a lifelong, chronic recurring condition. It can vary in severity from small localized areas to covering the entire body. The diagnosis of psoriasis is based on the appearance of skin, not on blood tests or specialized diagnostic procedures. Occasionally a skin biopsy may be needed to rule out other proliferative skin disorders. Psoriatic plaques are formed through an increase in inflammation in the epidermis, deregulation of cell cycle processes, increase in keratinocyte proliferation and epidermal differentiation changes. Together this results in the formation of raised, red or silvery scaly patches on the surface of the stratum corneum.

The genetic predisposition for psoriasis was known through family-based and population-based epidemiological studies, which suggested that genetic factors play a key role in the development of psoriasis^[6-7]. Perhaps a third of psoriatic patients report a family history of psoriasis; reports on monozygotic twins find a 70% chance of a twin developing psoriasis if the other twin has psoriasis while this number is around 20% for paternal twins. More recently, genome-wide association scans have fine-mapped the nine susceptibility loci (PSORS1-PSORS9) and located many previously unsuspected genomic markers on human chromosomes^[6,8-11]. A current list of psoriasis susceptibility loci is given in Table 1. However, the known genetic factors for psoriasis do not account for all observed genetic susceptibility to psoriasis; additional genetic factors remain to be discovered^[6]. Thus, the genetic contribution to psoriasis is not fully understood^[3].

Of the five types of psoriasis (plaque, guttate, inverse, pustular, and erythrodermic), the most common is the plaque psoriasis. Plaque psoriasis is seen as red and white silvery hues of scaly patches appearing on the top of the epidermis. Plaques frequently occur on the extensor aspects of the knees and elbows, but can affect any area, including the scalp, genitals, palms and soles. Fingernails and toenails are often affected, which can be an independent symptom. Additionally, psoriasis can be associated with inflammation of the joints, which is known as psoriatic arthritis. Guttate psoriasis presents as numerous small, scaly, pink or red lesions over large areas of the body, the trunk, limbs and scalp. Inverse or flexural psoriasis occurs in skin folds, *e.g.*, around the genitals, the armpits or under the breasts. Pustular psoriasis presents as raised pus-filled bumps, commonly on the hands and feet (*i.e.*, palmoplantar pustulosis), or generalized, occurring randomly widespread on any part of the body. Erythrodermic psoriasis involves the widespread inflammation

Table 2 Transcriptional profiling studies targeting psoriasis in the GEO database

	Microarrays	Platform	Samples	Ref.
Comparison studies				
GSE34248	14 + 14	HG- U133_Plus_2	Lesional + NonLes	[21]
GSE41662	24 + 24	HG- U133_Plus_2	Lesional + NonLes	[21]
GSE41663	15 + 15 (+ 51 treated)	HG- U133_Plus_2	Lesional + NonLes	[21]
GSE30999	85 + 85	HG- U133_Plus_2	Lesional + NonLes	[19]
GSE11903	15 + 15 (+ 59 treated)	HG-U133A_2	Lesional + NonLes	[18]
GSE6710	13 + 13	HG-U133A	Lesional + NonLes	[24]
GSE14905	21 + 33 + 30	HG- U133_Plus_2	Healthy + Les + NonLes	[16]
GSE13355	64 + 58 + 58	HG- U133_Plus_2	Healthy + Les + NonLes	[12]
GSE32407	20 + 20 (+ 20 IFN γ treated)	HG-U133A_2	Healthy + NonLes	[17]
Related studies				
GSE42305			Monocytes	[54]
GSE41905			Kcytes transfected wt Antimir31	[55]
GSE31652			All lesional, treated placebo	[56]
GSE26952			Nonlesional only Psor AD	[57]
GSE18948			PBMCs	[58]
GSE11307			PCR study	¹
GSE6601			Psor <i>vs</i> AD	[59]
GSE41745	3 + 3		RNA Sequencing	[60]
GSE26866	11 + 11 (different regions)	HG-U133A_2	Single <i>vs</i> double amplification	[61]
GSE30768	2 + 4 (+ 8 flare and relapse)	HG-U133A_2	Small number of samples	[62]
GSE2737	3 + 4 + 4	HG_U95Av2	Small array	[63]

¹Shin J and Detmar M, unpublished. PBMCs: Peripheral blood mononuclear cell; PCR: Partido comunista revolucionario.

and exfoliation over most of the body skin. While the shared symptoms, *i.e.*, the underlying inflammation and epidermal hyperproliferation, characterize all types of psoriasis, the distinct clinical presentations, the extensive and dispersed genetic underpinnings and inconsistent, variable clinical responses argue that psoriasis comprises a cluster of related but distinct disorders.

The superb international success in GWAS mapping the psoriasis susceptibility loci has been joined recently by equally outstanding transcriptional profiling studies from several laboratories that recruited very impressive numbers of patients and samples (Table 2). These studies provide deep and comprehensive insights into the molecular mechanisms of the pathology of psoriasis. Also an international effort, the transcriptional profiling is lead by two teams in the United States, that of Drs. G. Gudjonsson and J.T. Elder at the University of Michigan, and the team of Dr. J.G. Krueger at the Rockefeller University. The researchers compared the genes expressed in psoriatic plaques with those expressed in the nonlesional skin of patients, and both of these with the skin of healthy

control subjects. Investigators also searched for diagnostic markers of psoriasis in the blood of patients. The current status and insights from these efforts is the subject of this review.

DISCUSSION

In a very influential study Gudjonsson *et al.*^[12] analyzed a large cohort of psoriatic patients and healthy controls using transcriptional profiling. Importantly, their analysis included 58 paired samples of lesional and nonlesional skin, allowing comparisons of matched samples from the same patients, and 64 control biopsies, allowing large-scale comparisons of lesional and nonlesional skin with healthy skin^[11-15]. The sheer size of this study allowed the authors to identify close to a thousand differentially expressed genes in the lesional skin. The genes over-represented in the psoriasis lesions included Serpins, β -defensin-2, *S100A* genes and IL-8. Suppressed genes included β -cellulin, *IL1F7* and *CCL27*. The ontological categories induced in the lesions incorporated cell cycle, expected in this hyperproliferative disease, keratinocyte differentiation markers and three categories that contained cytokines, chemokines and their receptors, namely immune response, defense response and response to wounding^[14]. The suppressed ontological categories incorporated lipid and fatty acid metabolism. The nonlesional and healthy skin, however, appeared rather similar, confirming the results of Yao *et al.*^[16] (see below).

In an important follow-up a team in United Kingdom, collaborating with Dr Gudjonsson, used sophisticated bioinformatics methodologies to classify psoriatic patients and identify distinct molecular subtypes^[15]. Again, the nonlesional and healthy skin appeared quite similar. Among the psoriatic plaque samples, two subtypes were identified using multidimensional scaling, one a tightly clustered group of patients at the apex of the less congruent and more dispersed subtype. The authors proposed that TGF and the ErbB pathways may be involved in distinguishing the two subtypes.

The ground-breaking large-scale transcriptional profiling of psoriatic samples was reported by the team of Dr Krueger in 2009^[16]. They analyzed 33 lesional, 30 nonlesional and 21 healthy control samples. The nonlesional skin was more similar to healthy skin of other donors than to the lesional skins from the same patient. The transcriptional signatures of the plaque biopsies pointed to the infiltration of T cells and dendritic cells in the lesions. Yao *et al.*^[16] recognized the signatures of several cytokines implicated in psoriasis. Specifically, they compared genes differentially expressed in the lesions with the gene sets regulated by IFN- α , IFN- γ and by TNF- α in keratinocytes. The significant overlaps substantiated the proposed roles of these cytokines in psoriasis. Several members of IFN- α family, IFN- α 1, IFN- α 2, IFN- α 6, IFN- α 7, IFN- α 8, IFN- α 14 and IFN- α 21, were overexpressed in the lesions. The results validated the TNF- α -targeting and the T cell targeting therapies currently in wide use to

treat psoriasis, as well as suggested IFN- α as a potential target.

Interestingly, in a separate study, Dr. Krueger's team found that a single injection of IFN- γ into the dermis of nonlesional sites of psoriatics can recapitulate the transcription profile changes seen in the psoriatic plaques^[17]. Apparently, IFN- γ can initiate the psoriasiform immune responses by promoting influx of T cells and dendritic cells. A similar influx was seen even in the IFN- γ -injected sites of healthy, non-psoriatic individuals.

The same team followed transcriptional changes in psoriatic patients treated with Etanercept^[18]. Baseline transcriptional profiles were compared with those in treatment for up to 12 wk. The patients were divided into responders (11 patients) and non-responders (4 patients). Interestingly, the TNF- α -regulated genes (*e.g.*, *IL-1 β* and *IL-8*) were silenced in both groups; however the responders specifically inactivated the genes associated with the Th17 immune responses. The study highlighted the distinguishing and important role of the Th17 pathway in the pathology of psoriasis.

The largest transcriptional profiling study of psoriasis patients, to date, was reported by Suárez-Fariñas *et al.*^[19] in 2012. The Rockefeller University team compared 85 matched pairs of lesional and nonlesional biopsies from patients. The impressively large study identified 2725 individual genes differentially expressed 2-fold or more in the plaques. Serpins and S100A proteins were among the most overexpressed genes, but also many proteases/peptidases, including Kallikrein-related peptidase-6, -13, *etc.* Conversely, β -cellulin, CCL27 and lipid and fatty acid metabolism enzymes were found suppressed in the plaques, as seen by others^[12,19]. The authors confirmed the results of transcriptional profiling using extensive RT-PCR and immunohistological experiments.

In this study by Suárez-Fariñas *et al.*^[19], the sets of regulated genes were compared with the sets identified in two previous studies^[12,16]. Very high correlation was seen (scores ranging from 0.83 to 0.94) demonstrating very high concordance of the gene expression changes in psoriasis across the three large studies in two different centers. The concordance among different studies received extensive scrutiny^[20-21], and it was found that, provided appropriate statistical methodologies are used, the studies are very highly concordant. The concordance allowed a meta analysis of psoriasis transcriptomics studies^[22]. The meta analysis identified over 1000 genes that were consistently differentially expressed over 5 different studies. Moreover, this study provided a link between changes in the psoriasis transcriptome and atherosclerosis signaling, lipid and fatty acid metabolism and cardiovascular disease, thus providing a crucial link between the psoriatic skin conditions and these systemic diseases. Tian *et al.*^[22] in 2012, defined a "core" 20-gene set that distinguishes the psoriatic lesions. Interestingly, this core contained genes overexpressed even in psoriatic skin after successful treatment, as well as distinct genes epigenetically labeled by differential methylation in plaques.

Suárez-Fariñas *et al.*^[19] also compared serum protein levels of 12 important secreted proteins detected as over-represented in psoriatic plaques^[19]. In large cohort of approximately 150 patients and as many controls, all 12 proteins were found at increased levels in the sera of patients. The proteins included CCL2, CCL22, CXCL5 and TNF- α , which are all markers of psoriasis.

Using transient unresponsiveness to the stimulation of dendritic cells as a model of chronic inflammation, such as in psoriasis, Filkor *et al.*^[23] found the expression of feedback regulators of innate immunity to be suppressed, such as TNFAIP3 and TNFAIP8; these are also suppressed in the dermis of psoriatic patients.

In a study of matched lesional and nonlesional samples from 13 patients, in 2007, Reischl *et al.* identified 179 genes differentially expressed 2-fold or more^[24]. Interestingly, 16 statistically significant genes were associated with the Wnt/ β -catenin pathway, leading the authors to propose an important role for this pathway in psoriasis. Attempts to distinguish differences in the transcriptomes of plaques from different body sites, and between patients with symmetric and asymmetric plaques have not been successful^[25]. In a more limited study of just 44 genes, Aubert *et al.*^[26] found that in psoriasis of the scalp, treatment with topical steroids restores expression of the 10 inflammation-related genes to the more basal, healthy levels. Similar results were found in a study of 5 lesional and 5 nonlesional samples, compared with similar number of blood samples^[27]. Using a completely different approach, involving meta analysis of data in public repositories, specifically the BodyMap gene expression database^[28], and RNA sequencing, Itoh *et al.*^[29] found very similar sets of differentially expressed genes. Others have noted the overlaps between genes differentially expressed in psoriasis and regulated by cytokines in epidermal keratinocytes^[30-36].

In a study of matched lesional and nonlesional samples from 15 patients and 6 healthy controls, the team of Bowcock *et al.*^[37] a collaboration of Washington U. and Baylor U., also found overexpression of serpins and S100A proteins, but also of keratins KRT6, KRT16 and KRT17, known markers of epidermal hyperproliferation^[38]. These studies also addressed the transcription factors responsible for the expression of differentially expressed genes and found NF- κ B and AP1 sites evident, as expected. In addition, sites for nuclear receptors, ROR α 1, VDR and PPAR are found in the regulated genes, as are the motifs bound by Ikaros proteins, zinc finger transcription factors characteristic for lymphoid cell lineages. A similar set of transcription factors associated with psoriasis, additionally including E2F1 was proposed in another study^[39]. Using a completely different approach, involving proteomics, NF- κ B, AP1, STAT1 and STAT3 proteins were identified as important in psoriasis transcriptional deregulation^[40].

In an exciting and sophisticated skinomics approach, Swindell *et al.*^[41] were able to assign most of the differentially expressed genes in the psoriatic plaques to the

different cell types that contribute to the disease^[41]. Specifically, they found that the genes induced in the plaques derive mainly from the activated keratinocytes, 56%, infiltrating T-cells, 14%, and macrophages, 11%. The suppressed genes were derived from the adipose, epidermis and dermis 4%. Swindell *et al.*^[41] also distinguished the patients who responded to Etanercept from the non-responders by their respective transcriptional profiles. Moreover, they confirmed the induction of genes responding to several cytokines, including IFN- γ , IL-1, IL-17A and TNF- α .

Importantly, skin samples can be obtained using noninvasive and (almost) painless technique of tape-stripping. This method provides RNA samples of quality and quantity adequate for microarray analysis^[42]. Using tape-stripping followed by RT-PCR, Benson *et al.*^[43] have detected increased levels of mRNAs for TNF α , IF γ and KRT16, among others, in psoriatic plaques.

CONCLUSIONS AND FUTURE PROSPECTS

Whereas the future is inherently unpredictable, currently several trends seem to guide the research in transcriptional changes in psoriasis. First, stratification of patients into categories (*e.g.*, etanercept responders) will allow personalized medicine approaches to be developed and used in the treatment of psoriasis. Second, the exact roles of the immune cell types, the cytokines and chemokines they produce and the signaling pathways consequently activated in the responding keratinocytes will provide scores of additional targets, which will further advance patient-specific treatments. And third, an exciting new area of research, that of the effects of the cutaneous microbiome on psoriasis initiation, progression and resolution^[44-47] has the potential to revolutionize our conceptual and practical approach to this intractable and difficult problem.

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Gender medicine and psoriasis

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Core tip: The study of specific differences between women and men is arousing huge interests in various fields of medicine, including dermatology. The available data on gender medicine applied to common skin diseases are unfortunately still scanty. The objective of this brief review is to provide hints for the presence of sex differences in various aspects of psoriasis, from epidemiology to pathogenesis, from clinical aspects to therapeutic management, trying to examine the evidence available in the literature.

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Abstract

The study of specific differences between women and men is arousing huge interests in various fields of medicine, including dermatology. The available data on gender medicine applied to common skin diseases are unfortunately still scanty. Psoriasis is a chronic immune-mediated skin disease which affects 1%-3% of most populations worldwide and can involve also the joints and entheses. The pathogenesis of the disease is very complex, resulting from the interaction between genetic predisposition and several environmental triggers. The pathogenic role of sex hormones has also been hypothesized. The analysis of gender-specific differences in psoriasis seems to suggest some interesting findings, such as an earlier age of disease onset in females, a higher probability of severe disease in men, or different tendencies in care utilization, adherence to treatment, development of psychological distress, and coping strategies. Moreover, sex-related differences have been recently described in some epidemiological and clinical features among patients with psoriatic arthritis. The objective of this article is to review briefly the available evidence regarding gender differences in various aspects of psoriasis, such as epidemiology, genetics, risk factors, associated conditions, quality of life, clinical and therapeutic aspects.

INTRODUCTION

The ever-increasing interest in the study of gender medicine in the last years has led to gain awareness of the differences between men and women in the clinical presentation, pathophysiology, management and prognosis of a wide variety of human diseases, including skin diseases^[1].

Gender differences in disease characteristics can be influenced by complex interactive mechanisms involving the effect of sex hormones, ethnic background, anatomy, physiology, immunity, genetics, epigenetics, as well as geographical, sociocultural, and environmental factors. Differences in the skin structure and physiology between the sexes can also contribute to different expression of some skin disorders^[1,2].

Psoriasis is a common chronic inflammatory skin dis-

ease that affects 1%-3% of most populations in developed countries, with a predilection for Caucasians^[3]. Histopathologically, the disease is characterized by signs of increased proliferation and abnormal differentiation of keratinocytes (hyperkeratosis with parakeratosis, loss of granular layer, acanthosis and elongation of rete ridges), dilatation and tortuosity of the capillary loops, and inflammatory infiltration of the papillary dermis and the epidermis, with a preponderance of lymphocytes and neutrophils.

Psoriasis is considered an immune-mediated disease characterized by a predominant Th1-type and Th17-type cytokine profile, although a complex interplay between various cells of the innate and adaptive immune system contributes to the induction of inflammatory processes, epidermal hyperplasia, and ultimately to the development of clinical manifestations. Pathogenesis is only partially known and particularly complex, involving an interaction between genetic factors and several environmental triggers^[4,5].

The objective of this brief review is to provide hints for the presence of sex differences in various aspects of psoriasis, from epidemiology and pathogenesis to clinical aspects and therapeutic management, trying to examine the evidence available in the literature.

EPIDEMIOLOGY

Psoriasis can present at any age and most studies have identified a bimodal age of onset, with a first peak between the ages of 15 and 20 years and a second one occurring at 55-60 years^[6]. In spite of minor deviances in some studies, psoriasis prevalence is estimated to be equal in males and females^[7]. An earlier age of psoriasis onset has been reported in females^[8], although other authors did not confirm this finding^[7]. Interesting results were extrapolated by a survey conducted in a historical cohort of Norwegian twins aged 19-31 years^[9]. There were no sex differences in the overall prevalence rates, but significantly higher point-prevalences emerged in females in the teenage-year intervals. The mean age at onset was also significantly lower in females than in males. The absolute risk of developing psoriasis appeared higher for females across the entire age range. However, by the age of 31 the cumulative risks were similar in females and males.

A population-based retrospective study carried out in the United States examined the incidence of adult-onset psoriasis over three decades and found that the overall age- and sex-adjusted incidence in males was more elevated than in females, except for the sixth decade of life, when there was a peak incidence in women^[10], thus suggesting the potential pathogenic relevance of sex hormones in psoriasis. Previous observations indicated the role of menopause not only in the onset but also in the exacerbation of psoriasis^[11].

PATHOGENESIS AND RISK FACTORS

Psoriasis pathogenesis is multifactorial and recognizes a

strong genetic background, as suggested by the frequent presence of a positive family history and the identification of putative susceptibility loci on several chromosomes^[4]. One of the most important loci is the MHC region on chromosome 6p21 named PSORS1, harboring the human leukocyte antigen-C (*HLA-C*) gene. HLA-Cw6 (HLA-Cw*0602) was found to be the most relevant risk allele and has been associated with a lower age at onset. It was reported that Cw6-positive women might have an earlier disease onset than Cw6-positive men, but such a difference was not observed for the Cw6-negative patients^[12].

There is interesting evidence concerning the impact of sex of the transmitting parent (genomic imprinting). The sex of the psoriatic parent was found to influence the birth weight of offspring, with children from psoriatic fathers being heavier than offspring of female psoriatic patients, and also the disease manifestation, which was more likely to occur when the father was affected^[13]. In the opinion of some authors^[14], the genes underlying this imprinting might contribute to a higher disease activity in males although there is a paucity of information on this aspect.

As above mentioned, the development of psoriasis is a complex phenomenon resulting from the action of environmental triggers in predisposed individuals. These triggers include trauma, psychogenic stresses, infectious agents (*i.e.*, streptococcus, HIV and other viruses), drugs (*e.g.*, lithium, antimalarials, interferon, beta-blockers, nonsteroidal anti-inflammatory drugs, or rapid tapers of high-dose steroids)^[5]. The possible role of hepatitis C virus infection is discussed in the paragraph regarding comorbidities and clinical associations.

The influence of stressful life events on psoriasis has also been suspected for long time. The association with stressful events occurring in the year preceding the diagnosis of psoriasis was documented in one study^[15], which showed that this risk was more evident for women.

Alcohol has long been suspected to be a triggering and precipitating factor of psoriasis. Alcohol misuse is common in patients with moderate-to-severe psoriasis and appears to interfere with the course of the disease and treatment outcome^[16]. An increased alcohol consumption was shown in both male and female psoriatics as compared to controls, with a statistically significant difference reached only for men^[17], whereas other data suggested a tendency to drink more after psoriasis diagnosis especially in women^[18].

Smoking has also been implicated in the development of psoriasis. The cumulative association between smoking and psoriasis seems stronger in women^[15,19], although one study identified smoking as a risk factor only in males^[18]. A recent report highlighted the role of smoking as an independent risk factor for psoriasis, without however disclosing differences in the association among younger vs older women or between women and men^[20]. Other results supported a positive association with both adulthood exposure to passive smoking^[20], and the ex-

smoker status only for men^[17].

CLINICAL ASPECTS

Psoriasis is a papulo-squamous disease with variable morphology, distribution, and severity of skin lesions. It has a variable course, that is usually lifelong, chronic and recurrent^[3,21]. The most common clinical presentation is chronic plaque psoriasis, which can affect any body site with preferential involvement of the scalp, the extensor aspects of limbs, and the lumbosacral area. The presence of lesions in body folds depicts the so called flexural or inverse psoriasis. Psoriasis may also develop at the site of trauma, known as Koebner's phenomenon. The progressive diffusion of lesions can lead to psoriatic erythroderma, which is a rare severe form characterized by generalized erythema and scaling in more than 90% of the body surface area. Other variants include guttate psoriasis, consisting of eruptive small papules usually distributed on the trunk and the proximal aspects of limbs, and pustular psoriasis, that can be distinguished into localized palmoplantar forms and the more severe generalized forms.

Nail changes may be present, especially in patients with concomitant arthritis. Morphological differences in psoriasis between males and females have not been documented so far^[7]. Some observations seem to suggest that moderate to severe extent of involvement is more frequent in men than in women^[22]. With respect to the distribution of clinical variants, a remarkable gender-related feature regards palmoplantar pustulosis that more commonly affects women, with a female/male ratio of 9:1^[6]. Palmoplantar pustulosis has a special predilection for female smokers^[23]. A retrospective evaluation of 102 patients with adult-onset generalized pustular psoriasis reported a female to male ratio of 2:1^[24].

PSORIATIC ARTHRITIS

Psoriasis may also affect the joints and the entheses. The estimated prevalence of psoriatic arthritis (PsA) among patients with psoriasis has varied widely from 6% to 42% according to different case series^[25]. In the vast majority of psoriasis patients with PsA, the skin manifestations precede arthritis^[5].

Uncertain data exist on the prevalence of PsA in men and women. PsA is generally thought to occur equally in both sexes^[25]; indeed, recent findings indicate that the incidence of PsA is less in women than in men until the sixth decade of life^[26], thus providing indirect evidence of the potential role of sex hormones in PsA pathogenesis. PsA in Iceland seems to be more common in women, with the female to male ratio close to 2:1^[27]. A female predominance was also registered in Kuwait while other studies noted a male predominance^[28,29].

Very limited information is available about gender differences in PsA patients. A positive family history of psoriasis and PsA was reported more frequently by women with PsA in some instances^[30]. Females appear

to progress more than males^[25]. The results of a recent cross-sectional analysis have shown that there was a clear-cut trend towards a polyarticular involvement in women, whereas oligoarthritis was the most common pattern in men. Moreover, men with PsA were more likely to have psoriatic nail lesions, to develop axial involvement and also more severe radiographic damage in the peripheral joints, while women had more fatigue and severe limitations in function, as well as a worse quality of life^[30]. It is unknown whether these findings can be secondary to differences in occupational physical activity, hormonal changes, or genetic factors. A differential overexpression of certain *MHC* genes between the two genders has been hypothesized^[31]. A close correlation between male sex, HLA-B27 positivity, and the risk of psoriatic spondyloarthritis was also described^[32,33]. On the contrary, in accordance to other authors^[30], no difference in the frequency of HLA-B27 was detectable across the genders among PsA patients. The analysis of a cohort of PsA patients revealed an increased frequency of the HLA-Cw6 allele in women as compared to men^[30]. Another recent study confirmed that women were affected more frequently by polyarthritis as the main joint pattern during follow-up, and had significantly greater functional impairment and higher number of swollen joints^[31]. Among the PsA patients with psoriasis developing before 40 years of age, a significantly shorter psoriasis-PsA latency period was noted in men^[31].

Work disability in PsA patients below 45 years of age was shown to be independently related to educational level, disability score, erosive disease, disease duration, and female gender^[34].

COMORBIDITIES AND CLINICAL ASSOCIATIONS

Psoriasis is associated with a number of systemic disorders including Crohn's disease, obesity, type 2 diabetes mellitus, essential hypertension, dyslipidemia, metabolic syndrome, nonalcoholic fatty liver, and depression^[5]. The persistent systemic inflammation and endothelial activation may predispose to the increased risk for cardiovascular disease existing in patients with psoriatic disease^[35]. Few studies systematically examined gender-specific differences in comorbidities associated with psoriasis. On recent occasions^[36,37], higher prevalence rates of diabetes and metabolic syndrome were detected in psoriatic women than in psoriatic men, although other authors demonstrated that the increased association of psoriasis with diabetes consisted of similar proportions in men and women^[38]. Another study investigated the prevalence of masked hypertension, defined as normal office blood pressure with elevated ambulatory blood pressure, which represents a risk factor for full-blown hypertension, cardiovascular morbidity and mortality^[39]. For this purpose, normotensive and non-obese subjects with psoriasis and controls were evaluated. Male sex was detected as an in-

dependent predictor of masked hypertension, together with waist circumference and psoriasis severity.

Regardless of obesity and psoriasis, there are pronounced differences in body fat distribution between men and women, and these differences become more evident in puberty due to changes in sex hormone levels. Women have more body fat, and more peripheral or subcutaneous adipose tissue, while men have a relatively more central distribution of fat, with more visceral and hepatic adipose tissue^[40,41]. These differences, in combination with differences in sex hormones and adipokines, can at least in part explain a greater propensity of men to develop insulin resistance, dyslipidemia, and nonalcoholic fatty liver disease^[40]. It is not known if these distinct gender-related features in body composition may have direct effects on the development of metabolic and cardiovascular comorbidities, as well as on the proinflammatory state of psoriasis patients, taking into account that adipose tissue should be regarded as a source of endocrine and proinflammatory mediators. Compared with men, premenopausal women were shown to have increased concentrations of C-reactive protein, a well-established marker of inflammation and an independent predictor of cardiovascular events, and this result was correlated to subcutaneous adiposity^[42].

In a population-based case-control study, psoriasis was found to be associated with osteoporosis among males, but not among females^[43], although a recent report documented the association of osteoporosis with prior psoriasis diagnosis in both men and women^[44].

Significantly, more male patients appear to have migratory glossitis compared to female patients^[45]. Even though thyroid autoimmune disorders have shown no differences between psoriasis patients and the general population^[46], other findings suggested a significantly elevated prevalence of thyroid autoimmunity in men and women with PsA and of subclinical hypothyroidism in women with PsA than in the general population^[47].

An increased prevalence of concomitant extragenital psoriasis and anogenital lichen sclerosus was revealed in adult women^[48]. Currently, there are no published reports of this clinical association in men.

Retrospective population-based cohort studies in Taiwan disclosed that psoriasis may carry a high risk of malignancies, particularly in male and younger patients^[49]. The most common cancer was nonmelanoma skin cancer (NMSC) which was more frequent in women^[49,50]. Moreover, a Danish follow-up study showed that the significantly increased risk of cancer in psoriasis patients was mainly related to NMSC and lung cancers in both sexes, and cancer of the pharynx and larynx in men^[51]. Women had the highest risk of basal cell carcinoma in the age range 20-40 years, while men in the age range 30-60 years run an elevated risk of cutaneous squamous cell carcinoma. In a Swedish PUVA cohort study^[52], the relative risk of skin squamous cell carcinoma was 5.6 for men and 3.6 for women, and significant increases were also found in the incidence of respiratory cancer in men and women

and of kidney cancer in women.

An epidemiological association between psoriasis and hepatitis C virus infection has been recently reported, suggesting a potential role of the infection as an induction factor for psoriasis, especially in late-onset forms, and showing a consistent male predominance^[53,54].

QUALITY OF LIFE

Although psoriasis generally does not affect survival, it has pronounced negative effects on physical and psychosocial well-being, demonstrable by a significant detriment to quality of life. Quality of life is significantly worse in patients with psoriasis than in healthy subjects and similar to patients with major illnesses, such as diabetes and heart disease^[6,55].

The effect of gender on quality of life is less clear, as controversial results have been obtained so far. Based on earlier observations^[56], the male gender has been associated with lower psychosocial morbidity. In another work, no gender differences were observed in items linked to socialization, although men reported greater work-related stresses as a result of their psoriasis^[57]. A recent Japanese experience demonstrated the presence of a more severe deterioration of quality of life in female patients with psoriasis^[58], whereas German authors observed a moderate but significant relevance of feeling of stigmatization over time only in psoriatic men^[59].

In an Italian cross-sectional study in 936 patients hospitalized with a diagnosis of psoriasis, women had consistently worse quality of life than men and older women suffering from anxiety or depression had the greatest impairment in quality of life^[60]. The same authors more recently analyzed the prevalence of some psychosocial features^[61]. The problems most frequently experienced were shame, anger, worry, difficulties in daily activities and social life. Shame, worry and annoyance were more common in women than in men.

In the Italian multicenter study named PSYCHAE, the presence of minor and major psychological distresses was investigated in more than 1580 patients with psoriasis^[62]. Overall, minor psychological distress was present in 46% of patients and major psychopathological distress in 11%. Female gender was the most important predictive factor for the onset of psychological distress, while no association between severity of psoriasis and psychological distress was disclosed. Among the strategies most commonly employed by patients to cope with psoriasis, women tended to have lower (worse) scores compared with men in different areas, such as diverting attention, religion, use of emotional support, and negation. Women had a higher score only in the area related to humor.

Social support may be an important strategy capable of controlling the negative effects of psoriasis-associated psychosocial stress and improving the quality of life and adaptation to the disease. The strengths of these effects were found to be different in women and men suffering from psoriasis. In fact, higher social support was slightly

Table 1 Main gender-specific features among patients with psoriatic disease

Disease onset	Earlier in females
Prevalence	Reported as similar in men and women Some studies however showed an overall higher incidence in males and a peak incidence in women during the sixth decade of life
Genetic aspects	Earlier disease onset in Cw6-positive women than in Cw6-positive men Higher risk of disease manifestation and higher birth weight in offspring of psoriatic fathers
Triggering and risk factors	Association with stressful events more frequent in women Alcohol: increased consumption in both sexes, with statistical difference reached only for men (in one study); increased consumption after diagnosis more evident for women Smoking: association more consistent in women (one study identified smoking as a risk factor only in males); association with adulthood exposure to passive smoking and the ex-smoker status among men
Clinical features	Moderate to severe extent of involvement more frequent in men Palmoplantar pustulosis particularly frequent in females
Psoriatic arthritis	Controversial data on the prevalence in men and women (different results collected in case series from different countries) Most common clinical forms: polyarthritis in females and oligoarthritis in men Females with higher risk of disease progression, greater functional impairment, fatigue and work disability, and worse quality of life; men with higher risk of nail psoriasis lesions, axial involvement and more severe radiographic damage in the peripheral joints
Clinical associations	In a few studies (not always confirmed by others), different prevalence rates of some comorbid conditions among men and women (<i>i.e.</i> , increase of diabetes, metabolic syndrome, anogenital lichen sclerosis, and subclinical hypothyroidism in women, and increase of masked hypertension, osteoporosis, migratory glossitis, and hepatitis C virus infection in men) High risk of malignancies particularly in male patients
Quality of life	More severe impact on quality of life, more psychological and sexual distress in females Greater work-related stresses in men Moderate but significant relevance of feeling of stigmatization over time in men Gender differences in coping strategies and effects of social support
Treatment	Men more likely to receive intensive systemic treatments for severe psoriasis Gender differences in psoriasis care utilization Overall higher medication adherence in women (however, survival of anti-tumor necrosis factor therapies longer in male patients) Sporadic reports of gender differences in a few aspects of the efficacy and safety profiles of some treatment modalities

more strictly associated with better acceptance of life with the disease in men than in women. However, higher social support was more closely associated to lower depression and better quality of life in women than in men^[63]. Other data seemed to support that women with psoriasis, similarly to those suffering from other serious diseases, were more inclined to use social support resources for coping purposes than men^[64]. As for the satisfaction with specific life domains, no gender differences were noted, but the only psoriasis-specific effect in this context was the satisfaction with sexual life, which was better in men. While confirming the psychosocial morbidity in psoriatic subjects, with more anxiety, depression symptoms and phobic fears compared to general population, the presence of gender differences in such issues was denied, as the distribution in frequency and severity among males and females closely resembled that documented in the general population^[64].

Psoriasis can have a significant impact upon sexual function and health. Sexual distress was found to be particularly present when the genital area was affected^[65]. Sexual distress and dysfunction were also more prominent in women^[65,66].

The relationship between psoriasis and sexual behavior was assessed in two distinct studies in United States women and men, respectively, analyzing data from the

National Health and Nutrition Examination Survey^[67,68]. Psoriasis was not associated with differences in sexual orientation in both men and women. Psoriasis has been associated with a significantly reduced number of sexual partners in nonheterosexual women, and of female oral sexual partners in heterosexual men^[67,68].

THERAPEUTIC MANAGEMENT

There are many treatment options which can control the clinical manifestations of psoriasis without being curative. These options vary from simple topical medications to phototherapy, from traditional systemic drugs (*i.e.*, cyclosporine, acitretin, and methotrexate) to biologic drugs, such as those targeting tumor necrosis factor (TNF) or interleukin-12 and -23. The choice of therapy is strictly dependent on the severity of the disease, but also on several other variables, such as patients' characteristics, the response to previous therapies, and the impact on quality of life. Some drugs, particularly methotrexate and retinoids, have a known teratogenic risk which limits their use in women of child-bearing age.

Some studies performed in the "pre-biologics era" have found that men were more likely than women to receive intensive systemic treatments for severe psoriasis, partly because of the teratogenic potential of some of

these treatments^[69-72]. The majority of patients registered in European registries for psoriasis systemic therapies were men^[14,73], and more male patients have been treated with biologic drugs^[14]. This discrepancy was recently attributed to the higher probability of severe psoriasis in men, rather than to a mere discrimination against women for the access to systemic therapy including biological therapy^[14]. Data taken from the Swedish registries of patients treated with biologics showed no significant differences between men and women in the choice of biologics. At treatment start, psoriatic women had worse scores than men in the subjective disease measurements while men with psoriasis had worse scores for objective disease activity measures^[74].

Psoriasis care consumption seems to be strongly conditioned by several factors, including the gender. In a cross-sectional survey, female patients with psoriasis were 1.47 times more likely to seek care compared with males^[75]. A questionnaire-based study carried out in Sweden demonstrated gender differences in psoriasis care utilization, showing that men visited a dermatologist more often, while women visited a general practitioner, treated themselves topically and wanted information about the disease more frequently^[76]. These differences between genders were explained on the basis of diversities in income and gender roles. Other authors confirmed that women prescribed self-care more often than men^[70].

As for other chronic disorders, compliance and adherence to treatment are fundamental requisites to ensure treatment effectiveness but are difficult to be preserved in the long-term also because patients can be dissatisfied with the management of their disease. Adherence can be affected by a range of disease-related and social factors, including the gender. In fact, women with psoriasis were found to have a significantly higher mean medication adherence rate than men^[77]. A German study evaluated treatment preferences according to some specific attributes (such as probability and duration of benefit, tolerability profile, frequency and methods of delivery), and the subgroup analysis did not disclose any gender differences^[78]. Male sex was included among the conditions associated with longer drug survival in patients with either PsA or psoriasis treated with anti-TNF biologics^[79-82].

To the best of our knowledge, there are very limited data concerning gender differences in the safety and efficacy profiles of treatments available for psoriatic disease. To cite a few examples, in some studies, phototherapy with narrowband ultraviolet B radiations was reported to be more efficacious in females^[83], while females with PsA were less likely to achieve a response, defined using the European League against Rheumatism improvement criteria, to anti-TNF therapies^[84].

As concerns the tolerability of treatments, a retrospective cohort review among patients with either rheumatoid arthritis or psoriasis treated with at least one dose of methotrexate revealed that the pre-disposing factors predictive of liver damage were female gender and a higher cumulative dose of methotrexate without any ap-

parent effect of the disease itself^[85]. Moreover, infliximab-related hepatitis is thought to have an immune-mediated nature resembling autoimmune hepatitis type I, with a clear-cut preference for female sex^[86]. The paradoxical induction and exacerbation of psoriasis in patients treated with TNF inhibitors was described more frequently in females according to some case series or literature reviews^[87-90] but not to others^[91]. A significant weight gain has been described in patients with psoriasis treated with anti-tumour necrosis factor-alpha agents. Male gender and psoriasis severity were identified as risk factors for weight gain (defined as an increase of more than 2% of baseline weight) in psoriatic patients on infliximab^[92].

CONCLUSION

There is paucity of information derived from systematic assessment of differences between men and women with psoriatic disease. However, the literature review seems to suggest the existence of some interesting gender-specific differences among patients with psoriasis and PsA. The main aspects are summarized in Table 1.

There are very limited data concerning the safety and efficacy profiles of treatments for psoriatic disease in the two genders, especially with respect to the “real-life” setting. In this context, one paradigmatic example of a gender-specific study in psoriasis is represented by a multicenter Italian study, recently completed, that is named “GENDER ATTENTION”^[93]. This study was aimed at assessing the influence of gender and hormones on the incidence of adverse events and adverse reactions in patients with plaque psoriasis treated with cyclosporine.

We think that this topic should deserve more extensive and adequate attention in future evaluations, with special focus on the practical implications that gender-specific characteristics may have on the prognosis and therapeutic management.

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Pathogenesis and diagnosis of contact dermatitis: Applications of reflectance confocal microscopy

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Core tip: Contact dermatitis (CD) is the most common professional skin disease. CD is classified into irritant (ICD) and allergic (ACD), with both subtypes displaying sub-acute, acute and/or chronic eczema. The gold standard in CD diagnosis is patch-testing, although its validity and reproducibility are under question. Real-time reflectance confocal microscopy is a very promising tool for the diagnosis and management of ACD and ICD, providing significant advantage over conventional histology (due to the possibility to manage the disease through repetitive assessment) and patch-testing, due to increased sensitivity and specificity.

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Abstract

Contact dermatitis (CD) is the most common professional skin disease, with frequencies ranging from 24 to 170 every 100000 individuals. Approximately 20% of the United States population suffers from CD. CD can be classified according to its origin and severity. ICD stands for irritant CD, whereas ACD means allergic CD. Their clinical presentation includes acute, sub-acute and chronic eczema. Despite their different origin, ICD and ACD often present similar clinical and histologic findings. The current gold standard for diagnosis is patch-testing. However, patch-testing is being questioned in terms of validity and reproducibility, as it relies heavily on the skill of the observer. Real-time reflectance confocal microscopy is a non-invasive imaging technique that bears strong promise for the study of CD, and it enables the evaluation of cellular and subcellular changes over time with similar resolution compared to that of conventional histology.

INTRODUCTION

Contact dermatitis is the most common professional skin disease, with frequencies ranging from 24 to 170 every 100000 people^[1]. Approximately 20% of the United States population suffers from CD^[2], causing loss of over four million work days and costing approximately \$400 million per year^[3-5]. CD is classified into irritant (ICD) and allergic (ACD), with both subtypes displaying sub-acute, acute and/or chronic eczema^[6]. Despite their different origin, ICD and ACD often present similar clinical and histologic findings. Interestingly, the physiopathology of ICD and ACD is different, particularly during the initial phases of the inflammatory process. ACD requires pre-sensitization

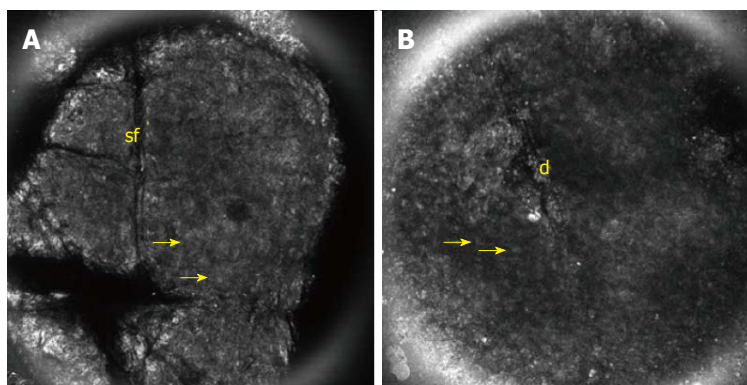


Figure 1 Reflectance confocal microscopy image (0.5 mm × 0.5 mm). A: Shows preservation of the stratum corneum in early stages of allergic dermatitis with parakeratotic corneocytes (yellow arrow) between skin folds (sf); B: Shows disruption (d) with early parakeratosis of the stratum corneum in irritative contact dermatitis.

to haptens, *i.e.*, low molecular weight antigens^[7]. This means that ACD actually is a delayed-type hypersensitivity inflammatory reaction mediated by memory T cells^[8-11]. Conversely, ICD is a non-specific inflammatory dermatosis caused by direct toxicity of the chemical inducer on skin cells. Cell damage produces inflammatory mediators that activate the innate arm of the immune system^[6].

The gold standard in CD diagnosis is patch-testing^[12], although its validity and reproducibility are under question^[13,14]. According to the North American Contact Dermatitis Group (NACDG), the sensitivity/specificity of this technique is just below 85%, with false positives in the 15%-18% range^[15,16]. Evaluation depends on the skill and experience of the medical practitioner, *e.g.*, to evaluate weak positive results with low clinical relevance. In cases like this, establishing an ACD or ICD diagnosis becomes complicated^[12].

RCM is a non-invasive technique that enables detailed study of CD over time^[17,18]. Several studies have correlated the CD findings obtained using RCM to those using conventional histology^[19]. RCM criteria are: disruption of the integrity of the stratum corneum; parakeratosis; spongiosis of the stratum granulosum, and exocytosis^[19] (Figure 1). Conventional histology is limited to a complementary role in ACD since the presentation of the disease evolves over time and multiple biopsies would be required^[2]. RCM is therefore a promising tool to study CD since it enables following the temporal evolution of the disease at a cellular and even subcellular level, unlike conventional histology^[2].

PATHOPHYSIOLOGY AND CLINICAL PRESENTATION OF ACD AND ICD

Allergic contact dermatitis

ACD is, at its etiological core, a memory T cell-mediated, delayed-type hypersensitivity reaction to haptens that enter into contact with the skin. Sensitization is initiated by professional antigen-presenting cells in the skin, *e.g.*, Langerhans cells (LC) and/or skin dendritic cells (sDC), which process the haptens and migrate to the lymph nodes, where they initiate the adaptive immune response. This causes amplification of memory T cells^[13]. Keratinocytes also contribute to the inflammatory reaction: some

haptens, *e.g.*, nickel, induce them to produce IL-23, which promotes the clonal expansion of Th17 T lymphocytes^[20]. ACD clinical manifestations appear in response to the activation of CD8⁺ and IFN-gamma-producing Th1 CD4⁺ T cells that mediate the elimination of the hapten-carrying keratinocytes^[20]. A summary of pathophysiologic features of ACD and ICD can be found in Table 1.

Clinical findings include erythema and edema, followed by the appearance of numerous papulae and vesicles. Other phenomena ensue in chronic phases of the disease, including lichenification, fissures and pigmentation. These manifestations are associated to intense itching, initially in the contact area, but that can spread to other regions of the skin^[6].

Irritant contact dermatitis

ICD is currently described as an inflammation not mediated by the immune system. However, eczema is caused by the activation of the innate arm of the immune system^[6]. Most chemical substances, depending on their concentration, can cause ICD. For example, 0.5% dinitrofluorobenzene causes ICD, whereas it takes up to 50% genarol to cause a similar reaction. Penetration through the skin layers induces expression of cytokines and chemokines that cause the inflammatory reaction. Keratinocytes represent 95% of skin cells and they produce a plethora of inflammatory mediators upon chemical challenge. The best described in ICD are: IL-1 α and β , IL-6, IL-8, TNF- α , GM-CSF and IL-10^[6] (Table 1).

ICD is a risk factor to develop ACD, due to the maturation of skin DC^[21], which present antigens to T cells in lymph nodes and bridge innate and adaptive immunity^[22,23].

Clinical findings of ICD include erythematous maculae and/or papillae, or erythematous-desquamative patches with frequent blistering. Lesions are commonly limited to the skin area in contact with the irritant. In ICD, burning sensation around the affected area is more frequent than itching compared to ACD^[6].

CONVENTIONAL HISTOLOGY AND RCM IN THE EVALUATION OF ACD AND ICD

Differential diagnosis of ACD and ICD using conven-

Table 1 Pathophysiologic features of allergic contact dermatitis and irritant contact dermatitis

	ICD	ACD
Blood immunology	No specific T cells	Presence of specific T cells
Skin immunology	No activated T cells	Presence of activated T cells
Innate immune system	+++β	+ (it due to the maturation of skin DC)
Adaptative immunity	-	+++ (delayed-type hypersensitivity response)
Cytokines and chemokines	IL-1α and β, IL-6, IL-8, TNF-α, GM-CSF and IL-10	IL-23, IL-36Ra, IL-2 and IL 17

+++; Strong positive association; +; positive association; -: negative association. ACD: Allergic contact dermatitis; ICD: Irritant contact dermatitis; TNF: Tumor necrosis factor; IL: Interleukin; DC: Dendritic cells.

Table 2 Diagnostic features to differentiate irritant contact dermatitis and allergic contact dermatitis with reflectance confocal microscopy

	ICD	ACD
Stratum corneum	Parakeratosis: +++ (early stage) Corneocyte detachment: +++ (early stage)	-
Stratum granulosum and spinosum (1 st wk)	Exocytosis: +++ Spongiosis: +++ Necrosis: +++ Vesicles: +++	Exocytosis: + Spongiosis: + Necrosis: + Vesicles: ++
Stratum granulosum and spinosum (2 nd wk)	Exocytosis: +++ Spongiosis: +++ Necrosis: +++ Vesicles: +++	Exocytosis: +++ Spongiosis: +++ Necrosis: +++ Vesicles: +++
Superficial perivascular infiltrate	+	+
Capillary dilation in the dermal papillae and leukocyte traffic	+	+

+++; Strong positive association; ++; Moderate positive association; +; Positive association; -: Negative association. ACD: Allergic contact dermatitis; ICD: Irritant contact dermatitis.

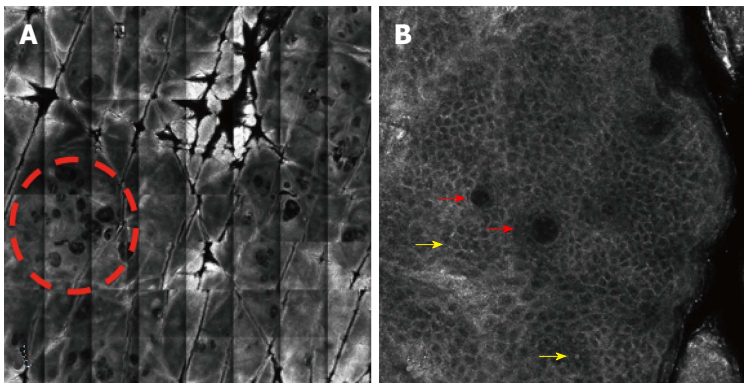


Figure 2 Image. A: Vivablock image (4 mm × 4 mm) shows the spinous layer in a process of allergic contact dermatitis. Note the presence of multiple microvesicles (dashed circle); B: Reflectance confocal microscopy image (0.5 mm × 0.5 mm) reveals spongiosis and exocytosis (yellow arrow); in addition, microvesicle with lymphocytes inside (red arrow).

tional histology is very difficult due to the fact that most histologic findings are similar^[10]. However, minor differences sometimes enable forming an educated diagnosis. For example, inflammatory infiltrate is more prominent and deep in ACD than in ICD; in the latter, infiltrate is predominantly found in the epidermis^[24]. Also, ACD induces a follicular spongiosis pattern not observed in ICD^[25]. However, these observations are minor differences that usually do not justify the use of conventional histology: the two major reasons are its lack of temporal range as well as the damage caused to the affected area during biopsy collection and the introduction of handling artifacts due to handling, fixing and staining^[2]. In this regard, RCM appears superior to conventional histology

and patch-testing^[2]. In addition to its non-invasive nature that enables repetitive observation of the affected area, its resolution (1 μm lateral × 3 μm axial) enables an accurate follow-up with a resolution close to that of conventional histology during exploration of areas situated between the stratum corneum and the upper layers of the reticular dermis^[26].

RCM findings reveal additional differences between ACD and ICD. ICD displays a significant increase in the disruption of the stratum corneum as well as parakeratosis and increased epidermal thickening compared to ACD^[27]. On the contrary, ACD exhibits increased exocytosis and microvesicle formation, reaching a maximum difference at 96 h compared to ICD^[27]. Initial stages of

ACD also exhibit blood vessel dilation in the deeper layers of the skin² (Table 2). RCM also permits identifying the cells within the inflammatory infiltrate (Figure 2). During ACD, dendritic-shaped cells could be visualized forming contacts with keratinocytes. These cells are likely Langerhans cells, which are present in elevated numbers only in ACD, but not in normal skin^[2].

RCM permits the evaluation of the changes that occur during ICD and ACD over time to establish a chain of events. Disruption of the stratum corneum is commonly observed during the first few hours after contact with the irritant substance. These changes are frequently absent in ACD at the same temporal point, but can appear later in sub-acute eczema produced during the development of ACD^[28]. The levels of exocytosis and spongiosis at the initial stages are similar in ICD and ACD, but latter stages reveal increased spongiosis in ACD, which is likely due to slower recovery compared to ICD^[28].

In 2005, Astner *et al.*^[12] developed an initial study to determine the sensitivity and specificity of RCM for the diagnosis of ACD. Stratum spinosum spongiosis was the best correlative marker of ACD (sensitivity = 100%; specificity = 92.6%, $P < 0.05$). Other useful parameters were spongiosis of the stratum granulosum (sensitivity = 96.3%; specificity = 95.8%, $P < 0.05$) and exocytosis (sensitivity = 77.8%; specificity = 100%, $P < 0.05$). At the level of the stratum corneum, no significant differences were found^[12].

CONCLUSION

Whereas the findings regarding ACD and ICD using RCM are still rather preliminary due to the limited sample size, they strongly indicate the usefulness of the technique for the diagnosis and management of both types of CD as well as additional steps in product safety and testing to prevent the onset of either type of CD. Some specifics include: (1) pre-market testing to assess the safety of drugs and cosmetics. At present, the gold standard for cosmetic testing includes patch-testing, which, as outlined above, compares poorly to RCM in terms of specificity and sensitivity; (2) establish the optimal sub-irritant concentration of haptens used in patch testing; and (3) determine thresholds for different irritants and their ability to induce ICD. Preliminary findings indicate that additional factors influence the ability of a given hapten to induce ICD.

In summary, RCM is a very promising tool for the diagnosis and management of ACD and ICD, providing significant advantage over conventional histology (due to the possibility to manage the disease through repetitive assessment) and patch-testing, due to increased sensitivity and specificity. Furthermore, RCM can be used to evaluate the response to therapy and evolution of the disease over time.

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What have we learned about non-involved psoriatic skin from large-scale gene expression studies?

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Abstract

Psoriasis is a chronic inflammatory skin disorder; its genetic background has been widely studied in recent decades. Recognition of novel factors contributing to the pathogenesis of this disorder was facilitated by potent molecular biology tools developed during the 1990s. Large-scale gene expression studies, including differential display and microarray, have been used in experimental dermatology to a great extent; moreover, skin was one of the first organs analyzed using these

methods. We performed our first comprehensive gene expression analysis in 2000. With the help of differential display and microarray, we have discovered several novel factors contributing to the inherited susceptibility for psoriasis, including the EDA+ fibronectin splice variant and PRINS. The long non-coding PRINS RNA is expressed at higher levels in non-involved skin compared to healthy and involved psoriatic epidermis and might be a factor contributing cellular stress responses and, specifically, to the development of psoriatic symptoms. This review summarizes the most important results of our large-scale gene expression studies.

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Key words: Non-involved psoriatic skin; Differential display; cDNA microarray; EDA+ fibronectin isoform; PRINS long non-coding RNA; mRNA maturation

Core tip: Large-scale gene expression studies, including differential display and microarray, have provided valuable data on the molecular background of psoriasis pathogenesis. This review summarizes the most important results of the available literature and our large-scale gene expression studies obtained from the clinically non-involved psoriatic skin: we identified the EDA+ fibronectin splice variant as an autocrine proliferation signal for psoriatic hyperproliferative keratinocytes and PRINS, a long non-coding regulatory RNA. We believe that the characterization of new candidate genes and proteins might establish new therapeutic approaches, which may allow treatment of already existing psoriatic lesions as well as non-involved psoriatic skin by affecting molecular aberrancies, and may lead to the development of prophylactic interventions.

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INTRODUCTION

Psoriasis is a hyperproliferative inflammatory skin disorder affecting approximately 2%-3% of the European population^[1]. However, in some other parts of the world, this disease is almost unknown: *e.g.*, in Africa the occurrence of psoriatic cases is remarkably rare^[2]. The exact trigger of the disease is still obscured and the subject of several investigations. Inherited and environmental factors (*e.g.*, mechanical trauma, UV exposure, stress) are responsible for the development of psoriatic symptoms^[2,3].

In the most typical cases, hyperproliferative psoriatic plaques are formed on the skin of the knees, elbows and the scalp. In addition, the disorder can affect skin annexes and joints. In the case of some patients with severe psoriasis, the entire body is covered with lesions. Severe psoriasis is often associated with metabolic syndrome; hence, psoriasis patients also have elevated cardiovascular and stroke risks^[2]. Unfortunately, psoriasis has a negative effect on the patient's quality of life due to serious psychosocial and emotional stress^[4]. A number of emerging arguments support the idea that psoriasis is a systemic disorder rather than simply a skin disease. Psoriasis has many common features with chronic autoimmune inflammatory disorders, such as progressive arthritis. Moreover, psoriasis and autoimmune syndromes often share common genetic loci^[5-7]. Similarities are especially evident when psoriasis is compared to chronic inflammatory bowel disorders, such as Crohn's disease, where internal barriers are involved^[8,9].

Similarly to autoimmune disorders, immune-activation plays an important role in psoriasis: the development of the characteristic erythematous, demarcated and scaly lesions is related to the abnormal functioning of the cellular immune system^[10-14]. Cytokines produced by aberrantly functioning T-lymphocytes are able to stimulate keratinocytes, which show an elevated sensitivity to these proliferative signals^[14,15]. However, it is still unknown whether the primary triggers of the disease phenotype are the professional immune cells or the keratinocytes. Inherited susceptibility of keratinocytes has been partially established. Identification and characterization of these factors may greatly facilitate the understanding of the molecular background of psoriasis. Large-scale gene expression profiling methods developed and used in the 1990s might be useful tools to answer these exciting questions.

DAWN OF THE LARGE-SCALE GENE EXPRESSION STUDIES: DIFFERENTIAL DISPLAY AND SAGE

In recent years, we and others have tried to characterize molecular factors responsible for the hyper responsiveness of keratinocytes to various stimuli^[8,12,14,16]. To reveal these processes, researchers need suitable and powerful methods that can detect more than one possible target.

Previously, altered expression of only a few candidate genes or proteins was possible. The development of large-scale gene expression analysis methods marked a significant breakthrough in this field. With the help of microarrays and their predecessors, differential display (DD) and the serial analysis of gene expression (SAGE), gene-expression patterns of serial samples can be compared for large data sets.

For DD, gene expression profiles are analyzed for pairs of corresponding sample sets. The most important steps of the method are the isolation of total RNA from the samples and its reverse transcription into cDNA. Subsequently, cDNA is amplified, subjected to gel electrophoresis and, after the expression pattern has been compared, bands representing differentially expressed genes are cut out from the gel and the DNA content is cloned into a plasmid vector. It should be mentioned that the DD method has some limitations due to the relatively frequent incidence of false positive results. Hence, the results must be validated using an independent technique. Validation is usually carried out by reverse Southern blot analysis, followed by sequencing the differentially expressed transcripts^[17-19]. The great advantage of DD is that it is an "open ended" analysis system, allowing unannotated differentially expressed transcripts to be identified.

Another sequence-based approach, SAGE, was developed at the Oncology Center of the Johns Hopkins University by Velculescu and his co-workers. Changes in gene expression patterns are detected by sequencing reverse transcribed cDNAs. Application of short oligonucleotide sequence tags allows quantitative changes to be monitored, in addition to the qualitative analysis^[20,21].

MICROARRAYS

Microarrays provide more extended and comprehensive methods for analyzing gene expression profiles than DD and SAGE. The biggest advantage of this approach is that it allows thousands of genes to be measured simultaneously. Moreover, complex regulatory networks can be assessed^[22,23]. In contrast to DD and SAGE, microarrays are a "closed" analysis system, allowing only known sequences to be screened. The introduction and widespread use of microarrays has facilitated advances in several branches of science, including experimental dermatology. In fact, the skin was one of the first human organs to be analyzed with this technique^[24-27].

Microarray technologies rely on complementarity for sequence-specific recognition of the DNA segments^[28]. Most commonly used probes are cDNAs derived from bacterial libraries and BACs or oligonucleotides. Long oligonucleotide probes (50-120 nt) might support a higher degree of specificity and sensitivity than short (15-25 nt) probes^[22]. The probes are fixed to a solid support, such as glass or plastic that are referred to as "chips" in common laboratory jargon^[23].

For microarray experiments, total RNA is isolated

from samples and reverse-transcribed with fluorescent dyes such as Cy3 and Cy5 or with radioactive isotope to label the synthesized cDNA. After hybridizing the labeled probes to the chips for approximately 16–24 h, the chips are washed and the fluorescence is scanned with a confocal microscopy. Data are then analyzed using specially developed software. Like DD, this method can identify false positives and, therefore, must be validated by RT-PCR, northern blot analysis or RNase protection assay^[22,28].

The outstanding advantage of microarray techniques is the simultaneous investigation of thousands of genes and, thus, the possibility to explore novel molecular pathways. This technique can be a powerful tool in tumor and biomarker research and may serve as the basis of personalized therapies^[27].

LARGE-SCALE GENE EXPRESSION STUDIES OF PSORIASIS: IDENTIFICATION OF MOLECULAR FACTORS CONTRIBUTING TO PATHOGENESIS

The use of large-scale gene-expression analysis methods has been fruitful for experimental dermatology. Microarrays have been used to study several disorders, such as melanoma, atopic dermatitis and autoimmune skin diseases. In the past decade, DD and microarray techniques have been widely employed alone or in combination with other methods in psoriasis research^[29].

Gene-expression profiling of peripheral blood cells and epidermis samples from healthy, psoriatic involved and psoriatic non-involved skin proved to be a powerful tool for the characterization of aberrant molecular patterns in the disease^[30]. The results of cDNA microarrays supported previous findings and were useful to describe novel pathways implicated in psoriasis pathogenesis. Psoriasis research was dominated by the so-called “immune theory” for many years, and microarray studies further proved the involvement of genes related to inflammation and immune responses. One of the earliest microarrays identified several inflammation- and immune-related genes (*IL4R*, *CD2*, *CD24* and *INF-γ* induced genes) that were not previously reported to contribute to the pathogenesis of this disorder^[30,31]. Moreover, Oestreicher *et al.*^[31] performed a longitudinal analysis in which they characterized changes in gene expression in response to recombinant human IL-1 or cyclosporine in therapy responder and non-responder populations. A study from Zhou, which compared samples from healthy, involved psoriatic and non-involved psoriatic skin biopsies further supported the involvement of the activated T-cell product *INF-γ* and transcription factors induced by this pro-inflammatory lymphokine^[30,32]. The role of IL-17 signaling was also demonstrated in large-scale gene-expression studies^[13]. In addition, Gudjonsson *et al.*^[3] emphasized the role of altered innate immune functions in psoriasis. Dif-

ferential expression of genes encoding chemokines and their receptors were also described by several research groups^[32–34].

Other important cellular pathways related to psoriasis regulate epidermal keratinocyte proliferation and apoptosis. The implication of *PPAR-δ*, *mTOR*, *NFκB*, *BCL-2* and *BAX* expression was verified for these mechanisms^[35–37]. In a study of Wnt pathways responsible for stem cell proliferation and differentiation, Reischl *et al.*^[38] found that only *Wnt5a* expression was higher in psoriatic involved skin than in non-involved samples. In addition, actin cytoskeleton organization can be affected: the *CCNA2* gene is responsible for the G₂/M transition in the cell cycle and affects intracellular cytoskeleton organization and cell migration^[39,40].

The clinical association of psoriasis and metabolic syndrome is a well-known phenomenon. Gudjonsson and co-workers were able to show that lipid metabolism pathways were altered in psoriatic non-involved epidermis compared to healthy samples^[3]. In this comparison, it was proven that lipid metabolism genes were down-regulated in non-involved skin samples as compared to healthy skin and further down-regulation was identified in psoriatic involved skin^[3]. Romanowska *et al.*^[35] studied the role of *PPARδ*, a transcription factor participating in metabolic and inflammatory processes, in psoriasis. *PPARδ* exerts proangiogenic and antiapoptotic effects and is suspected to be involved in the enhancement of keratinocyte proliferation^[35].

Most recently, bioinformatic meta-analyses were performed using publicly available databases of psoriasis-related microarray data. In one of the first microarray meta-analysis, Tian *et al.*^[41] analyzed the result of five previous cDNA microarrays experiments. In a subsequent meta-analysis, Manczinger *et al.*^[40] compared differentially expressed genes of psoriatic involved and non-involved epidermis. The findings of these two meta-analyses agreed and showed that the most important components of the molecular networks related to psoriasis are factors implicated in cell proliferation and immunomodulation. Importantly, these meta-analyses confirmed that several differentially expressed transcripts were also involved in metabolic disturbances, such as impaired glucose tolerance, insulin tolerance and atherosclerosis^[40,41].

It is important to note that most of the large-scale gene expression studies for the identification of molecular patterns in psoriasis pathogenesis have compared the gene expression profiles of psoriatic involved and non-involved skin or psoriatic involved and healthy skin. This research provided extremely valuable data for the molecular events of psoriasis^[40]. Much less information is available, however, on differentially expressed genes in normal epidermis compared to psoriatic non-involved epidermis. We and others believe that identifying aberrantly expressed genes and molecular patterns in non-involved psoriatic epidermis is important for understanding this disease.

DIFFERENTIAL DISPLAY AND MICROARRAY EXPERIMENTS OF OUR RESEARCH GROUP, FOR THE IDENTIFICATION OF NOVEL MOLECULAR FACTORS OF PSORIASIS

Our research group performed the first comprehensive gene-expression analysis for psoriasis in 2000 to compare psoriatic non-involved epidermal samples with control healthy epidermis. This approach allowed early and inherited molecular factors to be studied in detail and allowed novel susceptibility factors to be revealed. This study identified two known transcripts that were differentially expressed: *RAB10*, an oncogene that belongs to the small GTPase superfamily, and fibronectin, a well-known extracellular matrix component^[42]. Our subsequent studies focused on the role of fibronectin in the pathogenesis of psoriasis.

Fibronectin is a complex glycoprotein composed of repetitive modules^[43]. At least 24 differentially spliced variants of this gene have been described, and the presence of certain variants depends on age, developmental state and cell type^[44]. Alternative processing involves three preferred sites: extra domain A (EDA), extra domain B and extra type homology B^[43,45]. The splice variants containing the EDA domain play a crucial role in embryonic development and wound healing. However they are detectable only in modest amounts in adult normal tissues^[44,46,47]. Because it is also abundantly expressed in different types of tumors, it is referred to as the oncofetal fibronectin splice variant^[48]. Interestingly, in the brain, an organ in which fibronectin is poorly expressed, the inclusion of the EDA domain is abundant in young adults (88% as compared to fetal level) and decreases with age to 33%^[46].

The presence of the EDA+ fibronectin variant is associated with several pathological conditions and is suspected to participate in the development of psoriasis as well. The oncofetal fibronectin form was found to be present in a higher ratio at the dermal-epidermal junction of psoriatic non-involved skin compared to healthy normal skin^[14,49]. Unlike the conventional variant, the oncofetal EDA+ fibronectin form interacts with the $\alpha 5$ integrin subtype, instead of $\alpha 2$ and $\alpha 3$, and, as a result, its effect on cellular signaling processes is more robust. $\alpha 5\beta 1$ integrin receptors were shown to be upregulated in both non-involved and involved psoriatic skin^[14,50].

In addition, other authors reported that the EDA+ fibronectin variant is co-localized with CD11c+ macrophages. It was suggested that these cells might contribute to the production of the oncofetal variant; however, because of their relatively low number, they are likely not to be the most important source^[49]. Based on our results we supposed that keratinocytes themselves might produce EDA+ fibronectin and, as an autocrine molecular factor, may contribute to the induction and maintenance of ke-

ratinocyte hyperproliferation in psoriasis^[16].

We have also performed *in vitro* experiments to understand the role of EDA+ fibronectin in the regulation of keratinocyte proliferation. Subsequently, RT-PCR was carried out using immortalized HaCaT cells. Our results indicated that, after serum starvation and contact inhibition, the highest level of EDA+ fibronectin expression could be detected in the highly proliferative HaCaT cells, and the ratio of EDA+/EDA- fibronectin produced by the keratinocytes might well be a potent mitogen signal in cell cycle regulation. In contrast to fibroblasts and normal human keratinocytes, the ratio was altered in this cell line. Flow cytometry supported the RT-PCR results. The results of the HaCaT cell line experiments indicated that keratinocytes themselves might produce the oncofetal fibronectin variant^[16].

In addition to proteins with known functions, the DD experiment identified a novel transcript: the corresponding gene was subsequently named psoriasis-susceptibility-related RNA gene induced by stress (PRINS, accession number AK022043). During the structural investigation of PRINS, we found that the gene consists of two exons containing several stop codons, which prevent the formation of a longer open reading frame. *In silico* sequence comparison supported the hypothesis that PRINS functions as a non-coding RNA molecule, rather than serving as a template for protein translation. In addition, PRINS contains two repetitive *Alu* sequences and has 70% sequence similarity with the *Tetrahymena thermophyla* G8 small nucleolar non-coding RNA^[42].

In a quantitative RT-PCR analysis, we demonstrated that PRINS is expressed at higher levels in non-involved skin compared to healthy and involved psoriatic epidermis. Our *in vitro* experiments performed on synchronized HaCaT cells showed that PRINS expression dropped significantly when the cells were released from cell quiescence and the cells started to proliferate actively^[42]. These data suggested that PRINS might be a factor disposing keratinocytes to hyperproliferation and contributing to the development of psoriatic symptoms. The exact role of PRINS is still unknown, but it is very possible that it plays an important role in cellular stress responses. Silencing PRINS did not affect the survival of the cells; however under certain stress conditions (such as serum starvation) the cells died at a much higher rate when the expression of PRINS was down-regulated^[42,51]. Consequently, the PRINS-silenced cells became more vulnerable, supporting the cellular-stress response hypothesis. Moreover, our research group later showed that the G1P3 antiapoptotic protein might be regulated by the PRINS non-coding RNA^[52].

Since then, we have identified nucleophosmin as one of the possible cellular interacting partners of PRINS. Nucleophosmin is a phosphoprotein which is a member of the p53 pathway, and its movement in fibroblasts, cancer cells and keratinocytes is triggered by ultraviolet (UV) exposure^[53]. We also demonstrated that silencing PRINS prevents nucleolar-cytoplasmic shuttling of nucleophosmin.

This result indicates that PRINS might physically interact with the nucleophosmin protein and that the abnormal functioning of the PRINS-nucleophosmin ribonucleoprotein complex may contribute to psoriasis pathogenesis^[54].

Taken together, we consider the identification of novel factors implicated in the early molecular defects in psoriasis pathogenesis-the EDA+ fibronectin splice-variant and the PRINS non-coding RNA-the most significant outcomes of our DD experiments. Due to the success of the DD, we attempted to identify novel psoriasis susceptibility factors using newly available cDNA microarray technology for large-scale gene-expression analysis. In particular, we aimed to identify molecular patterns that are responsible for the differential reactivity of normal healthy epidermis and psoriatic non-involved epidermis.

Organotypic tissue cultures were created from four healthy and four psoriatic non-involved skin samples. Half of the samples were treated with a mixture of T-cell lymphokines, containing IL-3, IFN γ and GM-CSF, cytokines previously described to be implicated in the T-cell response and the formation of psoriatic plaques^[10]. After three days of treatment, the dermis and epidermis were separated. Total RNA was isolated from the epidermis, reverse transcribed and used to perform the cDNA microarray experiment. Based on the results, we selected genes that showed an altered gene expression in response to the lymphokine treatment^[12].

We identified 61 transcripts that exhibited altered gene expression. Of these, eleven had been demonstrated earlier to contribute to psoriasis. Using bioinformatics tools, such as Gene Ontology and Ingenuity pathway analysis, we demonstrated that most of these molecules are implicated in two important intracellular pathways: "apoptosis" and "metabolism of small molecules and lipids." Real-time RT-PCR validation experiments revealed that many of these genes are already upregulated in non-involved psoriatic epidermis, and the lymphokine treatment did not further increase expression. In contrast, expression of these genes was inducible in healthy samples. These data indicate that keratinocytes in psoriatic non-involved epidermis are in a presensitized status, which explains their altered response to different triggering stimuli^[12].

Among the differentially expressed genes, we also identified members of the serine-arginine rich (SR) proteins SR splicing factor 18 (SFRS18), peptidylprolyl isomerase G (PPIG) and luc-7 like 3 (LUC7L3), which regulate mRNA splicing. It was previously described that these proteins interact with pinin and SR-related nuclear protein^[55-60]. Splicing is a post-transcriptional regulatory process and one of the most important sources of mRNA diversity, permitting the production of different mRNAs from the same DNA template. Splicing dysfunction has been shown to be involved in several disorders, and some novel therapeutic modalities have been designed to repair them^[61-63].

Our research group has previously demonstrated that the fibronectin splice variants containing the EDA domain is implicated in the pathogenesis of psoriasis. This

suggests the interesting question whether the identified splicing genes, *LUC7L3*, *PPIG* and *SFRS18*, contribute to the production of the EDA+ fibronectin variant. We are currently investigating the role of *LUC7L3*, *PPIG* and *SFRS18* splicing regulatory genes in the production of EDA+ fibronectin, and we aim to identify further differentially spliced mRNA variants contributing to psoriasis pathogenesis.

CONCLUSION

Taken together, recent comparisons between psoriatic non-involved and involved epidermis dominated large-scale gene expression studies related to psoriasis. Relatively few studies have focused on the comparison of gene expression differences between healthy and psoriatic non-involved epidermis samples. Nonetheless, we believe that these experiments are valuable for identifying factors that increase the risk for developing psoriatic plaques. In our microarray studies, we identified several novel candidate genes and molecular patterns that might contribute the formation of typical lesions. The altered expression of EDA+ fibronectin and that of *LUC7L3*, *PPIG* and *SFRS18* suggests that some kind of splicing anomalies have an important role in the development of psoriatic symptoms. The exploration of cellular networks related to RNA-maturation processes gave us a deeper insight into the molecular pathogenesis of psoriasis and investigation of the splicing machinery might be a very new approach in this field. Results of wide-scale gene expression studies have provided pioneering advances in psoriasis research as well as in the recognition of different types of non-coding RNAs, including *PRINS*. This RNA is a long non-coding RNA (lncRNA), and most lncRNAs have been identified in their involvements in the central nervous system and certain tumors^[64-69].

The last decade has seen a rapid evolution in large-scale gene expression profiling methods. Techniques, such as RNA-Seq and digital gene expression profiling, provide an even greater resolution and wider dynamic range compared to either DD or cDNA microarray. Advancement of methods based on next-generation sequencing has accelerated the accumulation of data, and processing the results requires huge efforts. Thus, validation and interpretation of these newly discovered factors is a very important challenge. Identification of new candidates might establish new therapeutic approaches, which may allow treatment of already existing psoriatic lesions as well as non-involved psoriatic skin by affecting molecular aberrancies, and may lead to the development of prophylactic interventions.

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Red ginseng for atopic dermatitis

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Abstract

Red ginseng is known for its significant biological activities which include anti-inflammation. Red ginseng may be used for the management and prevention of atopic dermatitis based on its effect on an atopic dermatitis animal model. More therapeutic efficacies other than atopic dermatitis are also reviewed briefly.

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Key words: Red ginseng; Atopic dermatitis; Allergy; Dermatitis; Inflammation

Core tip: Red ginseng has been shown to possess various biological activities, including anti-inflammatory properties. Red ginseng may be a potential therapeutic modality for the management and prevention of atopic dermatitis based on its effect on an atopic dermatitis animal model. More therapeutic efficacies other than atopic dermatitis are also reviewed briefly.

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INTRODUCTION

It has been proven that red ginseng (the steamed and dried root of *Panax ginseng* C.A. Meyer, family Araliaceae) has significant biological activities, including anti-inflammation^[1]. Red ginseng is frequently consumed as an oral remedy, particularly within countries in Asia.

Ginsenosides containing an aglycone with dammarane (protopanaxadiol and protopanaxatriol) and oleanane skeletons are the known major components in raw ginseng^[2]. Numerous studies on the molecular mechanisms and functioning of red ginseng and its identified ginsenosides have been done successfully.

Ginsenosides harbor a broad range of biological activities: anti-allergic features and anti-inflammatory^[3-5], antitumor effects, aorta relaxation, wound healing and so on^[6-10]. Ginsenoside Rg3 has been known to inhibit mast cells from releasing histamine by compound 48/80 *in vitro*^[11,12]. Furthermore, ginsenoside Rb1 and Rc have also been shown to inhibit the release of both histamines and leukotrienes from pulmonary mast cells in an *in vitro* experiment with guinea pigs^[11].

Recently, we showed that the oral consumption of red ginseng can suppress inflammation in atopic dermatitis (AD)-like skin lesions by inhibiting Langerhans cells (LCs), Th-1 cytokines and regulatory T (Treg) cells^[13]. Moreover, oral red ginseng administration was found to markedly prevent the trinitrochlorobenzene (TNCB)-induced cutaneous inflammation in an atopic dermatitis animal model (NC/Nga mice)^[11].

THERAPEUTIC AND PREVENTIVE EFFECTS OF RED GINSENG IN AN ATOPIC DERMATITIS ANIMAL MODEL

Systemic administration of red ginseng noticeably decreased the clinical severity score, the various inflammatory mediators and infiltrating cells, including CD1a+ LCs in AD mouse models. Moreover, oral administration

of red ginseng markedly prevented TNCB-induced AD-like skin lesions in NC/Nga mice.

Oral red ginseng administration significantly reduced ear thickness, along with other clinical signs. The total clinical severity score, which evaluates dryness, edema, erythema erosion and itching, was significantly lowered by red ginseng. Skin hydration was well maintained with red ginseng administration, based on the results of the trans-epidermal water loss (TEWL).

Histologically, there was a significant decrease in skin thickness as well as the degree of infiltrating inflammatory cells in AD-like cutaneous inflammation with red ginseng treatment. Red ginseng was also able to prevent lymphocyte infiltration in the dermis and exhibited beneficial effects by suppressing all LCs, Th-1 related cytokines and Treg cells in the TNCB-induced AD-like cutaneous inflammation of an atopic dermatitis animal model^[13]. TNCB application caused CD1a+ dendritic cell (DCs) infiltration of the skin and this massive CD1a+ cell infiltration was greatly reduced by systemic red ginseng intake. Antigen-presenting cells (APCs) take an important role in the development of AD. These DCs play a critical role in the pathogenesis of AD, that is, recognition, phagocytosis and transmission of information from the environment to the immune system. Thymic stromal lymphopoietin (TSLP)-influenced DCs propagate the Th2 immune inflammation and the activated DCs accumulate in the epidermis and dermis of the AD cutaneous inflammation^[14]. Red ginseng administration markedly suppressed the CD1a+ cell infiltration, which was induced by TNCB application.

Historically, the Th1 and Th2 balance was considered important in the pathogenesis of AD from the immunological aspect^[15]. The concept was further progressed by exploring the role of the Th17 lineage and Treg cells^[16]. It is crucial for the control of AD to keep the delicate balance among Th1, Th2 as well as Th17/22 and Treg cells. Moreover, the cross-talk between immune responses aberration and defect of skin barrier function with feeble cornification, abnormal terminal differentiation proteins and reduced level of intercellular lipids are found in the lesional AD skin^[17]. Red ginseng was able to suppress the excessive TNF- α and TSLP expression in the AD-like cutaneous inflammation of an AD animal model. It has been suggested that an event of TNF- α production by epidermal cells initiates the development of AD^[18]. Pro-inflammatory cytokines, such as TNF- α produced at the earliest stages of AD, stimulate the expression of chemokines and adhesion molecules which affect leukocyte proliferation, survival and recruitment at the lesional skin^[18]. Red ginseng significantly lowered TNCB-induced TNF- α expression in cutaneous inflammation of an AD animal model which directs leukocyte recruitment. TSLP is considered a key factor in AD, with its ability to enhance the DCs shifting to Th2 immune reaction^[19]. TSLP has been quoted as a “master switch for allergic inflammation” because TSLP exerted great effects on key cells of cutaneous inflammatory reactions, such as basophils,

eosinophils and mast cells^[20]. Systemic red ginseng and cyclosporine down-regulated the overexpression of TSLP (both mRNA and protein) in the lesional skin of an AD animal model. Therefore, red ginseng and cyclosporine are able to inhibit the initial inflammatory process in AD involving either TNF- α or TSLP. Red ginseng may mediate therapeutic effects by influencing DCs, TSLP and ultimately the Th2 response, based on these findings.

Th2 polarization causes eosinophil recruitment and increase in IgE production by B cells. Approximately 70% of AD patients show an elevation in serum IgE level. Overproduction of IgE causes both acute and chronic cutaneous inflammation in AD. Although serum IgE is not essential for the diagnosis of AD, the increased IgE level in AD classifies the AD phenotype, extrinsic type AD (with elevated IgE) and intrinsic type AD (with normal IgE). The clinical AD severity highly correlates with systemic IgE levels^[21]. Itch intensity among AD patients is also closely related to IgE^[22]. Red ginseng significantly modulated the total IgE level which was markedly increased following TNCB application. Thus, red ginseng has the therapeutic potential for AD *via* suppressing the antigen presentation and preventing vicious progression into the “itch-scratch cycle” at an early inflammatory stage of AD development^[13].

Abnormalities of skin barriers, such as decreased skin hydration and increased TEWL, are significant indexes for the severity skin barrier defect and the intensity of itch in AD. TEWL also has a correlation with AD activity^[23]. TEWL is a reliable and reproducible measure in assessing AD severity^[24]. TEWL was increased in a TNCB-applied AD animal model where the elevated level of TEWL was reduced in the red ginseng and cyclosporine treated groups. By assessing TEWL, red ginseng may preserve skin hydration and modulate the disease activity in AD.

The increase of PGP 9.5 positive nerve fibers and substance P associated with AD^[25] were also decreased by red ginseng^[13]. It is likely that red ginseng inhibits neurogenic inflammation by decreasing the expression of PGP positive nerve fibers and substance P^[13]. Oral red ginseng prevented the development of cutaneous inflammation of an AD animal model by suppressing pro-inflammatory and Th-1 related cytokines as well as LCs and Treg cells. Furthermore, red ginseng suppressed the neurogenic inflammation by reducing PGP 9.5 positive nerve fiber and substance P expression.

It has been reported that topical red ginseng and ginsenosides Rh2 and Rg3 improve cutaneous inflammation of an AD animal model. It also decreased the mRNA expression of IL-4 in the cutaneous inflammation of an AD animal model^[26-28].

Intermittent use of topical steroids and/or the use of topical calcineurin inhibitors along with skin care and environment control are the only accepted methods for the prevention and maintenance of AD. For the prevention of recurrence and early treatment of AD, topical calcineurin inhibitors are allowed.

Table 1 Reported effects of red ginseng and its constituents on atopic dermatitis *in vivo*

Materials	Classification	Specification	Ref.
Korean red ginseng extract	<i>In vivo</i>	Alleviated clinical features, prevented the increase in TEWL, lowered IgE level, decreased lymphocyte infiltration, suppressed the protein expression of TSLP and TNF- α , decreased the mRNA expression of TSLP	[13]
Korean red ginseng extract	<i>In vivo</i>	Reduced the total clinical severity score, ear thickness and the level of IgE, decreased TNF- α , IFN- γ and substance P, reduced the infiltration of FOXP3+ regulatory T (Treg) cells and CD1a+ Langerhans cells	[1]

TEWL: Trans-epidermal water loss; TSLP: Thymic stromal lymphopoietin; TNF: Tumor necrosis factors; IFN: Interferon.

Table 2 Effects of red ginseng and its constituents *in vitro*, *in vivo* and clinically

Materials	Classification	Specification	Ref.
Ginsenoside Rh2	<i>In vivo</i> , <i>in vitro</i>	Preventing, treating diabetic disorders and improving vascular stiffness	[32,33,49]
Korean red ginseng extract	<i>In clinic</i>	Enhancing work memory, calming healthy young men and down regulating the expression of the tyrosine hydroxylase	[44,45]
Korean red ginseng extract	<i>In vivo</i>	Improving the hyperactivity and treating ischemia/reperfusion induced myocardial damage	[42,43]
Ginsenoside Rb3	<i>In vivo</i>	Protecting myocardial injury and heart function impairment	[35]
Ginsenoside Rg3	<i>In vivo</i>	Preventing the progression of renal damage and dysfunction in type 2 diabetic rats	[36]
Ginsenoside CK, Rg1	<i>In vitro</i>	Stimulating glucose uptake to treat the hypoglycemic properties	[37,50]
Korean red ginseng extract	<i>In vivo</i>	Treating human ophthalmic disease by improving the optical process	[46]
Ginsenoside Rg3,Rk1,Rg5	<i>In vivo</i>	Having beneficial effects on treating collagen induced arthritis	[48]
Korean red ginseng extract	<i>In vivo</i>	Protecting normal tissue during the radiation therapy and increasing tissue repair	[47]
Korean red ginseng	<i>In vitro</i>	Stimulating β adreno receptor and increasing various rate limiting enzyme activities	[40]
Korean red ginseng	<i>In vivo</i>	Up-regulating adipocytic peroxisome proliferator- activated receptor γ and inhibiting intestinal glucose absorption	[41]

Cyclosporine is allowed in Europe for short-term use for recalcitrant AD that cannot be controlled by topical treatment, despite FDA disapproval^[29]. Both oral cyclosporine and topical calcineurin inhibitors interfere with calcineurin and suppress T cell activation^[30]. Red ginseng prevented cutaneous inflammation of an AD animal model by controlling not only local but also systemic inflammation, which was proved by clinical findings, such as changes in ear thickness and TEWL, by the histological features decreasing the infiltration of inflammatory cells, and by immunological findings suppressing mRNA and protein expression of cytokines and IgE levels. Considering the red ginseng effects on cutaneous inflammation of an AD animal model, red ginseng may be an adjuvant therapeutic candidate in the prevention and treatment of early stage AD (Table 1).

MORE OF THE REPORTED CLINICAL EFFECTS OF RED GINSENG

Kim *et al*^[31] reviewed 470 publications which show the efficacy of red ginseng *in vitro*, *in vivo* and clinically. His reviews covered 10 categories of clinical studies, including brain function, cerebrovascular function, antitumor, immune function and anti-inflammatory effect, bone, anti-stress, anti-fatigue and tonic effect, anti-oxidant and anti-aging effect, liver and toxicity, diabetes and obesity, sexuality and others (insomnia, eye and vision, hyperactivity and gene expression). Each category was further subdivided into specific research areas of red ginseng,

such as the detoxification of anti-cancer agents, immune control, antioxidant properties and effect on allergy, obesity, blood vessels, peptic ulcers, dermatitis, cytotoxicity, brain neurons, liver disease, lipid metabolism, cancer, AIDS, stress, inflammation, sexuality, diabetes, tiredness and others.

Red ginseng can keep the ecological surroundings of the colon in metabolic equilibrium. The ginsenoside Rh2 especially can prevent and treat diabetic disorders. Red ginseng can also improve vascular stiffness in patients with coronary disease^[32-34].

Ginsenoside Rg3 from red ginseng protects patients from myocardial injury and heart malfunction induced by isoproterenol and limits the aggravation of kidney dysfunction in type 2 diabetic rats by reducing oxidative stress and the formation of advanced glycation end product. Compound K and ginsenoside Rg1 increase the glucose uptake in 3T3-L1 cells, demonstrating insulin-like activity and showing potential for the treatment of metabolic syndrome and diabetes. A nutritional compound mixed with a P. ginseng extract reduces age-related mitochondrial functional degeneration and maintains physical status^[35-38].

Some experiments were conducted to obtain solid scientific evidence that different ginsenosides from red ginseng have therapeutic potential for diabetes. Both protopanaxadiol type ginsenosides (Rb1, Rb2, Rc, Rg3, Rh2, compound K, PPD) and protopanaxatriol type ginsenosides (Re, Rg1, Rg2, PPT) have shown anti-diabetic activities in cell and animal studies. The possible

mechanisms underlying red ginseng's hypoglycemic effects were suggested as follows: (1) modulation of insulin production and secretion; (2) modulation of glucose metabolism; (3) modulation of glucose uptake; and (4) modulation of inflammatory pathways. The effect of red ginseng on lowering blood sugar level is also due to the increased aerobic glycolysis from the stimulation of beta adrenoceptors plus the increase of a number of rate-limiting enzyme activities related to the tricarboxylic acid cycle. In a particular study conducted to investigate the anti-diabetic property and mechanism in KKAY mice, red ginseng showed hypoglycemic effects through up-regulation of adipocytic peroxisome proliferator activated receptor gamma (PPAR- γ) expression as well as by inhibiting intestinal glucose absorption in KKAY mice^[39-41].

Red ginseng may have beneficial effects on ADHD, as red ginseng decreases the neonatal hypoxia-induced hyperactivity while increasing locomotor activity in lay animals. Red ginseng may also treat ischemia/reperfusion induced myocardial damage effectively due to its antioxidant effects^[42,43].

Other studies show that red ginseng enhances working memory and improves calmness. This anti-stress efficacy of red ginseng is mainly driven by the suppression of the expression of the tyrosine hydroxylase and dopamine beta-hydroxylase gene^[44-45].

Some scientists suggest that red ginseng can be used for treating certain human ophthalmic diseases in a study that showed significant improvement of the optical process in the eyes of a bullfrog. Other data demonstrate that red ginseng helps to increase the therapeutic effect of radiotherapy on tumor tissues and effectively treats collagen-induced arthritis^[46-48]. Reported clinical effects of red ginseng are summarized in Table 2.

CONCLUSION

Red ginseng has both preventive and therapeutic efficacies for AD through immune modulation at the early stages of the disease. Oral red ginseng was shown to block the development of the cutaneous inflammation of an AD animal model by suppressing DCs, TSLP and Th2 cytokines. Early administration of red ginseng is capable of preventing the emergence of the itch-scratch cycle and maintenance therapy with red ginseng can inhibit AD progression into the chronic phase. Taken together, we suggest that red ginseng administration is a novel approach in the prevention and treatment of early stage AD.

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d-limonene prevents ultraviolet irradiation: Induced cyclobutane pyrimidine dimers in Skh1 mouse skin

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Abstract

AIM: To establish whether *d*-limonene can protect against induction of cyclobutane pyrimidine dimers (CPDs) and sunburn in ultraviolet irradiation (UVR) irradiated mouse skin.

METHODS: The *d*-limonene was given in 4 daily oral 20 μ L aliquots at different concentrations as follows: 100%, 10% or 1% in liponate and 100% liponate as control. One day after the final *d*-limonene treatment, the mice were anesthetized with *i.p.* sodium pentobarbital and placed in boxes to allow a rectangular (2 cm \times 4 cm) region of dorsal skin to be irradiated with a single, ultraviolet radiation dose of 1.5 kJ/m². Skin samples from UVR irradiated area were obtained at 5 min after UVR exposure for CPD detection, at 6 d after UVR exposure, skin samples were obtained for in situ analysis for N-myc downstream regulating gene 1 (NDRG1) (a stress response gene), proliferating cell nuclear antigen

(PCNA) (an S-phase marker) and filaggrin (a barrier integrity gene). Based on immunohistochemistry staining, the number of CPD, NDRG1 and PCNA positive cells, as well as unstained cells was counted in 3 different individually selected areas and percentage of positive cells was established.

RESULTS: CPD reduction occurred as follows: liponate only-none; 1% *d*-limonene-54.3% reduction of CPDs; 10% *d*-limonene-73.4% reduction of CPDs; 100% *d*-limonene-86.1% reduction of CPDs, the latter equivalent to a UV dose of only 0.21 kJ/m². Sunburn was also dose-dependently reduced by *d*-limonene. The NDRG1 protein was strongly induced by UVR (70.0% \pm 10.4% positive cells), but 1% *d*-limonene reduced the response to 64.6% \pm 9.2%, 10% *d*-limonene reduced the response to 16.2% \pm 3.4% and 100% *d*-limonene reduced the response to 6.3% \pm 1.7%. Similarly, PCNA was 52.4% \pm 9.9% positive in UVR exposed skin, and 1% *d*-limonene reduced it to 42.9% \pm 8.1%, 10% *d*-limonene reduced it to 36.2% \pm 6.7% and 100% *d*-limonene reduce it to 13.8% \pm 3.4%. NDRG1 and PCNA were increased by *d*-limonene or UVR separately, but combined they produced less than either agent separately owing to the protective effect of pre-exposure to *d*-limonene.

CONCLUSION: Overall *d*-limonene acted to protect against ultraviolet B-induced DNA photodamage and sunburn in UVR exposed skin.

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Key words: Sunburn; Ultraviolet irradiation; *d*-limonene; Cyclobutane pyrimidine dimers; N-myc downstream regulating gene 1; Proliferating cell nuclear antigen

Core tip: Skh-1 hairless mice were given 4 daily 20 μ L aliquots of different concentrations of *d*-limonene, and then irradiated to a single ultraviolet irradiation. Skin samples from the ultraviolet-exposed area of mice showed that

ultraviolet irradiation induced cyclobutane pyrimidine dimers formation, N-myc downstream regulating gene 1 and proliferating cell nuclear antigen expression, pre-treatment of *d*-limonene significantly reduced these responses. Pure *d*-limonene also induced the expression of epidermal barrier protein filaggrin. In conclusion, *d*-limonene protected the mice skin from UV-induced DNA photodamage and sunburn in mice skin.

Uddin AN, Wu F, Labuda I, Tchou-Wong KM, Burns FJ. *d*-limonene prevents ultraviolet irradiation: Induced cyclobutane pyrimidine dimers in Skh1 mouse skin. *World J Dermatol* 2014; 3(3): 64-72 Available from: URL: <http://www.wjgnet.com/2218-6190/full/v3/i3/64.htm> DOI: <http://dx.doi.org/10.5314/wjd.v3.i3.64>

INTRODUCTION

Understanding how aroma terpenes prevent sunburn and/or skin cancer in mice could lead to more effective and safer ways of blocking sun damage to human skin. As one of the most common terpenes in nature, *d*-limonene is listed in the Code of Federal Regulations as generally recognized as safe (GRAS) as a flavoring agent (<http://www.cfsan.fda.gov/~lrd/fcf182.html>) and is found in common foods, such as, fruit juices, soft drinks, baked goods, ice cream, and pudding at low concentrations^[1]. Limonene has well-established chemopreventive activity against many cancer types in animal models^[2,3], including mammary^[4], skin^[5], liver^[6], lung^[7] and forestomach cancers^[8].

Previously, we showed that β -damascenone, an aroma terpene, protected against sunburn by activating both keratinocyte and sebaceous gland pathways that fortified and thickened the cornified barrier layers of mouse epidermis^[9]. Our immunohistological and gene expression results of keratin, caspase 14, filaggrin or loricrin were consistent with the idea that fortification of the cornified envelope by the activation of new sebum secretion was the key mechanism of β -damascenone-induced sunburn protection by absorbing ultraviolet irradiation (UVR) and reducing its penetration into the skin^[9].

In the current study, the effect of *d*-limonene on the protection of mouse skin against UVR-induced sunburn and DNA photodamages was quantified in UVR-irradiated mice skin. The stress-related N-myc downstream regulating gene 1 (NDRG1) gene protein, proliferation [as assessed by proliferating cell nuclear antigen (PCNA)] and expression of skin barrier function gene, filaggrin, were detected by immunohistochemistry. Results indicated that *d*-limonene protected against DNA photodamages and sunburn of the mice skin. The protection was likely associated with activation by the *d*-limonene of keratinocyte and sebaceous gland proliferation and induction of endogenous UV absorbents in the outer cornified envelope of skin, thereby increasing UVR absorption and protecting underlying cutaneous tissues.

MATERIALS AND METHODS

Experimental animal

Albino, female Skh-1 mice of 6 wk old used in all experiments were purchased from *Charles River Laboratories (Wilmington, MA)*.

d-Limonene

The test terpene, *d*-limonene, was obtained as a 99.99% pure compound from Biokeys for Flavors (Norwood, NJ, United States). For 10% or 1.0% compounds, pure *d*-limonene was diluted with the triglyceride, liponate. *d*-Limonene was administered orally, sometimes topically.

Sunburn dose-response experiments

Thirty mice were grouped as follows: (1) control (3 mice); (2) UVB alone (3 mice); (3) 100% *d*-limonene (6 mice, 3 topical, 3 oral); (4) 100% *d*-limonene + UVR (6 mice = 3 topical *d*-limonene + 3 oral *d*-limonene); (5) 10% *d*-limonene + UVR (6 mice = 3 topical *d*-limonene + 3 oral *d*-limonene); and (6) 1.0% *d*-limonene + UVR (6 mice = 3 topical *d*-limonene + 3 oral *d*-limonene). *d*-Limonene was given topically or orally. For topical exposure, 20 μ L *d*-limonene (100% or diluted) was applied on the dorsum of the mice in the same amounts as was administered by feeding tube.

Exposure of mice to UVR

One day after the final *d*-limonene application, mice were exposed to a single dose of 1.5 kJ/m² of UVR (7.5 min duration). For positional restraint during UVR exposures, the mice were anesthetized with *i.p.* sodium pentobarbital (Nembutal) at a dose of 35 mg/kg body weight and placed in boxes configured to allow a rectangular (2 cm \times 4 cm) region of dorsal skin to be exposed to UVR. The UVR was generated by of a bank of four parallel Westinghouse fluorescent sun lamps (FS-20, Westinghouse, Bloomfield, NJ, United States). The lamps were positioned 24 cm above the skin surface. The dose rate of UV was 0.20 kJ/m² per minute as measured with a digital radiometer/ photometer (1400A, International Light Inc., Wilmington, MA, United States). Sunburn was evaluated and photographed at a peak response generally 4 to 6 d after UV exposure. A minimal erythema dose (MED) experiment was performed in the dose range of 0.25 kJ/m² to 2.0 kJ/m². All experiments were conducted according to protocols approved by the Institutional Animal Care and Use Committee of New York University School of Medicine.

DNA photodamage experiments

For detection of cyclobutane pyrimidine dimer (CPD) photoproducts, a separate group of 27 Skh1 mice were used as control, UVR alone, UVR + 100/10/1.0% *d*-limonene for oral applications. Four daily *d*-limonene doses and a single UVR exposure was applied as described in sunburn experiments. Skin samples from the dorsal area of mice exposed to UVR were obtained at 5 min after



Figure 1 *d*-Limonene prevented sunburn formation. Mice were exposed orally to 20 μ L of pure or diluted *d*-limonene daily for 4 consecutive days followed by 1.5 kJ/ m^2 of ultraviolet B exposure generated by a commercial sunlamp 1 d later. The maximum sunburn response occurred as shown by skin erythema on 6th day of UVR exposure was completely eliminated by pure *d*-limonene. A: UVR alone; B: UVR + 1.0% *d*-limonene in liponate; C: UVR + 10% *d*-limonene in liponate; D: UVR + 100% *d*-limonene. Topical application of *d*-limonene followed by UVR yielded similar results (data not shown). UVR: Ultraviolet irradiation.

each UVR exposure for CPD detection. For NDRG1, PCNA and flaggrin detection, skin samples were obtained at 6 d after UVR exposure.

CPD detection

CPDs were detected with conventional streptavidin-biotin methods. Formalin-fixed paraffin-embedded sections were deparaffinized in xylene and absolute ethyl alcohol. The DNA was denatured by incubating slides in 2N HCl for 10 min and then neutralizing by incubating in 50 mmol/L Tris-base for 5 min at room temperature. After blocking with non-immune serum, slides were incubated overnight at 4 °C with mouse monoclonal anti-CPD antibody (Cosmo Bio Co., Tokyo, Japan) at a dilution of 1:300 in PBS. Slides were then incubated for 15 min with biotinylated antibody and then with the streptavidin-biotin peroxidase system Ultra Streptavidin Detection System kit (Covance Research Products, Dedham, MA, United States).

Immunohistochemical analysis

Immunostaining of NDRG1, PCNA and flaggrin were performed on paraffin sections of skin samples. The sections were incubated overnight at 4 °C with different antibodies as follows: a rabbit polyclonal anti-NDRG1 antibody (Abcam, Cambridge, MA, United States) at a dilution of 1:300 in PBS, a mouse monoclonal anti-PCNA antibody (Covance Research Products) at a dilution of 1:100 in PBS, a purified polyclonal anti-flaggrin antibody

(Covance Research Products) at a dilution of 1:300 in PBS. Then immunostaining was performed according to the protocol of with the streptavidin-biotin peroxidase system Ultra Streptavidin Detection System kit (Covance Research Products).

Quantitative analysis of CPD, NDRG1 and PCNA-stained cells

Stained cutaneous tissues were observed under a light microscope and images were created by using a Canon Powershot SD500 digital camera with a Scopetronix microscope adapter. The number of CPD, NDRG1 and PCNA positive cells as well as unstained cells was counted in 3 different randomly selected areas of equal length for each sample and the percentage of positive cells was calculated. Values are expressed as mean \pm SE.

RESULTS

Sunburn protection

Administration of 100% *d*-limonene orally significantly prevented DNA photodamage as well as sunburn/erythema in Skh-1 mice exposed to 1.5 kJ/ m^2 of UVR. Four doses of 20 μ L each (0.95 μ g/g body weight) of 100% *d*-limonene provided complete protection from UVR-induced sunburn. Topical *d*-limonene prevented UVR-induced sunburn slightly more effectively than oral *d*-limonene. Sunburn protection was gradually re-

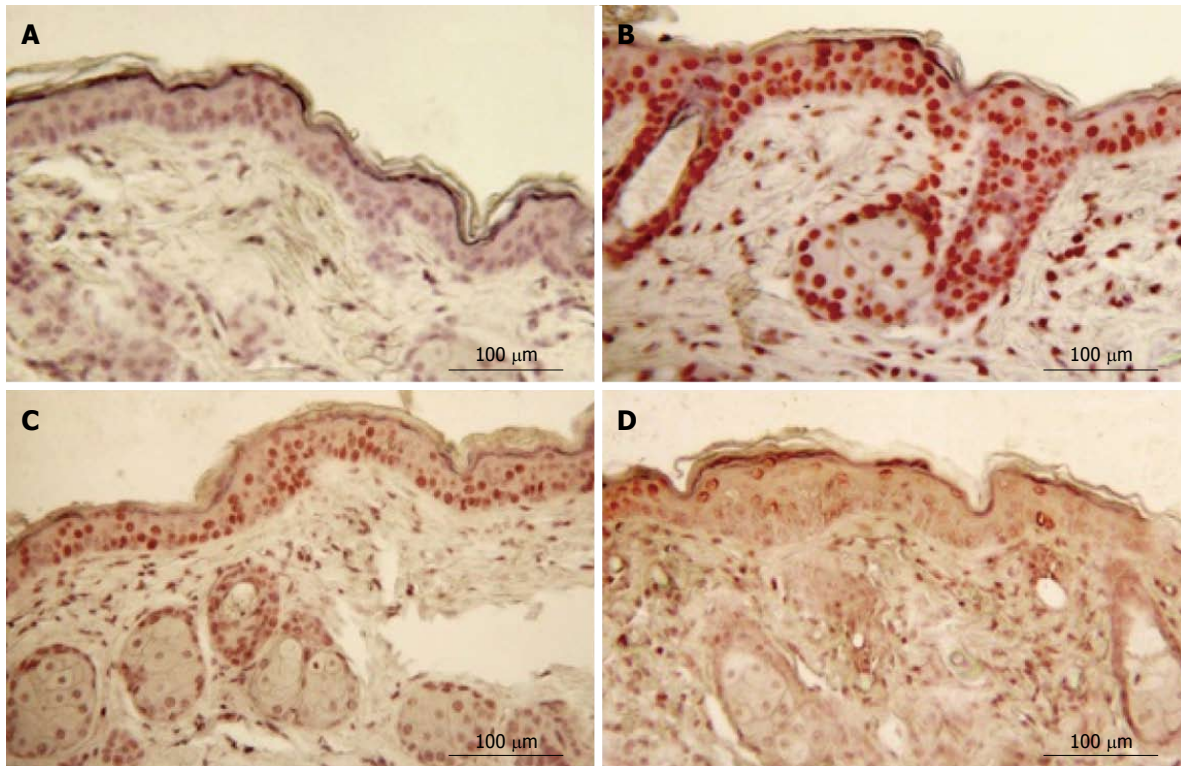


Figure 2 Immunostaining for cyclobutane pyrimidine dimers following oral exposure to *d*-limonene. Skin samples were collected 5 min after UVR exposure. (A) Only unstained, CPD-negative cells are seen in control epidermis (B) intense CPD-stained nuclei are seen in skin samples (C, D). Oral *d*-limonene prevented CPD photoproducts formation in dose-dependent manner. UVR: Ultraviolet irradiation; CPD: Cyclobutane pyrimidine dimer.

duced with lower concentrations such as 10%, 1% or 0% *d*-limonene in a dose-dependent fashion (Figure 1). The sunburn protection was less but still significant at 10% *d*-limonene but was absent at 1% *d*-limonene. A minimal erythematous dose (MED) for these mice was established at 0.75 kJ/m².

DNA photoproducts formation

No staining for CPDs was observed in epidermis that had not been exposed to UV (Figure 2). Five min after UVR exposure, CPD-stained cells were observed among the epithelial cells superficial dermal fibroblasts. UV irradiation significantly increased the CPD staining as shown in Figure 2B. Mice given oral 100% *d*-limonene before UVR exposure exhibited only 15% of the UVR-induced CPDs in compared to mice not treated with *d*-limonene (Figure 2D). The photoproducts were reduced for 10% or 1% *d*-limonene in a dose-dependent fashion as follows and as shown in Table 1. The percentage of CPD positive cells was 94.7% ± 11.1% in UV exposed, 45.7 ± 8.3% (52% reduction) in 1% *d*-limonene pretreated, 26.6 ± 5.8% (72% reduction) in 10% *d*-limonene pretreated, and 13.9 ± 4.5% (85% reduction) in 100% *d*-limonene pretreated mice skin epidermis.

NDRG1 protein analysis

Mice exposed to UVR strongly expressed NDRG1 (Figure 3C), however, mice exposed to UVR following treatment with *d*-limonene, showed reduced NDRG1 protein

in epidermis (Figure 3D-F), even though *d*-limonene alone produced an increased level of NDRG1 (28.1% ± 5.2%, Figure 3B). In control skin, little or no NDRG1 was observed in epidermis but low levels were detected in sebaceous glands. The NDRG1 protein, a cytoplasmic protein involved in stress response, indicated that 70.0% ± 10.4% of keratinocytes were affected by the DNA damaging effect of the UVR. The UVR-induced NDRG1 index remained at 64.6% ± 9.2 % at 1.0% *d*-limonene, but was significantly reduced at 10% *d*-limonene to 16.2% ± 3.4% and at 100% *d*-limonene to less than 6.3% ± 1.7% (Table 1); the latter indicating a nearly complete elimination of cellular damage or response to damage; a finding that is consistent with sunburn prevention and CPD inhibition.

Epidermal proliferation as measured by PCNA-positive cells

As shown in Figure 4 both *d*-limonene and UVR induced proliferative stimulation of in the epidermis, the hair follicles (not shown) and the sebaceous glands (not shown). However, prior treatment of mice with *d*-limonene exposure significantly reduced the PCNA-positive cells in skin compared to that of UVR alone mice. The percentage of PCNA-positive nuclei (S-phase nuclei) in epidermis of *d*-limonene-treated mice was 74.6% ± 11.1%, *vs* 7.1% ± 1.7% in controls; a 10.5 folds increase (Table 1). The increased proliferation of keratinocytes was apparently balanced by an increased rate of differentiation, because

Table 1 Quantitative analysis of the effect of *d*-limonene on cyclobutane pyrimidine dimer, N-myc downstream regulating gene 1 and proliferating cell nuclear antigen induction

Groups	CPD-positive cells (%)	NDRG1-positive cells (%)	PCNA-positive cells (%)
Control	0.0	6.0 ± 1.4	7.1 ± 1.7
UVR only	94.7 ± 11.1	70.0 ± 10.4	52.4 ± 9.9
UVR + 1.0% <i>d</i> -limonene	45.7 ± 8.3	64.6 ± 9.2	42.9 ± 8.1
UVR + 10% <i>d</i> -limonene	26.6 ± 5.8	16.2 ± 3.4	36.2 ± 6.7
UVR + 100% <i>d</i> -limonene	13.9 ± 4.5	6.3 ± 1.7	13.8 ± 3.4
100% <i>d</i> -limonene alone	0.0	28.1 ± 5.2	74.6 ± 11.1

d-Limonene was administered orally daily for 4 consecutive days prior to 1.5 kJ/m² of UVB radiation. CPD samples were obtained on the 5th day 5 min after each UVR exposure. Skin samples for NDRG1 and PCNA were obtained 6 d after the UVR exposures. An approximate number of CPD, NDRG1 and PCNA positive cells as well as unstained cells were counted in 3 different areas of equal length for each sample and percentage of positive cells was calculated. UVR: Ultraviolet irradiation; PCNA: Proliferating cell nuclear antigen; NDRG1: N-myc downstream regulating gene 1; CPD: Cyclobutane pyrimidine dimer.

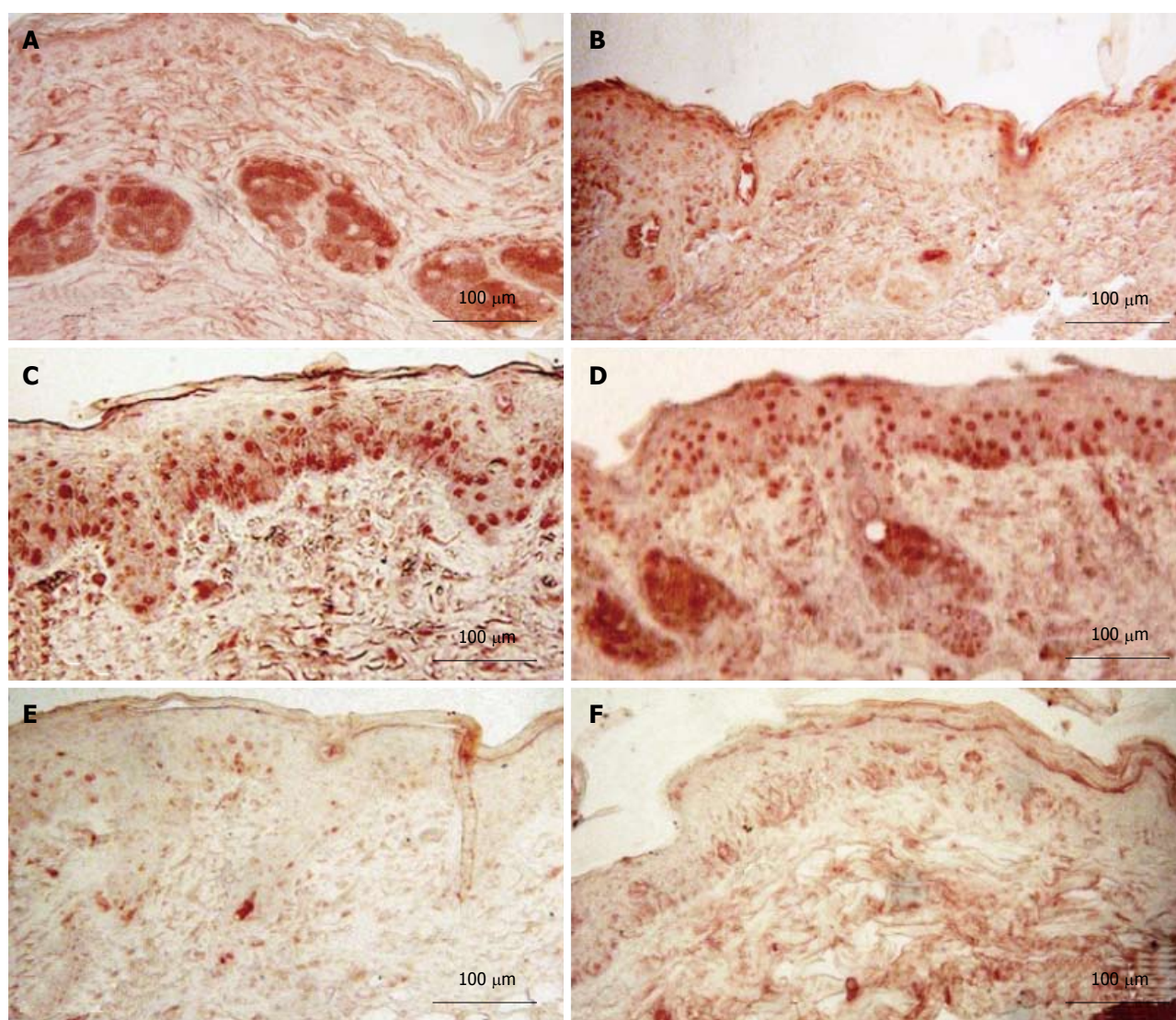


Figure 3 Immunostaining of N-myc downstream regulating gene 1. Skin samples were obtained 6 d after UVR exposure. A: In control skin little or no NDRG1 was seen in epidermis but low levels were detected in sebaceous glands, Control; B: 100% *d*-limonene alone, mouse skin exposed to UVR strongly expressed NDRG1 both in epidermis and sebaceous glands (C-E); C: UVR alone; D: UVR + 1.0% *d*-limonene; E: UVR + 10% *d*-limonene; F: UVR + 100% *d*-limonene. Skin exposed to UVR with prior treatment of *d*-limonene, show significantly reduced NDRG1 protein in epidermis and hair follicles (F). UVR: Ultraviolet irradiation; NDRG1: N-myc downstream regulating gene 1.

the total nucleated keratinocyte count was unaffected. The percentage of PCNA positive cells was $52.4\% \pm 9.9\%$

in UV exposed skin, but 1% *d*-limonene reduced the number to $42.9\% \pm 8.1\%$, 10% *d*-limonene reduced the

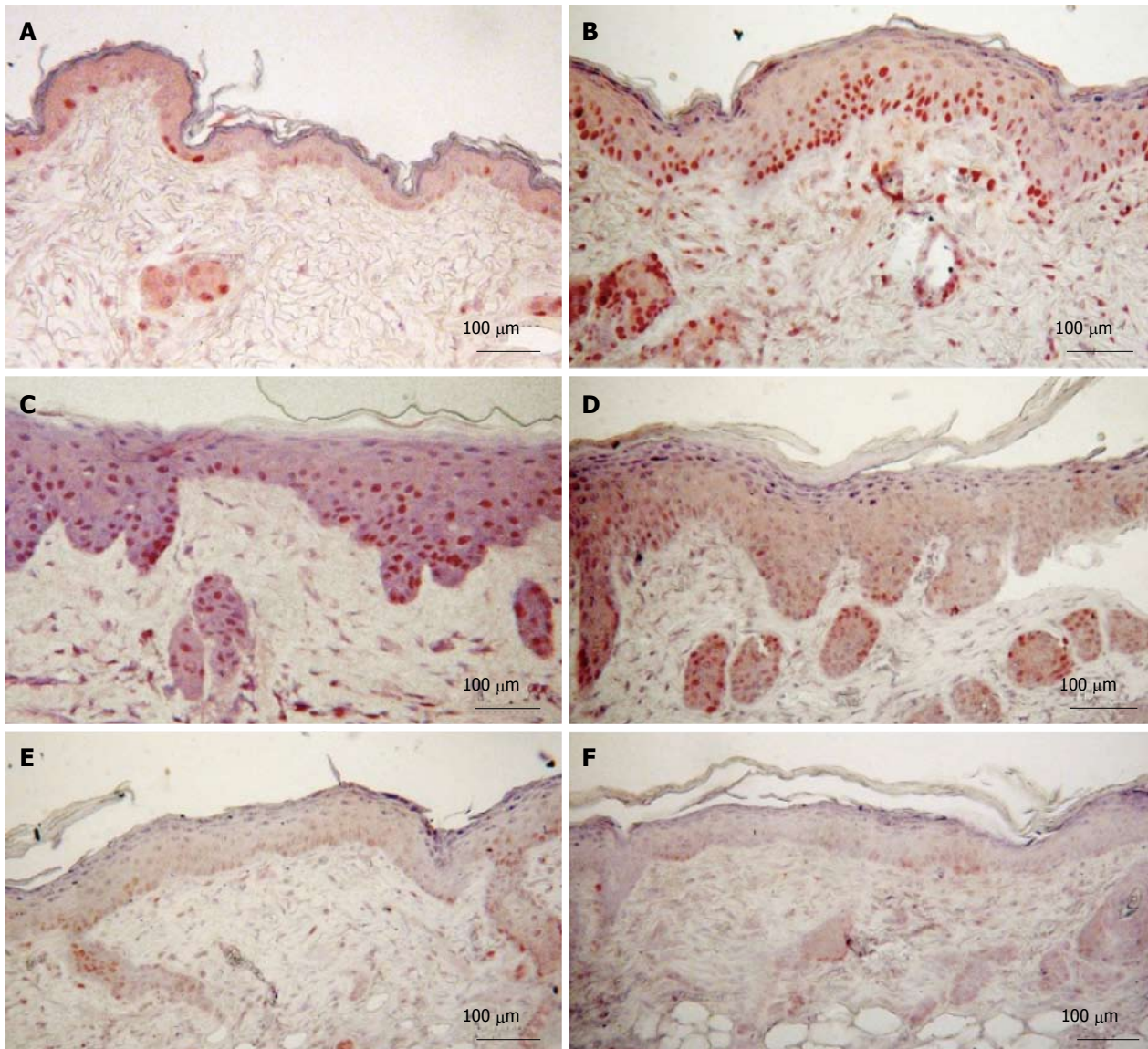


Figure 4 Immunostaining of proliferating cell nuclear antigen. Skin samples were obtained on 6 d after UVR exposure. A: Control; B: 100% *d*-limonene alone; C: UVR alone; D: UVR + 1.0% *d*-limonene; E: UVR + 10% *d*-limonene; F: UVR + 100% *d*-limonene. (A) In control skin few PCNA-positive cells are observed in epidermis. Both 100% *d*-limonene alone (B) and UVR alone (C) induced proliferative stimulation in epidermis and hair follicles. However, pre-treatment of mice with *d*-limonene significantly reduced the PCNA-positive cells in skin compared to UVR-only mice (D-F), which verifies the CPD finding that oral *d*-limonene was protective against UVR-induced tissue damage. UVR: Ultraviolet irradiation; PCNA: Proliferating cell nuclear antigen; CPD: Cyclobutane pyrimidine dimer.

number to $36.2\% \pm 6.7\%$ and 100% *d*-limonene reduced the number to $13.8\% \pm 3.4\%$.

Induction of filaggrin by *d*-limonene

As shown in Figure 5, *d*-limonene elevated the filaggrin level in the epidermis and sebaceous glands in comparison to control, similar to what was observed in our β -damascenone study^[3]. *d*-Limonene increased the thickness of the cornified envelope layer of epidermis for a prolonged period up to 12 d.

DISCUSSION

DNA damage induced by UVR is thought to play an important role in the pathogenesis of skin cancers^[10,11].

The major types of DNA damage induced by UVR are cyclobutane pyrimidine dimers (CPDs) and (6-4) photoproducts (6-4PPs). Approximately 75 % of UVR-induced DNA damage is CPDs and the remaining is 6-4PPs and the Dewar isomer of 6-4PPs^[12]. These types of DNA lesions are repaired by nucleotide excision repair system in normal cells^[13,14]. The formation and repair of DNA photoproducts appears to be crucial for cancer induction as cells from xeroderma pigmentosum (XP) patients, who are highly susceptible to UVR-induced skin cancer as a result of a mutation, cannot remove these photoproducts^[15-17].

The results that either oral or topical *d*-limonene blocked UVB-induced sunburn in Skh1 mouse skin (Figure 1) are consistent with our previous observations that

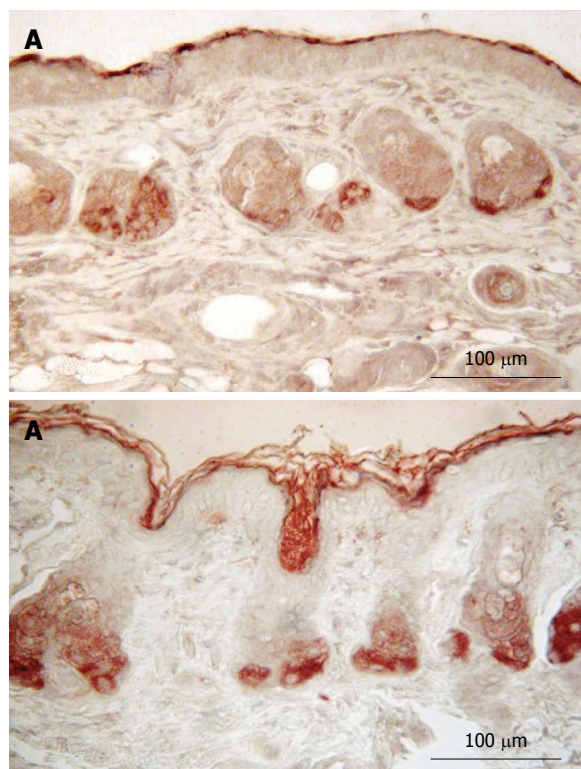


Figure 5 *d*-Limonene induced the expression of filaggrin. A: Control; B: 100% *d*-limonene alone. Sebaceous glands of *d*-limonene-treated mice show a higher filaggrin signal compared to control mice. Also shown is the typical increased thickness of filaggrin-negative materials distal to the dark, thin filaggrin-positive layer, in comparison to control skin.

β -damascenone, also an aroma terpene, acted as a sunburn protective agent similar to current observations^[9]. The preventive mechanism of *d*-limonene exhibited two components, reducing the formation of DNA photo-damages (Figure 2) and lowering of stress, proliferation genes, including NDRG1 and PCNA (Figures 3, 4). It is noteworthy that while pure *d*-limonene induced NDRG1, PCNA, it eliminated the response of these same genes to UVR exposure. This can be explained by invoking *d*-limonene's stimulation of proliferation and differentiation leading to a thickened outer cornified barrier prior to UVR as a protective, absorptive effect. Pure *d*-limonene is not a cutaneous sensitizer, but it is reported to be irritating at high doses. Applications of 25% or 40% of *d*-limonene solutions failed to cause long-term irritation in the ears of rabbits, although application of undiluted *d*-limonene caused skin redness and irritation^[18]. Present results are consistent with these earlier observations.

It is of utmost importance that mice given pure *d*-limonene followed by UVR exposure exhibited reduced UVR-induced CPD photoproducts in the epidermal DNA in a dose-dependent fashion. While the cellular response to *d*-limonene is still to be elucidated, the possibility of direct biochemical reaction between *d*-limonene and cellular DNA is unlikely as most of the oral *d*-limonene is rapidly excreted from the body after metabolized in liver to form perillyl alcohol and carveols which

distributes in the blood to other parts of the body^[19]. Possibly, *d*-limonene's ability to activate proliferation and differentiation of epidermis reflects an underlying, most likely vestigial, UVR protection system in mouse skin.

Another possibility is that *d*-limonene has triggered a gene cluster associated with the strengthening and thickening of UVR-absorbing cutaneous envelopes, possibly including the activation of NDRG1. *In situ* analysis showed an accumulation of NDRG1 in the suprabasal layers of the skin, as well as in the more differentiated areas of mouse skin papillomas^[20]. Although NDRG1 protein is up-regulated during a variety of cell stresses^[21,22], including DNA damage^[23], nickel^[24] and hypoxia^[25], *etc.*, its exact function remains unknown.

Prior treatment of mice with *d*-limonene followed by UVR exposure significantly reduced the NDRG1 expression in skin compared to that of UVR and *d*-limonene alone. UVR is known to initiate ROS and/or inflammatory stress responses^[26,27], but *d*-limonene was ineffective when administered after the UVB (data not shown), which implies that the anti-oxidative or inflammatory activity of the *d*-limonene was not a likely basis for its UVB protective effect. *In vivo* studies with *d*-limonene have shown its efficacy against hepatocellular carcinoma, and inhibition of the overexpression of c-myc and c-jun proteins as one of the mechanisms by which *d*-limonene exhibits its anticarcinogenic effect^[6]. NDRG1, as the downstream of target of N/c-myc may also involve the activity of the *d*-limonene.

Like β -damascenone, *d*-limonene increased the number and size of the sebaceous glands and also induced a higher level of the filaggrin protein in sebaceous glands and in follicular lumens near the skin surface. This result suggests that terpene-induced sebum formation may represent a secondary but inducible pathway whereby filaggrin is made available for strengthening and repairing the cornified envelop layer of epidermis, beyond the well-known filaggrin origin in keratinocytes. The latter filaggrin originates from the degradation of the large and insoluble polypeptide profilaggrin and is further proteolyzed to amino acids that serves as building blocks for epidermal structure, hydration and barrier function^[28,29]. Filaggrin knockdown study in a human skin model showed increased skin sensitivity to UVR and significant decreased amount of urocanic acid, a product from filaggrin degradation acts as an UV absorbent within the stratum corneum^[30]. More study will be needed to resolve the question whether treatment with the *d*-limonene increased this endogenous UVB protective chromophore.

Taking together current *d*-limonene data and previously reported β -damascenone results, suggest that *d*-limonene protected against UVR-induced DNA damage, sunburn by activating stress response and proliferation and gene NDRG1, PCNA and filaggrin which strengthen the skin barrier against UV rays. Even though pure *d*-limonene alone seemingly had some adverse effect, it will protect the skin from UV damage by optimizing the dosage.

ACKNOWLEDGMENTS

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COMMENTS

Background

d-Limonene, an aromatic terpene, has been reported to protect against many cancer types, including mammary, skin, liver, lung and forestomach. Skin cancer caused by the ultraviolet component of sunlight is a major risk in human populations lacking the protection of melanin.

Research frontiers

The research explores the possibility of using very low concentrations of a safe, natural substance taken orally to provide effective and long-lasting protection against ultraviolet radiation-induced sunburn and, if DNA damage is prevented, skin cancer.

Innovations and breakthroughs

Whether taken orally or applied directly to the mouse skin surface, *d*-limonene prevented UVB-induced DNA damage in the form of cyclobutane pyrimidine dimers (CPDs) and sunburn. Elevated ultraviolet irradiation (UVR) absorption was associated with a thicker and stronger skin barrier. *d*-Limonene also counteracted the UVR-induced expression of proliferating cell nuclear antigen and N-myc downstream regulating gene 1. These results show that aromatic terpenes prevent sunburn and DNA damage in mouse skin and are a new and innovative approach to protecting skin against ultraviolet radiation induced skin damage.

Applications

The ultraviolet radiation protection persisted for about 2 wk and might persist even longer in human skin because of its longer turnover time. The interesting discovery was that oral *d*-limonene was about equally effective as a topical application for activating what appears to be a previously unknown natural UVR protective system contained in mouse and human skin.

Terminology

Aromatic terpenes are non-nutritive substances found in citrus and other fruits and herbs. They contribute to the distinctive fragrance of plants, and are generally considered to be safe for consumption by humans and animals.

Peer review

This manuscript described an interesting finding that administration of *d*-Limonene is able to prevent UV-induced sunburn and CPD formation in mouse skin.

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Plantar lichen planus masquerading eumycetoma of dark grains

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Author contributions: Das A was the correspondent author and took the photographs; Das D also seen the case and discussed with other 2 contributors and did histopathology; Gharami RC previous two authors consulted the author for histopathology and the confusion between eumycetoma and plantar lichen planus and for further management and consultation for Verhoeff-Van Gieson.

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Core tip: The case was initially thought to be eumycetoma of dark grains as there was history of discharge of grains but after repeated antifungal therapy it did not resolve and in histopathology it was found as lichen planus. In this case the clinical features collaborating with perforating lichen planus but histopathology has failed to elucidate the perforating channel which is often missed and difficult to delineate. So, it is better to do a histopathology before giving the treatment as there is overlapping clinical features of various diseases.

Das A, Das D, Gharami RC. Plantar lichen planus masquerading eumycetoma of dark grains. *World J Dermatol* 2014; 3(3): 73-75 Available from: URL: <http://www.wjgnet.com/2218-6190/full/v3/i3/73.htm> DOI: <http://dx.doi.org/10.5314/wjd.v3.i3.73>

Abstract

Lichen planus is a common inflammatory disease but its perforating variety is not so common and it has been described in small number of text and articles. Here we reported a case of plantar lichen planus where there was a history of discharge of dark grains from the sole of foot and diagnosing the disease as eumycetoma of dark grains repeated antifungal therapy could not resolve the lesions and histopathologically it showed the classical pictures of lichen planus. Collaborating the clinical and histological features we have diagnosed the case as perforating lichen planus but Verhoeff-Van Gieson stain could not elucidate the perforating channel which is difficult to delineate and often missed. So, we have put the diagnosis of plantar lichen planus and treated with intramuscular triamcinolone and the lesions resolved.

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Key words: Plantar lichen planus; Masquerading eumycetoma; Perforating lichen planus

INTRODUCTION

Lichen planus (LP) is a common chronic inflammatory papulosquamous disorder of skin, hair, and nail generally characterized by shiny, violaceous, flat-topped polygonal papules. They may be closely aggregated or widely dispersed.

There are many variants of lichen planus including annular, linear or blaschkoid pattern, hypertrophic, atrophic, erosive, vesicular, follicular LP, micropapular or eruptive, lichen planus pigmentosus, *etc.* Involvement of palms and soles is not very common^[1]. Morphology of palmoplantar lichen planus is not like that of other areas. Lesions may be profoundly hyperkeratotic plaque, honey-comb pattern, perforating type, ulcerative type, *etc.*^[2]

Here we reported a case of plantar lichen planus presented with discrete keratotic papules with central crater and history of discharging of some material resembling mycetoma.

CASE REPORT

A 48-year-old farmer presented with solid elevated lesions



Figure 1 Few indurated papules at sole with central desquamation and ulceration resembling sinuses.

over medial border of left foot and a history of blackish discharge from the lesions for last 2 years. On examination 4-5 hyperkeratotic papules with central craters with a mild indurated background were found (Figure 1). Mucosae, nails and other areas of the body were normal. The case was provisionally diagnosed as mycetoma. Biopsy was done for histopathological examination and fungal culture. Fungal culture yield negative result. X-ray of the foot revealed no abnormality. Biopsy showed a finding consisting of lichen planus (Figure 2) without any epidermal channel. Verhoeff-Van Gieson stain excluded discharge of any altered tissue. Routine examination of blood, urine and stool, chest X-ray found no abnormality. Two doses of injection triamcinolone (40 mg/cc) intramuscularly were given at 2 wk interval, followed by 3 wk interval for another 2 such. Lesions resolved completely without any relapse during 6 mo period of follow up.

DISCUSSION

Perforating lichen planus is an uncommon variant of LP. It presents as hyperkeratotic papules or plaques topped by crust or a keratotic plug. Occasionally keratotic plugs might be dislodged, leaving behind pitted keratotic papules or plaques. Hanau and Sengel^[3] reported a case of perforating LP in 1984 in a 52-year-old woman where histology showed classic features of LP and there was a channel containing epithelial cells, hyaline bodies and fibrillar material. Hanau and Sengel^[3] speculated that hyaline bodies present abundantly at the base of perforation could irritate the dermo-epidermal junction and consequently initiate the process of perforation of epidermis.

Gutte and Khopkar^[4] again reported a case of perforating LP with acrosyringal accentuation of infiltrate.

In our case there were keratotic papules with central craters. Craters were formed due to dislodgement of superficial hyperkeratotic layers and probably partially detached material was described by the patient as discharge. Serial sections of the specimen also failed to reveal any epidermal channel. So, our case is not exactly a case of perforating lichen planus as mentioned by others^[3,4]. Or this might be a case of perforating lichen planus where histopathology was

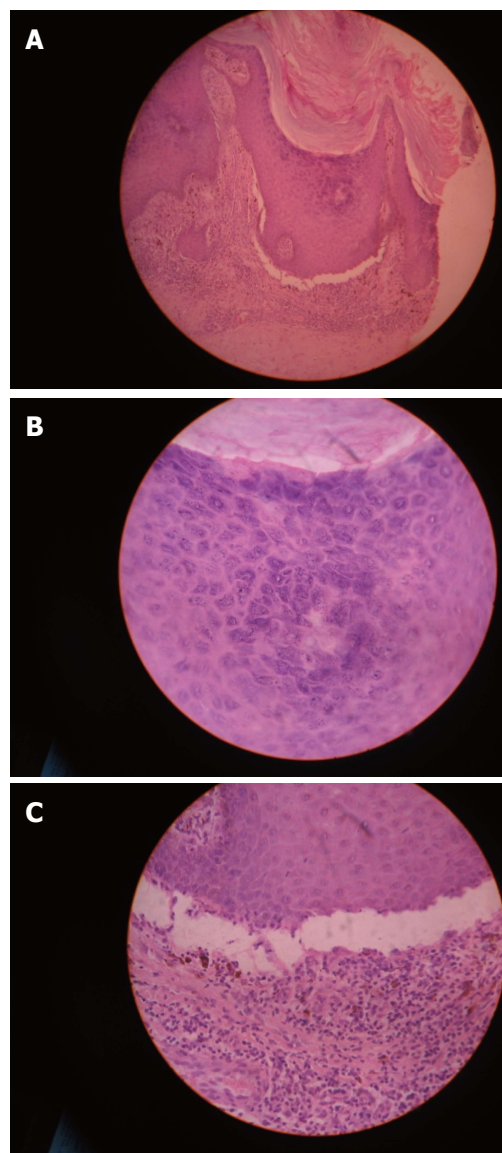


Figure 2 Biopsy showed a finding consisting of lichen planus without any epidermal channel. A: Hyperkeratosis, hypergranulosis, acanthosis, max Joseph's canal, basal layer degeneration with melanin incontinence and band-like infiltrate in dermis; B: Wedge shaped hypergranulosis; C: Max Joseph's canal with band-like infiltrate.

by chance failed to reveal the epidermal channel as it not an easy job to find out. Clinically the case is correlating what was described by previous authors^[3,4].

COMMENTS

Case characteristics

Dark grains coming out from the plaque over the sole.

Clinical diagnosis

Mycetoma.

Differential diagnosis

Eumycetoma, perforating disorders.

Laboratory diagnosis

Fungal culture yields negative result.

Pathological diagnosis

Histopathology suggestive of lichen planus but it is very difficult to elucidate the perforating channel of the lesion and we didn't get the same in histopathology.

Treatment

Systemic glucocorticoid (injection triamcinolone acetonide 40 mg/cc deep intramuscular every monthly).

Term explanation

Perforating lichen planus-lichen planus presents as hyperkeratotic papules or plaques topped by crust or a keratotic plug. Occasionally keratotic plugs might be dislodged, leaving behind pitted keratotic papules or plaques. There lies a channel containing epithelial cells, hyaline bodies and fibrillar material. Hyaline bodies present abundantly at the base of perforation could irritate the dermo-epidermal junction and consequently initiate the process of perforation of epidermis.

Experiences and lessons

Many dermatological lesions clinically misdiagnosed as other entity unless the histopathology helps to find the original lesion.

Peer review

This paper is a usefull clinical case and wrote well.

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Psoriasis: Biologic treatment and liver disease

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Abstract

Patients with moderate or severe psoriasis have a high prevalence of chronic liver disease. Chronic liver disease in these patients is related to metabolic syndrome, alcohol abuse or viral infections. Therefore, treatment of these patients is challenging. Classic systemic treatments may be contraindicated because of their immunosuppressive and hepatotoxic potential. First-line therapy in this setting is generally ultraviolet B phototherapy combined with topical treatment, but its feasibility and efficacy are sometimes limited. The therapeutic options are further restricted by concomitant psoriatic arthritis. Biologic treatments have shown to be effective in psoriasis and psoriatic arthritis, and they are largely devoid of liver toxicity. Anti-tumor necrosis factor-alpha (TNF- α) treatments have proven to be effective and safe in patients with chronic hepatitis C virus (HCV) infections and other non-infectious chronic liver disorders, including alcoholic and non-alcoholic liver diseases. However, in chronic hepatitis B virus (HBV), anti-TNF- α treatments carry a high risk of HBV reactivation. Anti-interleukin-12/23 treatments are also effective in patients with psoriasis, but data regarding their safety in chronic hepatitis infections are still limited. Safety reports in patients with psoriasis and chronic HCV infection are contradictory, and in chronic HBV

evidence indicate a potential risk of viral reactivation. Moreover, concerns remain about the long-term safety of both TNF- α antagonists and ustekinumab. Non-viral liver diseases such as alcoholic and non-alcoholic liver diseases are more prevalent in patients with psoriasis than in the general population. TNF- α antagonists have also been prescribed in these patients. Although data are still scarce in this setting, results suggest a favorable profile in patients with psoriasis and non-alcoholic liver diseases. We review the literature regarding all these aspects.

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Key words: Psoriasis; Liver disease; Biologic; Anti-tumor necrosis factor-alpha; Ustekinumab; Chronic hepatitis C; Chronic hepatitis B; Alcoholic liver disease; Non-alcoholic fatty liver disease

Core tip: We review and summarize the published data regarding the efficacy and safety of anti-tumor necrosis factor-alpha and anti-interleukin-12/23 therapies in patients with psoriasis and liver diseases, with special reference to hepatitis C, hepatitis B, non-alcoholic fatty liver disease, and fatty liver disease. Data collected and revised up to December 2013.

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INTRODUCTION

Treatment of moderate and severe psoriasis is challenging in patients with associated chronic liver diseases. Classic systemic treatments such as cyclosporine, methotrexate or acitretin may be contraindicated because of their immunosuppressive and hepatotoxic potential. Ultraviolet B phototherapy combined with topicals is considered the

first-line therapy in this setting but may not be feasible for many patients, and its efficacy is sometimes limited^[1]. Furthermore, the presence of concomitant psoriatic arthritis further restricts the therapeutic options^[2].

Biologic treatments have shown to be very effective and largely devoid of liver toxicity in patients with psoriasis and psoriatic arthritis, so they may provide a suitable therapeutic alternative in this particular background^[3,4]. Anti-tumor necrosis factor- α (TNF- α) treatments may cause acute liver injury, generally related to drug-induced autoimmune hepatitis, but these alterations are usually mild or moderate and reversible with drug discontinuation^[5]. Nevertheless, biologic treatments are immunosuppressive agents, and some concerns exist about their use in patients with viral hepatitis.

Published data on rheumatoid arthritis, inflammatory bowel disease and psoriasis suggest that anti-TNF- α treatments are effective and safe in patients with chronic hepatitis C virus (HCV) infection^[6,22]. However, in chronic hepatitis B virus (HBV) infection, anti-TNF- α treatments carry a high risk of HBV reactivation^[23-38].

Regarding anti-interleukin (IL)-12/23 antagonists (ustekinumab), data are still scarce^[39-47]. Reports in patients with psoriasis and chronic HCV infection are contradictory^[4,39-41], and some evidence in chronic HBV infection suggests a potential risk of viral reactivation^[42-47]. Moreover, the long term safety of both TNF- α antagonists and ustekinumab in these patients remains a cause of concern.

TNF- α antagonists have also been prescribed in patients with other chronic liver disorders, such as alcoholic and non-alcoholic liver diseases. These non-infectious liver diseases are more prevalent in patients with moderate and severe psoriasis than in the general population^[48-50]. Available data, though still limited, suggests a favorable risk/benefit profile of TNF- α antagonists in patients with psoriasis and non-alcoholic liver diseases^[49,50].

This review summarizes the published evidence regarding efficacy and safety of biologic therapies in patients with psoriasis and liver disorders. Special focus is made on chronic HCV and HBV hepatitis, and on alcoholic and non-alcoholic liver diseases due to their high prevalence in patients with psoriasis. Complications in the management of these patients are further compounded by the frequent coexistence of conditions such as metabolic syndrome, alcohol intake, HCV infection, or iron overload.

VIRAL LIVER DISEASE (HEPATITIS)

Hepatitis C

HCV infection, defined by a positive HCV viral load and detection of antibodies (anti-HCV), is the most common blood-borne infectious disease in the United States, with an estimated seroprevalence of 1.6%^[1-3]. The estimated prevalence in Spain is also around 2%^[1-3]. Psoriasis does not appear to be associated with an increased risk of hepatitis B, hepatitis C, or human immunodeficiency virus infection in the United States^[51,52], but the prevalence of HCV infection has been found to be higher in patients with psoriasis than in the general population in other

geographical areas, such as Taiwan, Japan, Brazil, Central America and Italy^[53-55].

Hepatitis C and TNF- α antagonists: TNF- α antagonists, namely infliximab, etanercept and adalimumab, have demonstrated their efficacy in the treatment of psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, and inflammatory bowel disease, among others, but their safety in the setting of chronic viral hepatitis is still a matter of debate.

Elevated TNF- α levels have been documented in patients with hepatitis C and are associated with a worse prognosis^[56-60]. Even though TNF- α appears to play a major role in immune defense against viral infections, in chronic HCV infection TNF- α is an inducer of apoptosis in infected hepatocytes and might also promote damage to adjacent non-infected hepatocytes by cytotoxic T lymphocytes^[11]. Moreover, serum TNF- α levels are significantly higher in patients with liver cirrhosis than in healthy volunteers, and they are positively associated with serum aminotransferase levels, inflammation, and fibrosis, even in patients with mild liver inflammation^[56,57]. There is also growing evidence that treatment resistance to interferon alfa-2b in chronic HCV infection may be related to the up-regulation of inflammatory cytokines such as TNF- α ^[8,61,62]. Therefore, anti-TNF- α therapy may be beneficial when used in cases of chronic HCV infection^[3,4,6-9,15-21,56].

In addition, standard treatments for chronic hepatitis C, such as interferon alfa and ribavirin, are associated with worsening of psoriasis and psoriatic arthritis, which can be attenuated by the administration of TNF- α blocking agents^[1,3,62].

In a phase II randomized, double-blind, placebo-controlled study, Zein *et al*^[56] compared the efficacy and safety of etanercept *vs* placebo in patients with chronic HCV infection who were receiving treatment with interferon alfa-2b and ribavirin. In these patients, adjuvant treatment with etanercept significantly improved the response to treatment. Clearance of HCV-RNA was achieved in 63% of patients treated with adjuvant etanercept, compared to 32% of placebo patients. The addition of etanercept was also associated with a decreased incidence of the most common adverse events associated to interferon and ribavirin treatment.

The published case series in a clinical setting also suggest that TNF- α blocking drugs such as etanercept, adalimumab and infliximab are a safe alternative for patients with rheumatic diseases or inflammatory bowel disease and concurrent hepatitis C^[3,15-21]. However, liver inflammation, necrosis and fibrosis can be observed in liver biopsies of some patients with normal serum liver enzymes^[16].

Case series and single case reports have also been published on the safety and efficacy of biologic therapies in patients with concomitant hepatitis C and psoriasis^[4,6-9]. Most of these publications deal with TNF- α antagonists, the most commonly used being etanercept^[2-4,6-9]. In some reports, etanercept has been prescribed simultaneously with interferon- α to prevent or ameliorate psoriasis flares^[14,20]. The efficacy of TNF- α blocking agents in psoria-

sis (and psoriatic arthritis) does not seem to be influenced by the presence of concurrent chronic hepatitis C infection^[1-14].

Regarding safety, in most cases, hepatitis C infection has remained asymptomatic, with normal liver function and stable viral loads^[1-14]. In some cases, there were even decreases in the corresponding values^[4]. Despite this, in the retrospective multicentric study published by Navarro *et al.*^[4], two out of 20 patients receiving anti-TNF- α agents presented increases in viral loads that were not accompanied by significant rises in liver enzyme serum levels. Two other patients were diagnosed with hepatocellular carcinoma 9 and 12 mo after the start of etanercept. One of them had a 9-year history of chronic hepatitis C infection and the other one had preexistent cirrhosis related to alcoholism. Three other patients showed either increases in their liver fibrosis or cirrhosis, demonstrated by ultrasonography or Fibroscan. Two of them had a personal history of alcohol intake.

Hepatitis C and IL-12/23 antagonist: Ustekinumab is a human monoclonal antibody against p40, a subunit shared by IL-12 and IL-23. It is currently approved for the treatment of psoriasis and psoriatic arthritis.

In contrast with TNF- α antagonists, ustekinumab might theoretically carry a risk of HCV reactivation, since IL-12 has a major role in the immune control of virus replication and elimination^[63-65]. Serum levels of IL-12 are higher in HCV chronically infected patients who achieve a normalization of liver enzymes and clearance of viremia at the end of interferon- α therapy than in those who do not^[63]. Likewise, in patients with chronic hepatitis C infection, ribavirin has been shown to upregulate the IL-12 receptor and induce Th1 polarization of T cells^[64]. Several studies have also suggested that recombinant human IL-12 is effective in suppressing HCV-RNA, but the effects are transient and the infection relapses when treatment is stopped^[65-68]. Furthermore, IL-12 has been shown to be of low efficacy and poorly tolerated when prescribed as monotherapy in patients who have failed prior treatment with interferon plus ribavirin^[66,69].

Therefore, some controversy exists regarding the use of ustekinumab in patients with psoriasis and chronic HCV infection, and the efficacy and safety data on the use of ustekinumab in this clinical setting are limited. There is only 1 case report and 2 case series of patients with psoriasis and chronic hepatitis C treated with ustekinumab^[4,39,40]. The three patients with chronic hepatitis C receiving ustekinumab in the series of Navarro *et al.*^[4] achieved a 75% improvement in their Psoriasis Area Severity Index (PASI) scores, and their HCV infection remained asymptomatic, with maintenance of normal liver enzymes and stable viral loads.

The case reported by Abuchar *et al.*^[39] was also characterized by a good clinical response of psoriasis, with normal liver function and an undetectable viral load.

Nevertheless, in the four patients reported by Chiu *et al.*^[40] the outcomes were less rosy: even though none

of them had significant increases in liver enzyme results, the HCV viral count increased in three of them during the course of treatment. One of these patients, who had liver cirrhosis, presented HCV reactivation and a recurrence of a previously removed hepatocellular carcinoma after 1 and 4 mo of ustekinumab treatment, respectively. Moreover, none of the four patients achieved a PASI 75 response during the course of treatment (mean duration, 8 mo).

Hepatitis B

HBV infection is a major global health problem. About 350 million of people are infected by HBV worldwide and at least one third of the world population has been exposed to the virus^[69-73].

HBV infection is usually diagnosed when circulating hepatitis B surface antigen (HBsAg) is detected, but it can also be present in HBsAg-negative individuals, with or without circulating antibodies to HBsAg (anti-HBs) and/or to hepatitis B core antigen (anti-HBc)^[52,74]. These individuals have an "occult" HBV infection, which can be detected by the persistence of viral DNA in the liver. The HBV-DNA is sometimes detectable in the sera, but not always^[70].

Once a patient has suffered an HBV infection, the HBV-DNA becomes integrated in the hepatocyte nucleus forever. Regardless of serological markers, this patient is at risk of developing a reactivation during any immunosuppressive treatment. This risk is higher in HBsAg positive and in hepatitis B e antigen (HBeAg) positive patients. Even though the risk of reactivation in occult HBV infection is low, checking for HBV-DNA and close monitoring are recommended^[45].

A high prevalence of HBV infection has to be expected in patients with psoriasis in endemic areas. Two studies from Taiwan have recently reported a higher prevalence of HBV infection in patients with psoriasis than in the general population^[52,74].

Hepatitis B and TNF- α antagonists: TNF- α levels are also elevated in patients with chronic HBV infection, but in contrast to HCV infection, TNF- α plays a crucial role against replication of HBV, and promotes its clearance^[75-77]. Therefore, TNF- α blockade carries a risk of enhanced viral replication and disease reactivation in these patients^[77].

There are several case reports regarding the use of TNF- α antagonists in HBV positive patients suffering from either rheumatologic diseases or inflammatory bowel diseases^[23-31], and several cases of reactivation or exacerbation of HBV infection have been reported^[23-25,28,29,31-33].

In a comprehensive review, Navarro *et al.*^[4] and Pérez-Alvarez *et al.*^[31] collected 35 cases of HBV reactivation among 257 patients with diverse autoinflammatory diseases who received anti-TNF- α treatments. As has been previously described with other immunosuppressive treatments, the risk of developing liver damage or reactivation of HBV while receiving anti-TNF- α therapy is higher in

HBsAg positive carriers than in HBsAg negative patients (with or without positive anti-HBc). These patients are at risk of acute liver failure and death, especially in HBeAg positive patients^[30,31].

Infliximab accounts for the majority of cases of HBV reactivation and fulminant hepatitis^[23-32], but cases in association with etanercept have also been reported^[29,31]. This is probably due to the differences in the two molecules and their mechanism of action: infliximab is a monoclonal antibody that neutralizes soluble and membrane-bound TNF- α , while etanercept is a fusion protein that can only bind soluble TNF- α .

Lamivudine has been successfully used to prevent HBV reactivation in patients with chronic HBV infection who are receiving anti-TNF- α treatments^[7,35], but its long-term use may result in the appearance of resistance^[3].

Similar outcomes have been published regarding the use of anti-TNF- α agents for the treatment of psoriasis and psoriatic arthritis in HBV carriers, either HBsAg positive or HBsAg negative patients (occult carriers)^[4,12,33-38]. The available evidence originates from retrospective analysis of single case reports and large case series^[4,12,33-38].

The efficacy of TNF- α antagonists in patients with psoriasis does not seem to be influenced by HBV status, and clinical outcomes are similar to those of patients without HBV infection^[3,4,12,33-38].

Safety concerns demand a close follow-up of liver enzymes serum levels and viral load, since cases of HBV reactivation have been reported, even in HBsAg negative patients^[30-36]. Furthermore, most authors and guidelines recommend antiviral treatment with nucleoside/nucleotide analogues, such as lamivudine, for prevention of HBV reactivation in all HBsAg positive patients (with or without active viral replication) during TNF- α therapy. HBV prophylaxis should be initiated 1 to 3 wk before starting the immunosuppressive therapy and must be prolonged until 3 to 6 mo after discontinuing the biological therapy^[3,33-36,78-82]. Nevertheless, resistance to lamivudine may develop with prolonged use in up to 30% of patients after 1 year and in up to 70% after 5 years of treatment^[82]. Therefore, when chronic immunosuppressive treatment is required, nucleoside/nucleotide analogues with lower rates of resistance development than lamivudine are preferred, such as tenofovir and entecavir^[24,83].

Despite the risks, some authors advocate prevention of HBV reactivation by monitoring HBV viral load, rather than routine anti-HBV prophylaxis therapy regardless of the HBV status (with the exception of HBeAg positive patients)^[37,38]. In the case series reported by Cho *et al.*^[37] two patients were inactive HBV carriers but five had chronic hepatitis B. HBV reactivation was observed in three patients, and one required antiviral treatment, but no cases of hepatitis were observed. These authors suggest that monitoring viral load is a cost-effective measure that may prevent the development of drug resistance, especially in endemic areas.

The results of Cassano *et al.*^[38] also suggest that the use of TNF- α antagonists may be generally safe without

simultaneous antiviral treatment in patients with psoriasis who are occult HBV carriers. However, they recommend close monitoring of virological markers to detect viral reactivation at an early stage.

Hepatitis B and anti-IL-12/23: As in HCV infection, IL-12 plays a crucial role in the control and suppression of HBV^[65], and this cytokine has proven to be critical for clearance of HBV^[82-85]. Pre-clinical data suggest that it inhibits HBV replication by stimulating the production of interferon-gamma^[82]. Moreover, the production of active IL-12 and Th1 cytokines increases in some patients when HBV infection is cleared and they become anti-HBe positive^[83].

Several studies have demonstrated the efficacy of recombinant human IL-12 in the treatment of patients with chronic hepatitis B^[65,84,85]. In 15 patients with HBeAg-positive chronic hepatitis B who received recombinant human IL-12 with lamivudine, the combination resulted in an enhanced and prolonged suppression of HBV replication in comparison with lamivudine alone^[84,85]. But IL-12 did not eradicate HBV replication, and the response did not persist when administered alone^[84,85].

IL-23 promotes the differentiation of naive T cells to Th17. Th17 cells stimulate the differentiation of B cells, activating the humoral immune response. Thus, IL-23 blockade may also impair the humoral response to HBV^[43,86,87].

The use of ustekinumab in chronic HBV infection is therefore controversial, and clinical experience is still limited. At the moment of writing, only 2 case series and 3 case reports have been published.

Opel *et al.*^[42] reported the first known cases of acute HBV infection in two patients with psoriasis treated with ustekinumab, during phase III (PHOENIX 1) and phase IV (TRANSIT) studies. Both patients were diagnosed with acute HBV infection during the course of treatment with ustekinumab. One of them was a confirmed case of primary infection, while in the other patient potential reactivation of a preexisting infection could not be absolutely excluded. The administration of ustekinumab was interrupted, and the infection did not require active treatment and was self-limited in both cases. None of the patients progressed to chronic infection. The authors suggest that ustekinumab had no impact on the immune response to acute hepatitis B.

The case series from Navarro *et al.*^[41] included a patient with chronic HBV infection and severe psoriasis who was treated with ustekinumab for 7 mo. Clinical results were good, the viral load was undetectable, and serum levels of transaminases were normal. This patient was receiving simultaneous antiviral therapy with entecavir.

Koskinas *et al.*^[43] reported the case of a patient with psoriasis who was HBsAg negative, anti-HBs positive and anti-HBc positive, and who developed HBV reactivation 16 mo after the initiation of ustekinumab treatment. The patient was asymptomatic throughout the whole process. The only sign of reactivation was a moderate increase in

alanine transaminase levels. Tenofovir was initiated while ustekinumab was continued.

Finally, the study of Chiu *et al.*^[40] included 14 patients with psoriasis and HBV infection who were treated with ustekinumab. Eleven patients were positive for HBsAg and 3 were HBsAg negative and anti-HBc positive. Two of the seven HBsAg positive patients who did not receive simultaneous antiviral treatment showed HBV reactivations, all of which were classified as very mild. Both had increases in their viral counts but neither of them presented elevation of transaminases. No cases of reactivation were reported among the occult HBV infected patients. The authors suggested that antiviral prophylaxis may minimize the risk of HBV reactivation and that serum levels of liver enzymes may not be good predictors of this reactivation^[40].

NON-VIRAL LIVER DISORDERS

Alcoholic and non-alcoholic liver diseases are common causes of liver disease in patients with psoriasis^[88-100]. Alcoholic liver disease is related to alcohol intake, while non-alcoholic (fatty) liver disease is associated with metabolic syndrome, a frequent comorbidity of psoriasis^[88-97].

Non-alcoholic fatty liver disease

Fatty liver (simple steatosis), non-alcoholic steatohepatitis (NASH) and fatty cirrhosis are included within the anatomic-clinical spectrum of non-alcoholic fatty liver disease (NAFLD). These liver diseases have shown to be more prevalent in patients with moderate to severe psoriasis, and are likely to be associated with metabolic syndrome and chronic inflammation^[48,92,95,96].

NAFLD is the most common cause of increased serum levels of transaminases and the most prevalent form of liver disease in developed countries, affecting approximately one third of the population^[95]. While individuals with simple steatosis have a low risk of developing terminal liver disease, those with steatohepatitis have a 37% risk of progression to fibrosis in 3.2 years when high body mass index (BMI) and diabetes are also present, and a lower life expectancy than the general population^[95,96].

Treatment of fatty liver disease is based on avoidance of alcohol and hepatotoxic drugs and weight loss targeted to normalize BMI^[88-92]. It has been observed that a certain degree of persistent inflammation, with secretion of pro-inflammatory cytokines such as TNF- α and ILs (IL-12 and IL-23, among others), favours the development of insulin resistance and metabolic syndrome in patients with psoriasis^[48,49]. Likewise, elevated serum levels of TNF- α have been associated with hepatic steatosis^[93], giving support to the observation that inhibition of TNF- α or IL-12/IL-23 may be helpful in both psoriasis and fatty liver disease^[93-96].

In a recent study, Campanati *et al.*^[50] compared the effect of etanercept *vs* PUVA on non-alcoholic fatty liver disease and metabolic syndrome in patients with psoriasis. These authors observed significant reductions in aspar-

tate transaminase/alanine transaminase ratios, fasting insulin serum levels, C-reactive protein serum levels and homeostasis model assessment index in patients receiving etanercept, after 24 wk of treatment. These changes were not detected in patients psoralen and UVA light (PUVA) therapy. They therefore conclude that etanercept can be more efficacious than PUVA therapy to reduce the risk of hepatic fibrosis in patients with NAFLD and psoriasis^[50].

Nevertheless, despite the fact that anti-TNF- α treatments can improve fatty liver disease by improving insulin resistance and decreasing systemic inflammation, they can also lead to weight gain and increased BMI in patients with psoriasis^[48,49]. Therefore, the cornerstone of treatment for fatty liver disease is still weight loss and control of metabolic syndrome risk factors-such as hypertriglyceridemia and hyperglycemia- and systemic inflammation itself.

Alcoholic liver disease

The major cause of chronic liver disease in Western countries is excessive alcohol consumption^[101]. High alcohol consumption is well recognized among patients with psoriasis and has been related to psychological distress^[100]. Using different measures of alcohol consumption, approximately one third of patients with psoriasis can be classified as having difficulties with alcohol, while 13% and 18% of patients with psoriasis believe that they have a current or past drinking problem, respectively^[97-99].

Several studies have investigated the relationship between high alcohol intake and the risk of developing psoriasis. Although alcohol was found to be a risk factor for psoriasis in four out of five studies, there is insufficient evidence to conclude that alcohol consumption is an independent risk factor for psoriasis^[100].

Alcoholic fatty liver is an early and reversible consequence of excessive alcohol consumption (> 280 g/wk in men, and > 168 g/wk in women)^[102].

Like non-alcoholic fatty liver disease, alcohol-induced liver disease can be classified into 3 groups: alcoholic fatty liver (simple steatosis), alcoholic hepatitis, and alcohol-related cirrhosis. Although fatty liver alone is considered non-progressive and reversible upon cessation of alcohol consumption, patients with alcoholic hepatitis can progress to fibrosis, cirrhosis, and hepatocellular carcinoma in up to 30% of heavy drinkers^[101].

Histologically, alcohol-induced hepatitis is similar to NASH (presence of macrovesicular steatosis), but the injury in the former is mainly attributed to a direct toxic effect of alcohol on hepatocytes^[102,103]. Alcohol produces this direct damage to hepatocytes by oxidative stress and toxic effect of its metabolites, but dysregulation of innate immunity also plays an important role in the pathogenesis of alcoholic liver disease^[99,104]. Alcohol consumption has been reported to cause activation of the complement system and interact with the Kupffer cells, leading to TNF- α production, which induces hepatocyte damage^[101]. These mechanisms of liver injury are similar to those observed in fatty liver disease^[105].

Moreover, in patients with alcoholic hepatitis, TNF- α levels are higher than in heavy drinkers without liver disease and healthy controls, and these high levels seem to correlate with mortality^[106].

Considering the important role of TNF- α in the pathogenesis of ALD, several clinical studies have addressed the potential therapeutic effects of infliximab or etanercept on alcoholic hepatitis^[107-109]. Anti-TNF- α agents were administered to these patients to improve the outcome of alcoholic hepatitis regardless of whether or not they had concomitant psoriasis (or other conditions responsive to TNF- α blockade). Preliminary studies in patients with alcoholic hepatitis had positive results in terms of survival and safety^[107], but increased mortality and risk of infection were associated with these drugs in later-stage clinical trials^[108,109]. Therefore, anti-TNF- α treatments are not recommended for the treatment of alcoholic hepatitis^[108,109]. Hence, the mainstay of treatment for alcoholic hepatitis is alcohol abstinence, nutritional support, and corticosteroids when required^[102-105]. Weight loss and control of the risk factors of metabolic syndrome, such as hypertriglyceridemia and hyperglycemia, can also be helpful if present.

CONCLUSION

Hepatitis C

Large placebo-controlled trials are needed before clear conclusions can be reached, but TNF- α antagonists appear to be effective and safe in patients with psoriasis and concurrent chronic HCV infection^[3-22]. Nevertheless, these patients require close follow up due to their inherent risk of developing cirrhosis or hepatocellular carcinoma, especially in those with longstanding chronic hepatitis^[2]. In addition, it is important to point out that liver enzyme tests may not sufficiently reliable as predictors of active liver disease, because cases of inflammation and fibrosis have been observed in liver biopsies despite persistently normal alanine transaminase values^[16]. Non-invasive explorations such as transient elastography or serological markers of liver fibrosis may therefore be useful to predict structural liver damage and to reduce the need for liver biopsies in these patients^[110].

Regarding ustekinumab, its use in the setting of HCV chronic infection is controversial. Cautious use of ustekinumab in patients with psoriasis and chronic hepatitis C is to be recommended, taking into account the role of IL-12 in host defense against HCV infection^[62-64]. Anyway, the published clinical data are scarce, based only on a few cases, and their results are contradictory^[4,39-41].

Hepatitis B

Patients with chronic HBV infection are at high risk of developing HBV reactivation during anti-TNF- α treatments^[3,32-36]. The risk appears to be higher in patients who are HBsAg positive and especially in those who are HBeAg positive^[3,30-38]. Among the TNF- α antagonists, infliximab apparently carries a higher risk than etanercept^[3].

Antiviral prophylaxis appears to minimize the risk of viral reactivation in patients with chronic HBV undergoing anti-TNF- α treatments, but it increases the risk of antiviral resistance^[3,31]. In patients with a low risk of HBV reactivation, such as occult HBV carriers, some authors recommend monitoring the HBV viral load in order to detect viral reactivation early, thus avoiding the need for prophylactic antiviral treatment^[37,38]. This approach may prevent the appearance of drug resistance, particularly in endemic areas^[37,38].

Since IL-12 and IL-23 appear to play an important role in the control of HBV replication, patients with HBV chronic infection and psoriasis who receive ustekinumab might be placed at risk of developing HBV reactivation^[4,42-45]. Even though all the reported cases of reactivation have been considered mild, caution is advised when considering prescription of ustekinumab in patients with HBV infection, and the risk/benefit ratio should be carefully assessed in every case^[42-45]. In these patients, antiviral prophylaxis may reduce the risk of viral reactivation^[4,43,44]. Close monitoring of the HBV viral load is also recommended, particularly for patients with high-risk factors, since determination of serum aminotransferase levels may not be useful for early detection of viral reactivation^[44]. Nevertheless, as the data regarding efficacy and safety of ustekinumab in this setting are still scarce, no definitive conclusions can be made.

Non-viral liver diseases

TNF- α plays an important role in the maintenance and progression of liver injury both in alcoholic and non-alcoholic fatty liver disorders^[101,102].

In patients with non-alcoholic fatty liver disease and psoriasis, TNF- α antagonists seem to have a positive effect on the inflammation that predisposes to metabolic syndrome and fatty liver progression^[48,50]. Nonetheless, available data are still limited and treatment should be focused on controlling BMI and other risk factors for fatty liver progression, such as hyperglycemia and alcohol intake^[48,49].

Regarding alcoholic liver disease, studies with anti-TNF- α therapies have failed to demonstrate a benefit in patients with moderate or severe alcoholic hepatitis^[97,101,105,106]. Both infliximab and etanercept carry an increased risk of infections and even mortality in these patients^[97,101,105,106]. However, the efficacy and safety of TNF- α antagonists in patients with psoriasis and milder forms of alcoholic liver disease have not yet been studied. Nevertheless, the mainstay of treatment for any stage of alcoholic liver disease is alcohol abstinence^[97,102,105,106].

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Phytotherapy and psoriasis: Complementary and alternative medications

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Abstract

Psoriasis comprises severe skin problems affects on quality of patient's life. It affects 2% of the general population with age before 35 years old. Most potent and cheap psoriatic drugs are still largely unavailable. Recently, as a result of the apparent side effects of chemical drugs, treatments of herbal origin gains the popularity among patients with skin disorders especially those for psoriasis. In this review, the uses of complementary and alternative medications of various topical herbal formulae with different potency against psoriasis was greatly assessed. Modified Psoriasis scoring systems were performed as evident of improvement when various topical herbal formula including traditional Chinese medicine ingredients such as *Camptotheca acuminata*, *Oleum horwathiensis*, Capsaicin, furocoumarins, Curcumin, and Tars were used against psoriasis. Also, plant extracts of *Aleo Vera*, and green tea were reported in topical form for the treatment of psoriasis. Most studies indicated a variety of biological activities of used herbs depending on their chemical constituents. This versatile range of biological activities explaining,

the apparent benefits of these herbs in monitoring of psoriasis.

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Key words: Psoriasis; Herbal medicine; Skin disorders; Chinese herbal medicine; Traditional Chinese medicine

Core tip: Herbal medicine plays a significant role in the treatment of psoriasis; this review gives a shed of light on some herbal medicine formulae and extracts including *Aleo Vera*, and green tea. These plants extracts and its formulae exhibited efficiency as anti-psoriasis agents. This may relate to the varying biological activities especially tissue repair actions.

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INTRODUCTION

Psoriasis occurs in most populations with a range of 1%-3%^[1,2]. As usual, synthesized drugs are more potent in psoriasis, however severe unexpected binary effects will appear with long period of drug use. Under advice of dermatologists, about 50% of psoriatic patients around the world used complementary interventions^[3-8]. These include herbal medicine^[9,10], which applied to psoriatic patients with different formulae, topically^[11], internally^[12], and in combination with other forms like acitretin^[13]. The biological activities of these constituents were discussed in most literatures^[14,15]. Whereas these interventions were prescribed to patients alone or in combinations with different forms^[16,17], to perform the targeted therapeutic effect with limited side effects.

Due to the beneficial prospects of traditional Chinese

medicine (TCM), it was applied in management of various dermatological conditions^[18]. However, much concerns should be performed regarding the safety of Chinese herbal treatment. Whereas, a normal action as liver toxicity was reported during treatment^[19-21]. So, the biological activities of some plant extracts used alone or in different combination forms against psoriasis were greatly reported in this review.

PSORIASIS

According to the type of diagnosis, it was reported as dermal disorders with varying shapes and severe lesions. This disease prevails among people with age ranges from 15-45 years. The extent of disease usually appears with chronic symptoms^[22]. Many factors ranged between genetic, apoptotic, cellular, and immunological parameters were attributed with the pathological severity of the disease^[23-25]. The diagnosis of the disease depends mainly on the type, location, and area of lesions or plaques. These parameters were included in many disease scoring systems. The most useful one is psoriasis area and severity index score which evaluated to measure disease severity especially during treatment trials^[26-32].

HERBAL MEDICINE AND PSORIASIS

Traditional Chinese medicine and psoriasis

For most dermatologic disorders, TCM with different formulations were used as an alternative method of therapy^[33]. Each part of the plant can be used as source for herbal remedies to words many diseases^[34,35]. The diversity of both function and plant parts used, promotes specialists developing new forms of biologically active constituents with minimum hazards^[7,36]. Whereas, natural plants provide the essential requirements for human safety. It was reported that TCM is special good choice for many patients which in turn requires a well experienced dermatologists to select the more convenient TCM^[37]. So, with TCM patients can be treated safely with little side effects^[38]. The use of TCM in various forms to treat psoriasis depend mainly on the type of disease. Whereas each type has the recommended and definite mixture of herbs for treatment^[39].

Local formulae of indigo plant was efficiently used to treat patients with severe psoriasis. However, recent ideas were discussed to enhance the potency of this crude herb by preparing extracts with better convenience and absorption^[40]. *Camptotheca acuminata* decne is another example of active topical agents in china^[41]. The biological activities of this herb mainly due to its alkaloids content with antineoplastic activities^[42]. In open clinical trials, the efficiency of this topical agent was applied for many cases with psoriasis. The data showed that *Camptotheca acuminata* decne was significantly more effective with noticed possible enhancement of post inflammatory hyperpigmentation^[43]. Whereas, in another study a hazard effect like dermal allergy was reported against *camptotheca*

acuminata decne which depends mainly on the type and disease intensity^[44-47]. Besides of local trials, some injectable forms of TCMs like *Radix macrotomia* seu *Lithospermum* was used with better potent and minimum side effects against psoriasis compared to other forms of therapeutic modalities^[7]. Similar to Western medications, another type of TCMs were used in capsules or tablets forms for monotherapies or in groups of herbs with higher safety and efficiency. It was found that, three years follow-up of psoriatic cases treated orally with TCM showed convenient results with no hematological or biochemical abnormalities compared to chemotherapeutic agents^[19,48].

Extensive growing evidence was reported for using natural plant forms to treat psoriatic patients. Complementary and alternative medicine (CAM) was used by most patients as a complementary treatment along with conventional treatment. So, teaching of CAM should be integrated into the dermatology residency curriculum, and dermatologists need to increase their awareness of CAM use by their patients in order to improve therapeutic communication^[49].

Some medicinal plants formulations with probable anti-psoriatic activity

Aloe vera extract: The plant characterized by its succulent pulpy leaves which contain clear gel. This plant was used since ancient times as potent remedy for many diseases^[47,48]. The versatile range of its active constituents as analgesic, antipruritic, wound healing and anti-inflammatory promotes its use as good anti-psoriatic agent^[50].

In double-blind, placebo-controlled study, 0.5% of local forms of Aloe vera extract were subjected for the treatment of psoriasis with diagnostic scores between 4.8 and 16.7 (mean 9.3). The data concluded that 0.5% of the extract has higher efficiency with no hazards, and could be used as successful herbal treatment against psoriasis^[51]. However, in other study a commercial Aloe vera gel form showed modest effective treatment against psoriasis^[52].

Oleum horwathiensis formula: *Oleum horwathiensis* formula contains many herbal constituents which showed higher potency in local forms against psoriasis. These constituents are; *Achillaea herba*, *Allium sativum*, *Calendula flos*, *Taraxaci radix*, *Urtica folium* and *Veronica officinalis*. This herb was applied locally to treat psoriasis with varying severity. The results showed a promising effect against disease severity after 12 wk^[53].

Capsaicin formula: It is the most popular active constituent present in cayenne pepper (*C. frutescens*) showed a probable activity towards psoriasis^[54], through activation of cellular apoptotic factors^[55]. Zero point zero two five percent of this formula was applied as local cream to enhance the psoriatic status of patients with varying disease intensity. The data obtained showed an obvious decrease in disease severity within short period of time, however a minimum hazard effect like local site burning

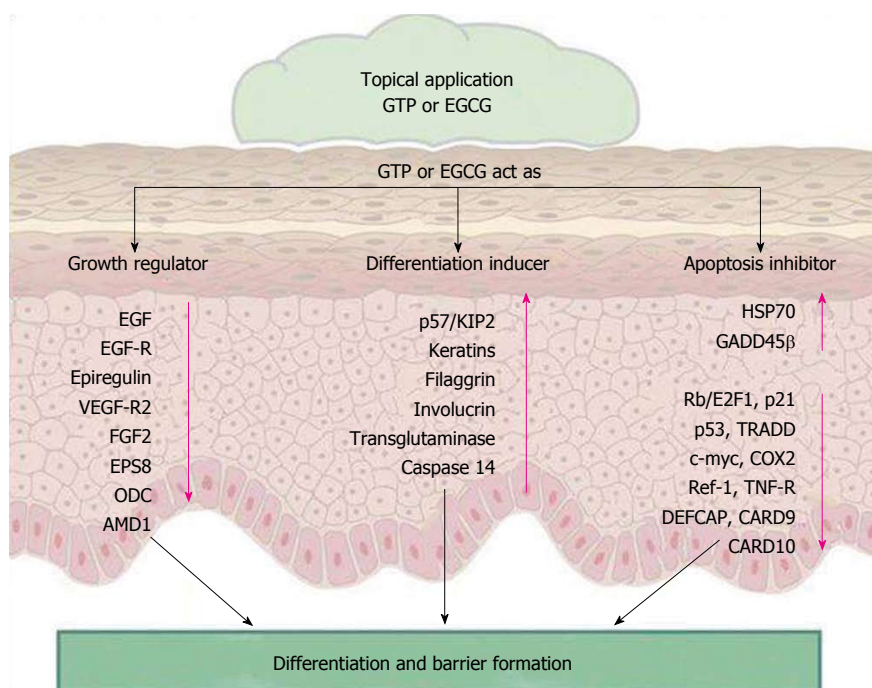


Figure 1 Green tea effects on human epidermal keratinocytes in molecular and immune response levels^[65-67]. EGCG: Epigallocatechin-3-gallate; GTP: Green tea polyphenols; AMD1: Adenosylmethionine decarboxylase 1; CARD: Caspase recruitment domain; COX2: Cyclooxygenase-2; EGF-R: Epidermal growth factor receptor; EPS8: A substrate for the epidermal growth factor receptor kinase; GADD45β: Growth arrest and DNA damage 45β; HSP70: Heat-shock protein 70; ODC: Ornithine decarboxylase; Rb: Retinoblastoma; TNF-R: Tumor necrosis factor receptor; TRADD: Tumor necrosis factor receptor 1 associated death domain protein; VEGF-R2: Vascular epithelial growth factor-receptor 2; FGF2: Fibroblast growth factor 2; DEFCAP: Death-effector filament-forming caspase protein.

was reported, so the formulae was advised to be applied for only 2 successive days^[56,57].

Furocoumarins formula: This formula contains many active agents obtained from different herbal plants including *Ammi majus*. The anti psoriatic activity of this formula depends mainly on photoactivation of furocoumarins *via* ultraviolet A (UV-A, 320-400 nm) when applied either locally or in oral forms. The activity mainly depend up on activation of skin cell apoptosis *via* photochemical linkage with DNA strands and in turn DNA fragmentation. Consequently, a reduction in overexpression of inflammatory and proliferative proteins was reported within psoriatic lesions^[58]. These activity was further investigated in relation to standard therapy, the data obtained showed similar enhancement of disease profile with minimum side effects^[59,60].

Curcumin formula of turmeric (*Curcuma longa*): This active formula is extracted from the rhizome of *Curcuma longa* plant, it is the most potent polyphenolic compound present as fumaric acid^[61]. The extract is characterized by its versatile activities ranged between anti-inflammatory, antioxidant, antitumor, and anti microbial activities^[33], the mode of action against tumor is through regulation of the role of some cellular and immunological parameters during cell cycle and apoptosis^[62]. For centuries, it was reported that Turmeric was applied to heal wounds and reduce scare formation^[63]. Similary, curcumin showed a significant enhancement of psoriatic lesions when applied

locally on diseased skin or orally through capsules. The extract worked *via* induction of skin cell apoptosis^[64-67].

Tars formula: It is one of the most efficient herbal formula applied since past times to treat skin disorders. This active ingredient was extracted from many herbal plants like birch (*Betula* spp.), beech (*Fagus* spp.), or juniper (*Juniperus* spp.) trees. The extract was applied as anti-psoriatic agent in different forms with 5%-10% concentration. The improvement capacity of extract depends on photoactivation mechanism using UV-B with varying light intensity^[68].

Green tea potential benefits for psoriasis: Tea considered the second worldwide beverage next to water. It consumed as green, black, or Oolong tea. It was reported that green tea is the most important agent targeting human health^[69]. This may be related to its higher content of polyphenolic compounds, like flavanols and catechins, whereas dried green tea leaves produce more than 30% of these active constituents. Most studies indicated that green tea constituents have awide range of medical uses as antioxidant, antimicrobial, anti-tumor, anti-inflammatory, and thermogenic agents^[70,71]. The vriable actions of green tea constituents along with its photo suppression action promotes dermatologists to use it as conventional treatment for skin diseases, especially psoriasis^[72-75].

The treatment of skin with green tea extracts protect the skin from developing skin cancer through damaging DNA *via* photochemical action of ultraviolet A radia-

tion^[76]. It was reported that green tea or its active constituents when applied in psoriatic skin, promotes the formation of skin cell apoptosis *via* activation of certain apoptotic biological enzymes included in epidermal differentiation, cornification of the epidermal keratinocytes and skin barrier formation^[77-82]. Finally, the activity of green tea against psoriasis summarized in, activation of a set of apoptotic genes which promotes epidermal differentiation and skin barrier formation along with enhancement of the healing process as in Figure 1^[83-87].

CONCLUSION

Clinical trials proved a significant potential benefits of herbs against psoriasis which appeared relatively safe. The varied biological activities of these topical herbal formulae may relate to its apparent benefits in psoriasis. Most advanced trials like molecular screening were needed for discovering new leads and drug safe candidates from plant natural products against psoriasis.

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