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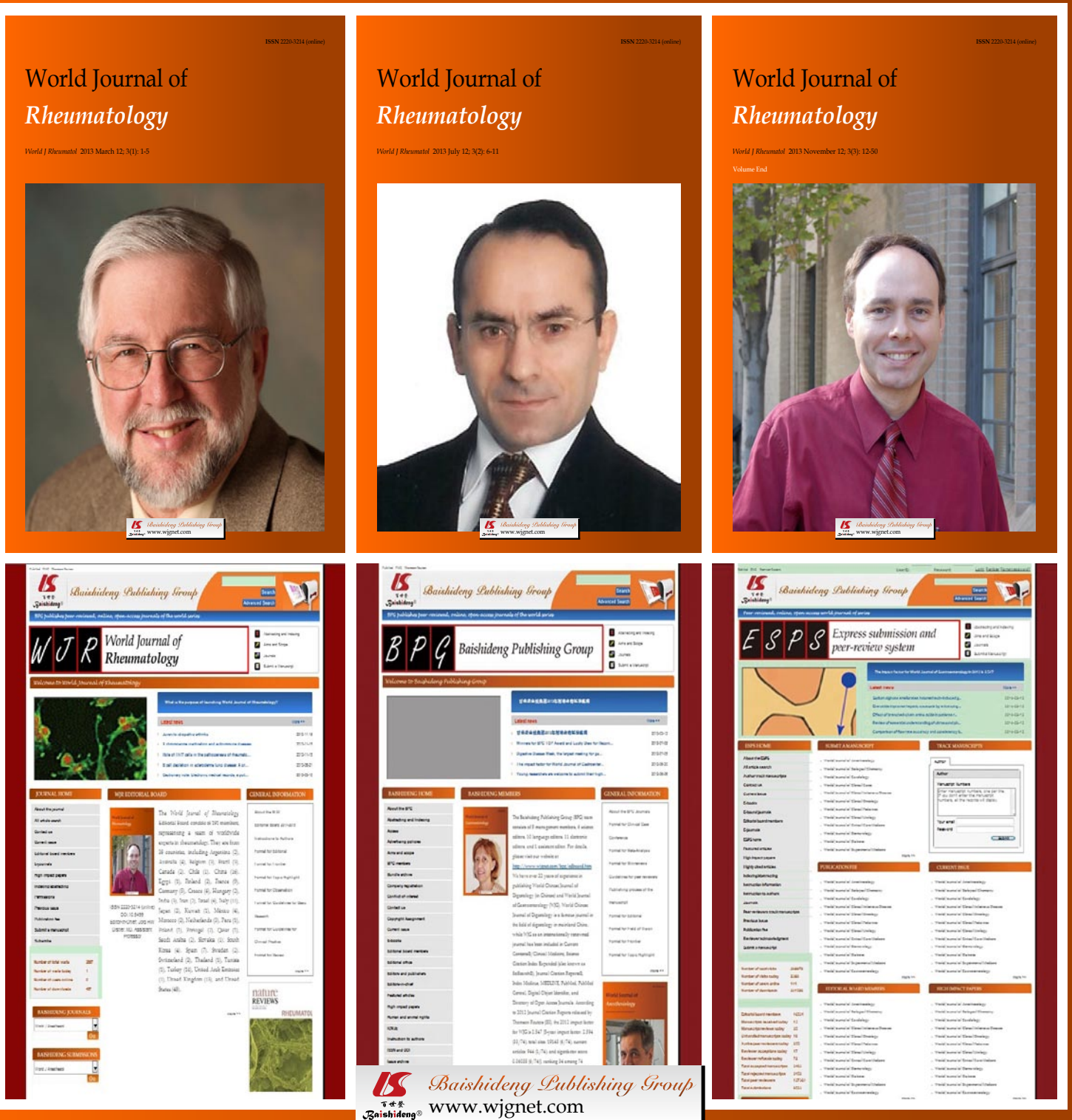

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EDITORIAL

Cautionary note: Electronic medical records, a potential disaster in the making?

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Abstract

Concern is expressed that electronic medical records may actually compromise care. Reports are electronically collated with patient charts, but when are they examined? Current electronic transmission of results to patients' electronic medical records do not seem to notify of new information. The unknown time from prescription to patient action and the variable time required for individual test performance seem to mandate that a physician attempting to be conscientious would have to examine all sections of every patient medical record in their practice, every day. That is quite inefficient and error-prone. Electronic medical record still contains what appear to be dangerous "bugs" which compromise our ability to provide the care we believe our patients deserve? I remain unsure that outpatient electronic medical records are "ready for prime time."

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Key words: Electronic medical records; Impediments to care; Laboratory results; Efficiency; Reports

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ELECTRONIC MEDICAL RECORDS

Independent of the issue of assuring confidentiality, [*e.g.*, exemplified by local on line (web) release of confidential hospital records on 10 000 patients], concern must be expressed that electronic medical records may actually compromise care in the outpatient setting. Especially pertinent to rheumatologists is concern as to how medical records are appended. Reports (laboratory, radiology, procedure, consultation) currently arrive at physician offices by multiple media. They are collated with patient charts, but when are they examined? As most laboratory providers (at least in this area) refuse to provide cumulative reports, the conscientious physician reviewing reports prior to collation is at disadvantage and can easily overlook significant changes of values that are still within "normal limits". Once the reports are collated (placed in patient chart), the physician has the opportunity to examine the report in real time, and compare it with previous results in the patient chart. The alternative is that the provider first sees the results at the patient's next visit. Such an approach risks timely information being buried in the chart, to the detriment of all involved.

LABORATORY RESULTS

Arrival of mailed or faxed reports clearly alerts physicians to new information. Current electronic records and electronic transmission of results to patients' medical records paradoxically do not seem to provide that alert. Results are automatically inserted in separate sections (*e.g.*, laboratory, radiology) of a given patient's record. A major challenge in actually reviewing results is the unknown time from the physician provision of the prescription to when the patient actually "activates" the prescription (*e.g.*, has blood drawn or X-rays taken) and the variable time required for individual test performance. One local hospital offered to delay transmission of results, so they can send all results from a given order in one transmission - unless of course there was an "urgent" value. That is less likely to occur

with automatic electronic transmission of test results, but also would delay the opportunity for timely physician action on values missed or not recognized as significant by the hospital or laboratory. To learn of new information, the provider would have to examine all sections of every patient medical record in their practice, every day. That is quite inefficient and error-prone. The more time spent reviewing records with no new information reduces attentiveness and opportunity to recognize those that do contain new information.

It was said that Winston Churchill had 100 new ideas a day; three of them were good. He had great advisors. If electronic medical records are to be one of medicine's good ideas, they should not aggravate an ongoing problem: Physician distraction by systematic inefficiencies.

Whether they relate to thwarting systematic insurance company-promoted compromise of patient care or to checking every patient's chart every day for any new results, such distractions compromise the ability of the conscientious physician to provide quality care. While we seem to have limited ability to address insurance company "excesses", we still have a modicum of opportunity to control our own house. Therefore, it seems appropriate to comment that the electronic medical record still contains what appear to be dangerous "bugs" which compromise our ability to provide the care we believe our patients deserve? I remain unsure that outpatient electronic medical records are "ready for prime time".

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EDITORIAL

What qualifies as rheumatoid arthritis?

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Abstract

Expansion of diagnostic criteria for rheumatoid arthritis and deletion of exceptions increases sensitivity, but at the expense of specificity. Two decades later, modification of criteria included the caveat: "absence of an alternative diagnosis that better explains the synovitis." That puts great faith in the diagnostic skills of the evaluating individual and their perspectives of disease. The major confounding factor appears to be spondyloarthropathy, which shares some characteristics with rheumatoid arthritis. Recognition of the latter on the basis of marginally distributed and symmetrical polyarticular erosions, in absence of axial (odontoid disease excepted) involvement requires modification to avoid failure to recognize a different disease, spondyloarthropathy. Skeletal distribution, pure expression of disease in natural animal models and biomechanical studies clearly rule out peripheral joint fusion (at least in the absence of corticosteroid therapy) as a manifestation of rheumatoid arthritis. Further, such studies identity predominant wrist and ankle involvement as characteristic of a different disease, spondyloarthropathy. It is important to separate the two diagnostic groups for epidemiologic study and for clinical diagnosis. They certainly differ in their pathophysiology.

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Key words: Rheumatoid arthritis; Spondyloarthropathy; Ankylosis; Accelerometry; Animal models

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INTRODUCTION

Perhaps the most problematic challenge to clinical diagnosis has been the 1987 revised criteria[1] for rheumatoid arthritis. It discarded the diagnostic exclusions portion of previous criteria[2], such that sensitivity may have been increased, but at the expense of specificity. The result has been a tendency[3-5] to group all individuals with a predominantly non-axial inflammatory arthritis in this rheumatoid arthritis category. The 1987 criteria do not address the nature of erosions, their specific distribution and the issue of joint ankylosis, characteristics which separate the those newly diagnosed (according to the criteria) as having rheumatoid arthritis into two groups. Such a binary approach[6-9] divides criteria-fulfilling individuals according to location of erosions on or around joints, skeletal distribution of erosions and presence or absence of reactive new bone formation and joint ankylosis. The 2010 criteria[10] address this question by the inclusion "absence of an alternative diagnosis that better explains the synovitis." These are clinical criteria designed to identify individuals who may have early rheumatoid arthritis. Their sensitivity and specificity seem predominantly determined by the clinician's ability to recognize evidence of alternative diagnoses.

The archeologic record provides unique insight to this question of the more generally applied 1987 criteria's specificity, as two segregated patterns of disease are observed. Rheumatoid arthritis is clearly recognized in 7 populations as the only polyarticular inflammatory disease present[11]. The erosions are marginal to joint surfaces' ankylosis is absent; metacarpal phalangeal joint involve-

ment is prominent and periarticular osteopenia, invariably present. This contrasts with other archeological sites, in which erosions, while polyarticular, are more usually limited in distribution, are predominantly subchondral in distribution, ankylosis is present, wrist and ankle involvement are prominent and periarticular osteopenia is absent in more than 50%[6,12-22]. The neologism "osseotropism" was introduced[23] to characterize the tendency of specific diseases to affect such specific areas of the musculoskeletal system. The characteristics of the second group of individuals were indistinguishable from other individuals in those same populations with spondyloarthropathy diagnosed on the basis of axial disease (sacroiliac joint erosions or fusion, syndesmophytes, or zygapophyseal joint erosion or fusion)[12,13,16,21,24]. Fusion of joints through the articular surface (ankylosis) is not surprising in a disease that primarily erodes subchondral bone. This exposes trabeculae, allowing growth across the joint, a process quite different than what is observed in true rheumatoid arthritis.

The two groups also have very different smoothness of movement or resistance of the joint surface to transitional movement, as determined by accelerometer studies. That translates joint movement into a quantifiable electric impulse, providing a measure of vibration intensity/power[25]. Individuals with periarticular osteopenia and symmetrical polyarticular marginal erosions, but no axial disease or peripheral joint fusion (classical rheumatoid arthritis) had low vibration/power, while those with subchondral erosions and/or peripheral joint fusion had high vibration/power. Individuals with spondyloarthropathy, diagnosed on the basis of axial disease, showed the same high vibration/power[25-27].

While it has been suggested that some dogs and pigs had rheumatoid arthritis[28-32], the presence of subchondral erosions and joint fusion[16,21,23,24] are actually more characteristic of spondyloarthropathy[33,34]. Indeed, evaluation of over 30 000 non-human mammalian skeletons reveals many cases of spondyloarthropathy, but not a single instance of actual rheumatoid arthritis[6,14,35-39]. There clearly are two distinct groups that fulfill the revised criteria for rheumatoid arthritis.

The archeologic record, biomechanical studies and the presence of only one of the varieties of this so-called "rheumatoid arthritis" in animals all support the contention that the revised criteria have limited value in distinguishing these groups, as Silman[9] previously suggested. The article by Can *et al*[40] illustrates this quite well. It describes a high frequency of spondyloarthropathy in patients who fulfill the 1987 criteria for rheumatoid arthritis. While it suggests two coexisting diseases, the more parsimonias interpretation is that the diagnosis of rheumatoid arthritis was incorrect in those patients. Robinson *et al*[41] suggest a third, unrelated group, but use the narrow comparison with ankylosing spondylitis, rather than the more general spondyloarthropathy categorization. These opinion pieces emphasize the importance of separating at least the two diagnostic groups segregated herein for epidemiologic study and for clinical diagnosis. They certainly differ in their pathophysiology.

CONCLUSION

Rheumatoid arthritis and spondyloarthropathy are clearly different disorders, distinguished by clinical appearance, radiologic findings, pathophysiology, biomechanical characteristics and representation (or lack thereof) in the zoological record. The significance of biochemical and inflammatory markers is difficult to assess, as rheumatoid arthritis criteria utilized in its classification are insufficiently specific. The tendency to group all individuals with a predominantly non-axial inflammatory arthritis as having rheumatoid has compromised any comparisons, as it also includes many with spondyloarthropathy. The neologism "osseotropism" was presented, to categorize the joint specificity of the two diseases, to facilitate discriminating between them. Utilizing the criteria of joint distribution, presence or absence of subchondral erosions or peripheral joint fusion, analysis of biochemical and inflammatory laboratory markers may provide additional insights at to the vary different pathophysiological processes represented by these phenomena.

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Patent (list all authors)

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Write as mean ± SD or mean ± SE.

Statistical expression

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EDITORIAL

Adrenocorticotropic hormone: A powerful but underappreciated therapeutic tool for acute crystal induced arthritis?

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Abstract

Treatment of acute gout is not always an easy task since patients usually have multiple comorbidities that preclude the use of nonsteroidal anti-inflammatory drugs and colchicine, the most widely used therapeutic tools. Adrenocorticotropic hormone (ACTH) has long been used in the treatment of acute gout and several studies have shown that it is highly effective and exhibits an excellent safety profile. ACTH belongs to a family of proteins called melanocortins; these molecules have strong anti-inflammatory properties and serve as natural inhibitors of inflammatory responses. We have recently reported that treatment of acute gout with 100 IU of synthetic ACTH is highly effective and associates with negligible side effects. It is note worthy that ACTH did not associate with significant "steroid related" side effects such as hypertension, hyperglycemia and hypokalemia. ACTH appears as a powerful and easy to use therapeutic tool for patients with multiple comorbidities. We believe that the role of ACTH as a treatment for acute gout should be reappraised, especially in light of new experimental data indicating that ACTH has pleiotropic anti-inflammatory properties and is not just a hormone that stimulates the release of steroids.

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Key words: Adrenocorticotropic hormone; Gout; Treatment; Melanocortins; Hyperuricemia

Core tip: The treatment of acute gout in patients with multiple comorbodities is problematic. Adrenocorticotropic hormone (ACTH) is an effective, safe and easy to use therapeutic tool for these patients. ACTH is probably the most attractive choice. Evidence suggests that it is safe and does not seem to associate with immunussupperssion; moreover ACTH is a low cost drug at least in Europe.

Daoussis D, Andonopoulos AP. Adrenocorticotropic hormone: A powerful but underappreciated therapeutic tool for acute crystal induced arthritis? *World J Rheumatol* 2013; 3(2): 6-8 Available from: URL: http://www.wjgnet.com/2220-3214/full/v3/i2/6.htm DOI: http://dx.doi.org/10.5499/wjr.v3.i2.6

INTRODUCTION

Gout is the most common form of inflammatory arthritis affecting 1% of the male population in Western countries[1]. The prevalence of hyperuricemia and gout has been constantly rising during the last decades. Many causes have contributed to this increase: dietary changes, widespread use of medications associated with hyperuricemia, increase in life expectancy and most importantly, the metabolic syndrome "epidemic"[2]. In the majority of cases, gout is treated with nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine. However, treatment of

gout is not always an easy task, since patients usually have multiple comorbidities that preclude the use of these agents. In difficult to treat patients steroids have been traditionally used; however, this therapeutic option is not ideal, since steroids associate with immunosuppression and metabolic side effects.

ADRENOCORTICOTROPIC HORMONE

Adrenocorticotropic hormone (ACTH) has long been used in the treatment of acute gout; as a matter of fact, the first relevant report was published more than half a century ago[3]. Several studies in the 1990's have shown that ACTH is highly effective in the treatment of acute gout and exhibits an excellent safety profile. More specifically these studies have shown that ACTH was equally effective than indometacin and steroids and in some cases faster acting; moreover it was effective and safe in patients with multiple medical problems[4-6]. ACTH belongs to a family of proteins called melanocortins; these molecules, apart from their pigment inducing capacity, seem to have a regulatory role in a wide range of biologic functions. Evidence suggests that melanocortins have strong anti-inflammatory properties and serve as natural inhibitors of inflammatory responses[7]. The prevailing hypothesis was that ACTH mainly acts by stimulating the release of endogenous steroids by the adrenal glands. However, experimental evidence, accumulated over the last decade, indicates that ACTH mainly acts in a steroid independent manner. In a rat knee joint model of inflammation where monosodium urate crystals were injected intra-articularly, local administration of ACTH was highly effective without altering systemic corticosterone levels[8]. More importantly, ACTH was also effective in rats subjected to adrenalectomy indicating that ACTH has a direct anti-inflammatory effect which is not related to endogenous steroid release. This effect was shown to be mediated by stimulation of melanocortin type 3 receptor located on macrophages. The role of melanocortin receptor signalling in modulating inflammatory responses, including gouty inflammation, has been increasingly recognized over the last years[9]. It is also interesting that melanocortins may even antagonize the action of interleukin (IL)-1, the key cytokine in gout pathophysiology[10].

In our department we have been using ACTH as a first line treatment for acute gout in hospitalized patients since 1995. We have recently reported that treatment of acute gout with 100 IU of synthetic ACTH is highly effective and associates with negligible side effects[11]. It is note worthy that ACTH did no associate with significant "steroid related" side effects such as hypertension, hyperglycemia and hypokalemia. ACTH appears as a powerful and easy to use therapeutic tool for patients with multiple comorbidities. We believe that the role of ACTH as a treatment for acute gout should be reappraised, especially in light of new experimental data indicating that ACTH has pleiotropic anti-inflammatory properties and is not just a hormone that stimulates the release of steroids. However, current therapeutic guidelines either ignore ACTH[12,13] or recommend it solely for patients unable to receive oral medications[14].

CONCLUSION

There is a clear need for effective therapies for gout that can be safely administered in patients with multiple medical problems. Recent studies have assessed the efficacy of IL-1 inhibitors; these agents are effective and have been proposed as an alternative therapeutic option for high risk patients. However, we believe that for these difficult to treat patients, ACTH is probably the most attractive choice. Evidence suggests that it is safe and does not seem to associate with immunussupperssion[11]; moreover ACTH is a low cost drug at least in Europe.

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EDITORIAL

B cell depletion in scleroderma lung disease: A promising new treatment?

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Abstract

Evidence suggests that B cells may participate in the fibrotic process Based on this experimental evidence, treatment with rituximab (RTX) has been tried in systemic sclerosis (SSc) with promising results. In a randomized controlled study from our research group it was shown that treatment with 2 courses of RTX leads to a significant improvement of lung function at 1 year compared to baseline. All relevant studies have so far reported clinical and/or histologic improvement of skin fibrosis something that adds further evidence in favor of a disease modifying role of RTX in SSc. It is more than obvious that novel therapies for SSc-associated lung disease are needed. A large scale, randomized, controlled study assessing the efficacy of RTX in SSc associated interstitial lung disease is warranted. If RTX turns out to be effective it would be a major therapeutic advance in SSc since it can be administered on a long term basis due to its acceptable safety profile.

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Key words: Rituximab; Scleroderma; Systemic sclerosis; Interstitial lung disease; Treatment

Core tip: Rituximab (RTX) may be an effective treatment for systemic sclerosis (SSc)-associated interstitial lung disease (ILD). A large scale study assessing the efficacy of RTX in SSc associated ILD is warranted. If RTX turns out to be effective, it would be a major therapeutic advance in SSc since it can be administered on a long term basis due to its acceptable safety profile.

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INTRODUCTION

Lung involvement, especially in the form of interstitial lung disease (ILD), is nowadays the leading cause of mortality in patients with systemic sclerosis (SSc). So far, treatment of this fearful complication has been disappointing. Therapy has been relied on intense immunosuppression in the form of cyclophoshamide (CYC). Administration of CYC leads to a modest reduction in the rate of pulmonary function decline but this effect wanes following drug discontinuation. Therefore, continuous treatment is needed; however long term treatment with CYC is not feasible due to its toxicity. It is more than obvious that we need to develop effective, less toxic therapies that can be safely administered over a long time.

A PROMISING NEW TREATMENT

Evidence suggests that B cells may be actively involved in the fibrotic process[1]. B cells are overactivated in both experimental models of fibrosis[2] as well as in humans with SSc[3]. Moreover, treatment with rituximab (RTX), a monoclonal antibody that depletes B cells was effective in

Table 1 All relevant studies have so far reported clinical and/or histologic improvement of skin fibrosis

Study	Participants (*n*)	Evaluation time point (mo)	Clinical assessment skin	Histologic improvement-skin	Lung function tests
Smith *et al*[9]	8	6	Improved	Yes	Stable
Lafyatis *et al*[8]	15	6/12	Stable	Yes	Stable
Bosello *et al*[10]	9	6-36	Improved	Not reported	Stable
Daoussis *et al*[11]	8	12	Improved	Yes	Improved

an animal model of fibrosis[4]. Based on this experimental evidence, RTX has been tried in SSc with promising results. In a randomized controlled study from our research group it was shown that treatment with 2 courses of RTX leads to a significant improvement of lung function at 1 year compared to baseline[5]. Based on this clinical improvement, patients remained on this treatment and received 2 additional courses of RTX. The beneficial effect on lung function was still evident with patients exhibiting an almost linear improvement of lung function parameters throughout the 2 years of treatment[6]. A favorable effect on lung function has also been recently reported by another research group[7]. Of note, patients with SSc associated ILD tend to worsen over time; improvement in lung function tests is something not usually seen within the natural course of the disease.

All relevant studies have so far reported clinical and/or histologic improvement of skin fibrosis, something that adds further evidence in favor of a disease modifying role of RTX in SSc[8-11]. Additional information is provided in Table 1.

So far, we do not know exactly how RTX mediates its beneficial effects in SSc (if indeed this treatment turns out to be effective). Our research group has recently shown that treatment with RTX associates with a significant decrease in platelet derived growth factor (PDGF) receptor expression and activation in the skin[12]. This is an important finding, taking into account the pivotal role of PDGF in fibrosis. Of note, agonistic auto-Abs against PDGF receptor have been found in patients with SSc[13]; one may hypothesize that RTX acts by eliminating these auto-Abs. However, RTX seems to have a broad effect on the immune system, beyond B cell depletion, and therefore other mechanisms may apply.

CONCLUSION

We believe that all efforts should focus on a large scale, randomized, controlled study assessing the efficacy of RTX in SSc associated ILD. Recently, the Rituximab group of EUSTAR reported encouraging results in 72 patients with SSc treated with RTX[14]. Taking into consideration that the beneficial effect of RTX on lung function in our study was evident at 12 mo, following two consecutive treatment courses, we propose that this scheme is the most appropriate if a randomized controlled study is to be performed (*i.e.*, at least 1 year duration, administration of two consecutive RTX courses). Based on the calculations made in the Scleroderma Lung Study[15], at least 160 patients (80 in the RTX group and 80 in the control group) will need to be recruited so that the study can have sufficient statistical power to detect significant differences between groups. If RTX turns out to be effective, it would be a major therapeutic advance in SSc since it can be administered on a long term basis due to its acceptable safety profile.

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EDITORIAL

X chromosome inactivation and autoimmune diseases

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Abstract

The pathogenesis of autoimmune diseases (AIDs) is characterized by a female preponderance. The causes for this sex imbalance are based on several hypotheses. One of the most intriguing hypotheses is related to an X chromosome inactivation (XCI) process. Females are mosaics for two cell populations, one with the maternal and one with the paternal X as the active chromosome. Skewed XCI is often defined as a pattern where 80% or more of the cells show a preferential inactivation of one X chromosome. The role of skewed XCI has been questioned in the pathogenesis of several AIDs, such as autoimmune thyroid diseases and rheumatoid arthritis.

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Key words: X chromosome; X chromosome inactivation; Autoimmune diseases

Core tip: The causes and mechanisms for sex imbalance are based on several hypotheses. X chromosome inactivation is an important hypothesis to explain the female preponderance.

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INTRODUCTION

Autoimmune diseases (AIDs) are a diverse group of complex diseases, characterized by loss of self-tolerance causing immune-mediated tissue destruction, and affect up to 5%-10% of the general population[1,2]. AIDs can be divided into two main categories: the organ-specific and systemic AIDs. In organ-specific AIDs, the immune attack is confined to one organ or organ system. In the majority of those diseases, target tissues are of a neuroendocrine character. The most organ-specific AIDs studied are type 1 diabetes (T1D), autoimmune thyroid diseases (AITD), Addison's disease and Sjögren syndrome. In systemic AIDs, target tissues and molecules are widespread in the body. Prototypes are systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).

The development and progression of AIDs is a multifactorial process that depends on the interaction between genetic background and a number of environmental factors. Clinically different autoimmune phenotypes may share common susceptibility genes, which may act as risk factors for autoimmunity. Evidence for shared susceptibility genes is obtained from the observation that several AIDs tend to cluster in the same families[3,4] and also that the chromosomal regions showing linkage to AIDs tend to overlap[5,6]. Genetic susceptibility to AIDs is predominantly associated with genes of the major histocompatibility complex (MHC). Human MHC molecules are encoded in several closely linked genes that comprise of the human leukocyte antigen system on the short arm of chromosome 6. However, inheritance of MHC haplotypes providing susceptibility to an AID is not sufficient for disease development. Evidence of linkage to numerous non-MHC-linked chromosomal regions has been

reported by several studies in humans[7-10].

FEMALE PREDOMINANCE IN AIDs

In most of the AIDs, females are more commonly affected than males. The causes and mechanisms for this sex imbalance are based on several hypotheses proposed. These include sex hormones and reproductive history, environmental factors, fetal microchimerism, a skewing in X-chromosome inactivation patterns, and major defects in the sex chromosomes[11]. Experimental data demonstrate a sexual dimorphism in the immune response in humans with stronger cellular and humoral immune reactions in females. Several studies have showed disease exacerbations during specific periods of the menstrual cycle or pregnancy in patients with AIDs such as SLE. Hormones are implicated in the immune response. In fact, estrogens can influence lymphocyte maturation, activation and synthesis of antibodies and cytokines[12,13]. Estrogen receptor ligands modulate antigen presentation[14]. However, despite the considerable work done on the relationship between sex hormones and autoimmunity, differences in sex steroid levels do not seem to provide a convincing explanation for the female predisposition to AIDs[11].

Environmental factors more commonly associated with women have also been suggested to play a role in autoimmunity initiation. Both a permissive genetic background and an environmental trigger have been suggested as being necessary to induce an AID[15]. Factors such as specific xenobiotics or bacteria are ideal candidates in the environmental model but solid evidence of a causative role is awaited.

The X chromosome contains genes that play a role in the maintenance of physiological sex hormones levels. It has been suggested that X chromosome abnormalities might play a pathogenic role. Genetic disorders associated with X chromosome abnormalities, such as Turner syndrome or premature ovarian failure, display autoimmune manifestations[16,17]. More importantly, women affected with primary biliary cirrhosis (PBC), scleroderma (SSc) and AITD are characterized by an enhanced X monosomy rate in peripheral blood cells, mainly T and B lymphocytes[18,19]. These findings support the thesis that sex chromosome instability may play a role in autoimmunity.

X CHROMOSOME INACTIVATION AND AUTOIMMUNITY

In early female embryonic development, one of the two X chromosomes is inactivated[20]. Females are therefore mosaics for two cell lines, cells with the paternal and cells with the maternal X chromosome as the active X. The inactivation process is random and permanent for each daughter cell and most females have approximately 50% of each cell type. A skewed X inactivation (XCI) pattern represents a marked deviation from this distribution (80% or more) and may be the result of chance, genetic factors or secondary selection processes[21] (Figure 1).

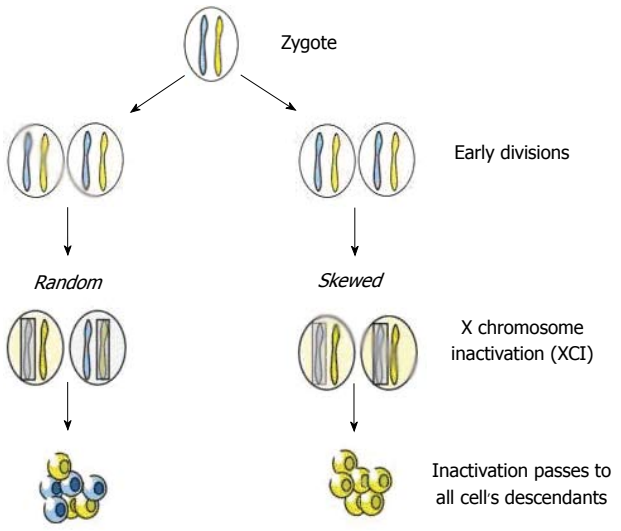

Figure 1 Suggested mechanism of X chromosome inactivation in women. The two parentally derived X chromosome homologues are depicted in different colors (blue, yellow); inactive chromosomes are included in grey boxes.

Because X chromosome choice is assumed to be mostly random, both paternal and maternal antigens will be recognized by the immune system within the thymus and any T cells that have high affinity for such antigens will be deleted by apoptosis[22]. It is immediately obvious that, if such deletion of self-reactive T cells was not successful for one set of X antigens or even just a few antigens, their expression in the periphery may be seen as foreign and the stage would be set for an autoimmune response as suggested for other antigens[23].

Loss of immunological tolerance to self antigens is an important feature of an AID. T cell tolerance, which appears to be broken in many of these diseases, is thought to be established by negative selection against potentially self-reactive T cells in the thymic medulla and cortex-medulla junction. Professional antigen-presenting cells, particularly dendritic cells, mediate the negative selection process[24,25]. It has been demonstrated that risk of autoimmunity could be increased by a lack of exposure to self antigens in the thymus and the presence of autoreactive T cells[26]. A potential mechanism through which lack of exposure to self antigens could occur in women is a disturbance in the XCI process[27-29].

The hypothesis that an altered XCI pattern might play a role in AID susceptibility was first proposed in SLE[28,30] but the lack of an increased frequency of skewed XCI between affected and non affected monozygotic twins did not support the working hypothesis[30]. Similarly, examination of XCI patterns in peripheral blood from female patients with autoimmune diseases (SLE, T1D, multiple sclerosis and juvenile rheumatoid arthritis) did not reveal skewed X inactivation patterns[29]. No evidence for a role of skewed XCI in the pathogenesis of multiple sclerosis was produced by the work of Knudsen and colleagues[31]. Furthermore, a case-control study on 166 women affected with PBC and 226 age-matched con-

trol women did not reveal a significant association of a skewed XCI between the two groups[32]. We should note that these negative data were obtained in DNA from blood and this may not be a representative tissue for all AIDs as the XCI pattern varies between tissues.

A different scenario seems to apply to SSc and AITD. In two subsequent studies with a total of 149 SSc patients, Ozbalkan studied the XCI patterns in peripheral blood cell DNA from 55 women affected by SSc and 124 control women. Their results indicated a greater proportion of a skewed pattern of XCI (49%) than in controls (2.4%) ($P < 0.0001$)[33]. Uz *et al*[34] reported an extremely skewed XCI pattern associated with this disease as well. Similar results were obtained in a Turkish and Tunisian cohort of control women affected with AITD. The prevalence of skewed XCI in females affected with AITD was 19% but only 2.4% in controls ($P < 0.0001$)[35,36]. Similar associations were independently recapitulated in case control studies in RA, JIA and Sjögren syndrome.

Skewed XCI has also been studied in monozygotic twins. Brix *et al*[37] conducted two twin case-control studies; one with twin individuals with and without AITD and the second with twin pairs discordant for AITD. Skewed XCI was significantly more common in twins than in unrelated women; we note that patterns were associated with the risk of disease in discordant twins[37].

However, these findings were based on limited numbers of informative subjects and did not include age matched controls; in fact, although variable prevalence rates of a skewed XCI status have been reported, studies taking into account age as a modifier factor clearly indicate that as many as 16% of healthy women over the age of 50 are characterized by a severe XCI skewing[26,38-40].

CONCLUSION

The X chromosome participates in different pathways involved in the immune response and offers some potential hypotheses for the development of autoimmunity and for the female predominance in AIDs. It would also be of interest to study the XCI pattern in females affected with other autoimmune diseases and to test the XCI patterns of many cell types. Moreover, it appears premature to conclude now that skewed XCI is associated with a female prevalent AID.

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REVIEW

Juvenile idiopathic arthritis

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Abstract

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatologic disease in childhood, which represents a nonhomogeneous group of disorders that share the clinical manifestation of arthritis lasting at least 6 wk under the age of 16. The exact diagnosis requires exclusion of other diseases that cause arthritis. The exact etiopathogenesis of JIA is still unknown. The interactions between genetic factors, environmental exposures and immune mechanisms are thought to contribute to pathogenesis of the disease. The "International League Against Rheumatism" classification divides JIA into 7 subtypes: oligoarticular JIA, rheumatoid factor (RF) positive polyarticular JIA, RF negative polyarticular JIA, systemic-onset JIA, enthesitis-related arthritis, juvenile psoriatic arthritis and undifferentiated JIA. Each subgroup of JIA is characterized by a different mode of presentation, disease course and outcome. The improvements in treatment of JIA in the last 2 decades, such as the early introduction of intraarticular corticosteroids, methotrexate and biologic agents, have dramatically upgraded the prognosis of the disease. If untreated, JIA may cause devastating results, such as disability from joint destruction, growth retardation, blindness from chronic iridocyclitis, and even multiple organ failure and death in systemic-onset JIA. The aim of treatment is the induction of remission and control the disease activity to minimize the pain and loss of function, and to maximize quality of life. JIA is a disease having a chronic course, which involves active and inactive cycles over the course of years. Recent studies showed that nearly half of the patients with JIA enter adulthood with their ongoing active disease. This review elucidates how recent advances have impacted diagnosis, pathogenesis and current treatment.

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Key words: Juvenile idiopathic arthritis; Classification; Etiopathogenesis; Treatment; Prognosis; Outcome

Core tip: Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatologic disease in children. Diagnosis of JIA is based on the history and physical examination findings. There is not a diagnostic laboratory test for JIA. Recent advances in the understanding of the immune system pathways involved in inflammation and self-tolerance have provided new targets for treatment of JIA. Biologic agents targeting key cytokines implicated in JIA, suh as tumor necrosis factor α, interleukin (IL)-1, and IL-6 as well as signaling molecules involved in the regulation of B-cell and T-cell lymphocyte responses, have promising results.

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JUVENILE IDIOPATHIC ARTHRITIS

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatologic disease in childhood, which represents a nonhomogeneous group of disorders that share the clinical manifestation of arthritis lasting at least 6 wk under the age of 16[1-7]. The exact diagnosis requires exclusion of other diseases that cause arthritis.

HISTORICAL BACKGROUND

The disease was used to be known as juvenile rheumatoid arthritis; however, this term was later changed as "juvenile idiopathic arthritis" to reflect the differences between childhood arthritis and adult forms of rheumatoid arthritis. In 1972, American College of Rheumatology (ACR) subgrouped the disease, which they called "juvenile rheumatoid arthritis", as systemic-onset, oligoarticular and polyarticular disease[8]. However, pediatric rheumatologists belonging to European League Against Rheumatism (EULAR) thought that ACR classification did not cover all the disease subtype. They named the disease as "juvenile chronic arthritis" and subgrouped the disease as oligoarticular, rheumatoid factor positive polyarticular, rheumatoid factor negative polyarticular, juvenile spondylarthropathy, juvenile ankylosing spondylitis, juvenile psoriatic arthritis and inflammatory bowel disease-related arthritis in 1977[9]. In order to set up an international classification system, the American and European rheumatologists came together in Santiago in 1995 and established "International League Against Rheumatism (ILAR)" criteria. They termed the disease as "juvenile idiopathic arthritis"[10]. ILAR criteria for classification of JIA was first revised in Durban in 1997[11] and finally revised in Edmonton in 2001[12]. There are several reasons for the admirable efforts of pediatric rheumatologists to establish an international classification for this disease. The primary aim is to define relatively homogeneous categories of idiopathic childhood arthritis based on predominant clinical and laboratory features that can be used for research purposes; as well as to give opportunity to pediatric rheumatologists all around the world to speak the same language.

JUVENILE IDIOPATHIC ARTHRITIS CLASSIFICATION

The ILAR classification divides JIA into 7 subtypes: oligoarticular JIA, rheumatoid factor (RF) positive polyarticular JIA, RF negative polyarticular JIA, systemic-onset JIA (sJIA), enthesitis-related arthritis (ERA), juvenile psoriatic arthritis (JPsA) and undifferentiated JIA (Table 1).

Table 1 Classification of subtypes of juvenile idiopathic arthritis[12]

Systemic arthritis
Definition: Arthritis in one or more joints with or preceded by fever of at least 2 wk' duration that is documented to be daily ("quotidian") for at least 3 d, and accompanied by one or more of the following:
1 Evanescent (non-fixed) erythematous rash
2 Generalized lymph node enlargement
3 Hepatomegaly and/or splenomegaly
4 Serositis
Exclusions: 1 to 4
Oligoarthritis
Definition: Arthritis affecting one to 4 joints during the first 6 mo of disease. Two subcategories are recognized:
1 Persistent oligoarthritis: Affecting not more than 4 joints throughout disease course
2 Extended oligoarthritis: Affecting a total of more than 4 joints after the 6 mo of oligoarticular disease
Exclusions: 1 to 5
Polyarthritis (Rheumatoid factor negative)
Definition: Arthritis affecting 5 or more joints during the first 6 mo of disease; a test fot RF is negative.
Exclusions: 1 to 5
Polyarthritis (Rheumatoid factor positive)
Definition: Arthritis affecting 5 or more joints during the first 6 mo of disease; 2 or more tests for RF at least 3 mo apart during the first 6 mo of disease are positive.
Exclusions: 1, 2, 3, 5
Psoriatic arthritis
Definition: Arthritis and psoriasis, or arthritis and at least two of the following:
1 Dactylitis
2 Nail pitting or onycholysis
3 Psoriasis in a first-degree relative
Exclusions: 2, 3, 4, 5
Enthesitis related arthritis
Definition: Arthritis and enthesitis, or arthritis or enthesitis with at least two of the following:
1 The presence or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain
2 HLA-B27 positivity
3 Onset of arthritis in a male over 6 yr of age
4 Acute (symptomatic) anterior uveitis
5 History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, reactive arthritis, or acute anterior uveitis in a first-degree relative
Exclusions 1, 4, 5
Undifferentiated arthritis
Definition: Arthritis that fulfills criteria in no category or in 2 or more of the above categories
Exclusion criteria for JIA
1 Psoriasis or a history of psoriasis in a first-degree relative
2 Arthritis in an HLA-B27 positive male following his 6th birthday
3 History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, reactive arthritis (Reiter's syndrome), or acute anterior uveitis in a first-degree relative
4 The presence of IgM rheumatoid factor on 2 or more occasions at least 3 mo apart
5 The presence of systemic JIA in the patient

JIA: Juvenile idiopathic arthritis; HLA: Human leukocyte antigen.

EPIDEMIOLOGY

The true frequency of JIA is not known. The incidence of chronic childhood arthritis varies from 5.3 to 19.6 per 100000 children per year in different population-based studies[13-18].

Reports from variable countries represent differences in the disease manifestation of JIA among different populations. For example, compared to reports from Western countries, remarkably different features of JIA

were found in Turkish children, which included higher frequency of ERA and higher prevalence among boys[19]. Besides, in European and North American populations the majority of patients were females with the predominance of oligoarticular JIA subset[17,20-22]. Saurenmann *et al*[23] studied the influence of ethnicity on the risk of developing JIA in a multiethnic community in Canada. In this study, children of European origin had a higher relative risk for developing any of the JIA subtypes except polyarticular RF-positive JIA, and were particularly more likely to develop the extended oligoarticular and psoriatic subtypes. A higher frequency of enthesitis-related JIA was observed among patients of Asian origin, while those of black origin or native North American origin were more likely to develop polyarticular RF-positive JIA in the same study[23].

ETIOPATHOGENESIS

The exact etiopathogenesis of JIA is still unknown. The interactions between genetic factors, environmental exposures, and immune mechanisms are thought to contribute to pathogenesis of the disease.

Genetic factors

Prahalad *et al*[24] reported that family members of JIA patients were at increased risk for other autoimmune diseases[24]. The most important issue in genetic predisposition is the existence of certain human leukocyte antigen (HLA) types. It is well-known that HLA-B27 is associated with enthesitis-related arthritis[25,26]. Besides, HLA DR4 was shown to be associated with systemic onset JIA and polyarticular JIA[27,28].

Environmental exposures

Infections are believed to be the most important environmental factors that contribute to development of JIA. The disease may develop during or after an infectious period. Clinical findings of the disease may appear following especially; enteric infections, Parvovirus B19, rubella, mumps, hepatitis B, Epstein-Barr virus, mycoplasma and chlamydia infections[29-35]. Emotional stress and trauma were suggested as other contributors. Particularly, oligoarticular JIA may develop by the trigger of immune system after trauma.

Immune mechanisms

Humoral and cell-mediated immunity contribute to the pathogenesis of JIA. Activated T helper lymphocytes are differentiated into Th1 and Th2 subtypes. T lymphocytes have a central role, releasing proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, IL-1 and favoring a Th1 response. Humoral immunity abnormalities include the increased presence of autoantibodies, especially antinuclear antibodies, increased serum immunoglobulins, the presence of circulating immune complexes, and complement activation[1-6].

Chronic inflammation of synovium is characterized by B lymphocyte infiltration and expansion. Macrophages and T-cell invasion are associated with the release of cytokines, which induce the proliferation of synovial cells. Scola *et al*[36] demonstrated that synovium contained mRNA for vascular endothelial growth factor and angiopoietin, as well as for their receptors, suggesting that induction of angiogenesis by products of lymphocytic infiltration may be involved in persistence of disease.

CLINICAL FINDINGS

Systemic-onset JIA

Systemic-onset JIA describes the form of the disease, which presents with intermittent fever, evanescent rash, and arthritis. It is known as the pediatric form of "adult-onset Still's disease". Systemic JIA is the most difficult subtype to diagnose for pediatric rheumatologists. Although arthritis lasting for at least 6 wk is necessary to establish the definite diagnosis, it may not exist in the early phase of the disease in some patients[3]. The exact diagnosis is suspected after exclusion of infections and malignancies as the initial differential diagnoses in majority of the patients.

Systemic-onset JIA equally affects males and females. The cases are distributed throughout the childhood. Articular manifestations are variable in this subtype. Arthralgias are common in the early course of disease and objective arthritis may not be prominent in this early stage. Any number of joints in any distribution such as wrists, knees, ankles, hands, hips, cervical spine and temporomandibular joints may be involved. Apart from oligoarticular and polyarticular JIA, the arthritis of systemic onset JIA may begin in the hips and may progress very rapidly. Micrognathia and cervical spine fusion are common manifestations of chronic systemic JIA. Patients with systemic-onset JIA require careful monitoring for the development of systemic complications, such as macrophage activation syndrome, pericarditis, and other forms of internal organ involvement, which are more common in this subtype of JIA than in any other form[3]. Macrophage activation syndrome is clinically characterized by persistent fever, hepatosplenomegaly, and lymphadenopathy, which is commonly accompanied by the laboratory evidence of cytopenia, decreased erythrocyte sedimentation rate, increased liver enzymes, high ferritin levels, and abnormalities of clotting profile[3].

Rheumatoid factor-negative polyarticular JIA

RF-negative polyarthritis describes the form of the disease, which presents arthritis that affects at least 5 joints during the first 6 mo of disease in the absence of IgM RF[11]. This form is probably the most heterogeneous subtype of JIA. A group of RF-negative polyarticular patients resemble early-onset oligoarticular juvenile idiopathic arthritis, by presenting asymmetric arthritis, early age at onset, female predominance, frequently positive ANA, increased risk of iridocyclitis, except for the number of joints affected in the first 6 mo of disease[3].

Another group resemble adult-onset RF-negative rheumatoid arthritis, by presenting symmetric synovitis of both large and small joints, onset in school age, increased erythrocyte sedimentation rate (ESR), and negative ANA[3]. Besides, a distinct small group of RF-negative polyarticular patients have dry synovitis, which shows negligible joint swelling but stiffness, flexion contractures, and normal or slightly raised ESR, which is often poorly responsive to treatment and cause destruction of joints[3].

Rheumatoid factor-positive polyarticular JIA

RF-positive polyarthritis describes the form of the disease, which presents arthritis that affects at least 5 joints during the first 6 mo of disease in the presence of IgM RF at least two occasions more than 3 mo apart[11]. This subgroup resembles the adult RF-positive rheumatoid arthritis and is particularly seen in adolescent girls[3]. The patients typically present with symmetric polyarthritis that affects the small joints of the hands and feet. The large joints, usually knees and ankles, may be affected at onset along with small joints. Rheumatoid nodules, which are rarely seen in other subsets of juvenile idiopathic arthritis, may be seen in the board of the forearm and elbow in some of the patients[3].

Oligoarticular JIA

Oligoarthritis describes the form of the disease, which presents arthritis that affects 4 or less joints during the first 6 mo of disease in the absence of psoriasis, a family history of psoriasis, HLA-B27-associated disease in a first-degree relative, and a positive rheumatoid factor[11]. The patients typically present with asymmetric arthritis, early onset (before 6 years of age), female predominance, high frequency of positive ANA, and high risk of iridocyclitis[3]. The ILAR classification subdivides oligoarticular JIA in 2 subsets: (1) persistent oligoarthritis, in which the disease is confined to four or fewer joints in the whole course of the disease; and (2) extended oligoarthritis, in which arthritis extends to more than four joints after the first 6 mo of disease. Oligoarthritis mainly affects the knees, followed by the ankles. In about half of the patients, only one joint is affected at disease onset. Acute-phase reactants are often normal or moderately increased; although in some cases ESR can be very high. Involvement of an upper limb joint and high sedimentation rate at onset have been identified as predictors for an evolution to the extended phenotype, which can take place in up to 50% of patients[37,38].

ANA is positive in about 70%-80% of oligoarticular JIA patients, and the presence of ANA increases the risk of iridocyclitis[39,40]. Iridocyclitis is a characteristic feature of oligoarthritis and affects about 30% of patients[39,40]. The onset of iridocyclitis is insidious and often entirely asymptomatic in contrast to painful acute iridocyclitis of enthesitis-related arthritis. One or both eyes may be affected and may be present before the onset of arthritis. Most patients develop iridocyclitis during the first 5 years of disease. The severity of ocular findings is not parallel to the clinical course of arthritis[39,40]. Since iridocyclitis is asymptomatic at onset, children with this disease should be screened periodically by slit-lamp examination according to the recommended frequencies by American Academy of Pediatrics[41].

Enthesitis-related JIA

Enthesitis-related arthritis (ERA) describes the form of the disease, which mainly affects male patients after the age of 6 years and is characterized by the association of enthesitis and arthritis. The asymmetric arthritis of the lower limbs is typical. Apart from other JIA subtypes, unilateral hip involvement is common at presentation. About half of patients have four or fewer joints affected throughout the entire course of the disease[3]. Small joints (dactylitis) as well as large joints may be involved. In some patients, arthritis could progress to affect the sacroiliac and spinal joints, thus producing the clinical picture of ankylosing spondylitis[3]. The most common sites of enthesitis are the calcaneal insertions of the Achilles tendon and plantar fascia. The course of the disease is often remitting and can be mild. However, presence of sacroiliitis, polyarticular involvement, high ESR, and ankle arthritis are associated with poor prognosis[42,43]. Most patients with ERA are HLA-B27 positive. This group of patients, especially if untreated, progress into ankylosing spondylitis[3].

Juvenile psoriatic arthritis

The diagnosis of juvenile psoriatic arthritis requires the presence of arthritis and a typical psoriatic rash at the same time. Or in the absence of typical rash, the patient with arthritis must fulfill at least 2 of the following: family history of psoriasis in a first-degree relative, dactylitis, and nail pitting or onycholysis[11]. The definition of juvenile psoriatic arthritis is controversial[44]. Some authors believe that this subtype does not represent a clearly defined entity because it has a heterogeneous clinical presentation[45]. A group of patients resemble early-onset oligoarticular juvenile idiopathic arthritis by presenting early onset, asymmetric oligoarthritis, and increased risk of iridocyclitis[46]. The main difference in this group of psoriatic arthritis is the greater frequency of dactylitis and involvement of both small and large joints than do children with oligoarthritis. Another group of juvenile psoriatic arthritis patients resemble ERA by presenting enthesitis with arthritis and/or sacroiliitis[46]. Depending on the case, the prognosis and treatment options appear to be similar to that for patients with oligoarticular JIA or ERA, but as the disease is very rare, few studies have been performed.

TREATMENT

If untreated, JIA may cause devastating results, such as disability from joint destruction, growth retardation, blindness from chronic iridocyclitis, and even multiple organ failure and death in systemic-onset JIA[43,47-49].

Table 2 American College of Rheumatology pediatric core set criteria for improvement in juvenile idiopathic arthritis[52]

Criteria	
1	Physician's global assessment of overall disease activity by VAS
2	Parent of patient global assessment of overall well-being by VAS
3	Functional ability
4	Number of joints with active arthritis
5	Number of joints with limited range of motion
6	Erythrocyte sedimentation rate
ACR Pediatric 30 response	A minimum of 30% improvement from baseline in a minimum of 3 out of 6 components, with a worsening by > 30% in no more than one component
ACR Pediatric 50 response	Requires 50% improvement in 3 out of 6 components with worsening of 30% in no more than one component
ACR Pediatric 70 response	Requires 70% improvement in 3 out of 6 components with worsening of 30% in no more than one component

VAS: Visual analogue scale 0-10 cm. ACR: American College of Rheumatology.

Table 3 Preliminary clinical criteria to define the inactive disease status and clinical remission in oligoarticular, polyarticular and systemic onset juvenile idiopathic arthritis[53,54] arthritis[52]

Criteria
1 No active synovitis
2 No fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to juvenile idiopathic arthritis
3 No active uveitis
4 Normal erythrocyte sedimentation rate and/or C-reactive protein
5 Physician's global assessment of disease activity indicates no active disease
6 Morning stiffness no more than 15 min
Inactive disease:
All criteria must be met
Clinical remission on medication:
Six continuous months of inactive disease on medication
Clinical remission off medication:
Twelve continuous months of inactive disease off all anti-arthritis and anti-uveitis medications

The aim of treatment is the induction of remission and control the disease activity to minimize the pain and loss of function, and to maximize quality of life. There is currently no exact cure for JIA. The treatment team of JIA should be multidisciplinary including pediatric rheumatologist, ophthalmologist, physiotherapist, psychiatrist and orthopedist.

JIA is a disease having a chronic course, which involves active and inactive cycles over the course of years[50]. Unfortunately, only a minority of patients may have sustained remission. Recent studies showed that nearly half of the patients with JIA enter adulthood with their ongoing active disease[43,51]. This means that many patients with JIA will be exposed to several periods of medications throughout their lifetimes.

In order to monitor the response to pharmacologic agents, the pediatric rheumatologists use the "pediatric core set", which identifies the level of ACR response (Table 2)[52].

The clinical criteria to define the inactive disease status and clinical remission were derived from studies including oligoarticular, polyarticular and systemic onset JIA (Table 3)[53,54]. However, there are still no studies defining the activity of ERA or juvenile psoriatic arthritis in the literature.

Since JIA is a heterogeneous disease, treatment algorithms differ between subtypes. The initial management of JIA has been relied on nonsteroidal anti-inflammatory drugs (NSAIDs) along with traditional disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate or sulphasalazine. Systemic corticosteroids or intraarticular corticosteroid injections may conjunct to therapy. Patients with polyarticular and systemic onset JIA are often unresponsive to traditional DMARDS and require chronic corticosteroid use to keep the disease under control or initiation of newer biologic therapies[50].

In order to provide guidance for treatment strategies in JIA, ACR published a guideline for treatment of JIA in 2011[55]. The ACR states that adherence to these guidelines and recommendations are voluntary, with the ultimate determination regarding their application are made by the physician in light of each patient's individual circumstances.

NSAIDs

NSAIDs have been the mainstay of therapy either alone or in conjunction with other drugs. The most widely used NSAIDs in children are non-selective ones, such as ibuprofen, indomethacin, tolmetine and naproxen. The patients with oligoarthritis may achieve clinical remission only with NSAIDs, while other subtypes require more potent and long acting anti-inflammatory therapies. Besides their several side effects, NSAIDs are generally well-tolerated by children. The most common side effects are abdominal pain and headache[56,57]. After the voluntarily withdrawal of rofecoxib from the market because of concerns about increased risk of heart attack and stroke associated with long-term use, selective COX-2 inhibitors could not find a strong place in the treatment of JIA by pediatric rheumatologists.

Corticosteroids

Corticosteroids are the most potent ones among anti-inflammatory drugs. However, they are limitedly used in JIA treatment because of their wide spectrum of side effects and their insufficiency in preventing the destructive joint damage. Corticosteroids are particularly used as bridge therapy for concise intervals while newly started DMARDs show their effects. There are no randomized-controlled trials about the initiation and tapering dosage of corticosteroids in the literature. Corticosteroids, either orally or parenteral, may lower the systemic clinical findings in systemic onset JIA, however; the destructive course in joints persists[58].

Intraarticular corticosteroid injection is an effective treatment choice in oligoarticular JIA, particularly in patients unresponsive to NSAIDs[58]. In the existence of leg length discrepancy, muscle atrophy and joint contracture;

Table 4 Biologic agents used in the treatment of juvenile idiopathic arthritis

Drug	Target	FDA approval for JIA	Administration	Dosage
Etanercept	TNF-α	Polyarticular JIA ages 2 yr and older	Subcutaneous injection	0.8 mg/kg per dose once a week, maximum 50 mg/dose
Adalimumab	TNF-α	Polyarticular JIA ages 4 yr and older	Subcutaneous injection	24 mg/m^2 every 2 wk, maximum 40 mg/dose
Infliximab	TNF-α	No	Intravenous infusion	6-10 mg/kg per dose week 0, 2 and 6; then every 4 to 8 wk
Anakinra	IL-1	No	Subcutaneous injection	1-2 mg/kg per day, maximum 100 mg/dose
Canakinumab	IL-1	Systemic-onset JIA ages 2 yr and older	Subcutaneous injection	2-4 mg/kg every 4 wk
Rilonacept	IL-1	No	Subcutaneous injection	2.2-4.4 mg/kg once a week
Abatacept	Cytotoxic T-lymphocyte-associated antigen 4	Polyarticular JIA ages 6 yr and older	Intravenous infusion	10 mg/kg week 0, 2 and 4; then every 4 wk, maximum 1000 mg/dose
Rituximab	CD20	No	Intravenous infusion	750 mg/m^2; two doses 2 wk apart or 375 mg/m^2; four doses, weekly × 4, maximum 1000 mg/dose
Tocilizumab	IL-6	Polyarticular JIA ages 2 yr and older	Intravenous infusion	8 -12 mg/kg every 2 wk

TNF-α: Tumor necrosis factor-alpha; IL-6: Interleukin-6; JIA: Juvenile idiopathic arthritis.

intraarticular corticosteroid injection may be performed without waiting the effect of NSAIDs in order not to lose time[59]. Besides, Sherry and colleagues demonstrated that early administration of intraarticular corticosteroid injection resulted in less leg length discrepancy in oligoarticular JIA when compared to NSAID use alone[60]. Triamcinolone hexacetonide is the first choice in the injection of large joints, while methylprednisolone acetate is preferred in small joints.

Disease-modifying anti-rheumatic drugs

DMARDs represent the main step of treatment of JIA. The analgesic and anti-inflammatory effects of these agents do not start immediately; they act their useful effects weeks-months later. Among these groups, only methotrexate and sulphasalazine were approved by Food and Drug Administration (FDA). After the studies showing the failure of D-penicillamine, hydroxychloroquine and azathioprine against placebo in the treatment of JIA, pediatric rheumatologists no longer use these drugs in the treatment schedules[61-63]. Leflunomide, thalidomide and cyclosporine A were the other DMARDs used in treatment of JIA. Cyclosporine A was only recommended in the treatment of macrophage activation syndrome, which is a complication of systemic-onset JIA. It is not an effective treatment option to prevent joint damage in any subgroup of JIA.

Biologic agents

Advances in the understanding of the immune system pathways involved in inflammation and self-tolerance have provided new targets for treatment of rheumatologic conditions. Biologic agents have been designed to target key cytokines implicated in JIA, including TNF-α, IL-1, and IL-6 as well as signaling molecules involved in the regulation of B-cell and T-cell lymphocyte responses[64-71]. Along with their promising results, these biologic agents may bring some severe risks such as susceptibility to infection and malignity, which require the careful monitoring of these agents. The biologic agents used in the treatment of JIA are listed in Table 4.

PROGNOSIS AND OUTCOME

The improvements in treatment of JIA in the last 2 decades, such as the early introduction of intraarticular corticosteroids, methotrexate, and biologic agents, have dramatically upgraded the prognosis of the disease. Most patients may continue active daily life. The comparison of earlier studies with those published in the last decade shows a decline in the frequency of patients with severe physical disability over years. However, many patients, particularly those with polyarticular disease, may have problems with active disease throughout adulthood, with sustained remission attained in a minority of patients[43,51]. Besides, patients with systemic-onset JIA tend to either respond completely to medical therapy or develop a severe polyarticular course that tends to be refractory to medical treatment, with disease persisting into adulthood[43,51]. Early hip or wrist involvement, symmetrical disease, the presence of RF, and prolonged active systemic disease have been associated with poor long-term outcomes[43,51]. Most children with oligoarticular disease may experience eventual permanent remission, although a small number progress to persisting polyarticular disease. It may be concluded that among the different JIA subtypes, the long-term outcome is best in persistent oligoarthritis and worst in RF-positive polyarthritis; the outcome of systemic arthritis is widely variable, perhaps reflecting the heterogeneity of this JIA subtype[72].

Several studies showed some psychosocial impairment among patients with JIA[73]. Patients with JIA were reported to have higher levels of depression, frustration, anxiety, fatigue and sleep disturbances when compared to healthy peers[74-76]. Therefore, careful psychosocial monitoring of children with JIA is essential to improve the quality of life.

There are concerns that the biologic agents may increase the risk of cancer among patients with JIA. However, lack of knowledge on the baseline risk of cancer in

this population has made this concern difficult to confirm. Based on a report of 48 children who developed malignancy while being treated with TNF-alpha antagonists, the FDA placed a boxed warning about malignancies on all TNF-alpha antagonists in 2009[77].

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Role of Th17 cells in the pathogenesis of rheumatoid arthritis

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Abstract

Since early description of CD4/CD8 T cell duality, continuous discovery of functional T lymphocyte subsets and their related cytokines constitutes major progress in our understanding of the immune response. T-lymphocyte derived lymphokines and environmental cytokines are essential for both innate and antigen-specific immune responses to a wide variety of agents. Following immune battle and aggression overcome, cytokines may return against neighbored cells/organs, causing pathogenic hypersensitivity reactions, including autoimmune diseases. Due to their cytokine production, $CD4^+$ T helper lymphocyte subsets may be considered as one the major players of the immune response. Among $CD4^+$ T cell subsets, the identification of interleukin-17-producing cells (Th17) led to better understanding of coordinated cytokine involvement during inflammatory reactions together with the subsequent clarification of complex interactions between these mediators. In this review, we discuss Th17 cell differentiation, functions, and the role of this cell subset during rheumatoid arthritis pathogenesis together with therapeutic strategies to control these cells.

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Key words: Interleukin-17-producing cells; $CD4^+$ T cells; Arthritis; Inflammation; Biotherapy

Core tip: identification of interleukin-17-producing cells (Th17) rise as important source of inflammatory cytokines, IL-17 in particular, with critical role during inflammatory diseases.In this paper, we reviewed the differentiation of these cells from naive lymphocytes, their role during inflammatory arthritis and therapeutic tools to control these cells.

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INTRODUCTION

Over 20 years ago, first description of $CD4^+$ T helper (Th) cell diversity (Th1/Th2) pointed to distinct cytokine production capacity of these cells[1]. As in B-cell differentiation, this diversity is dependent upon cytokines and antigens that trigger $CD4^+$ precursor cells through maturation into cells producing type 1 [interferon (IFN)-γ and interleukin (IL)-2] or type 2 (IL-4, IL-5, IL-13) lymphokines[1,2]. Two other subpopulations were subsequently identified: regulatory T cells (Treg) producing IL-10 and transforming growth factor (TGF)-β[3] and IL-17-producing $CD4^+$ T cells (Th17)[4-6]. These two subsets play a key role during tolerance and inflammatory responses[2,7]. Recent investigations added to our knowledge through precise definition of Th17 cells subpopulations and identification of additional effector subsets, such as Th22, Th9, and follicular helper (Tfh) cells[8-10]. The role of Th17 cells during development of autoimmune diseases has largely been described over the past few years[7,11]. The involvement of Th17/IL-17 pathway during the

pathogenesis of rheumatoid arthritis (RA)[12,13] led us to summarize, in this review, signals leading to the differentiation of Th17 cells, their cytokine secretion profile, *in vivo* correlation with other cytokines and possible targeting of IL-17 pathway as therapeutic approach in RA or other related diseases.

CD4$^+$ T LYMPHOCYTE DIVERSITY

Following antigen recognition on antigen presenting cells, naive Th0 lymphocytes go towards maturation into more specialized subsets depending upon various *in situ* factors including antigen itself, cellular and cytokinin environment (Figure 1). Differentiation into Th1 cells requires IL-12 induction of signal transducer and activator of transcription (STAT1/4) and subsequent induction of the transcription factor T-bet, with *in situ* IFN-γ as helper factor. These cells are essential for cell-mediated immune response to intracellular pathogens, cellular immunity and clonal lymphocyte multiplication through their ability to produce IL-2[1,2]. Maturation into Th2 cells seems to be dependent upon weaker T cell receptor signaling and IL-4-dependent or independent GATA-3 transcription factor induction. These Th2 lymphocytes help the development of humoral immunity together with limiting Th1 response[2]. Antibody response is also potentiated by Tfh lymphocytes, characterized by the expression of BCL6 transcription repressor and depends upon the *in situ* presence of IL-6 and IL-21[14] (Figure 1). Meanwhile, whether Tfh cells directly derive from Th0 cells or from other subsets is still unclear.

Th0-derived Th9 cells produce IL-9 and are polarized by IL-4-induced transcription factors including STAT6, GATA3 together with the presence of TGF-β, required for Smad activation and intracellular expression of PU.1 transcription factor[15]. Other cytokinin environments were shown to induce Th9 cell differentiation but the exact *in vivo* maturation pathway of these cells remains to be clarified. The presence of Th9 cells is associated with autoimmune and allergic diseases[15], but their definitive role remains unclear. Th22 and Treg cell differentiation is very close to Th17 cells and will be detailed below.

TH17 cell differentiation

If IL-17 (also known as IL-17A) was identified decades ago, the concept that Th17 cells represent an additional Th cell subset is recent[2,12]. Several cytokines are involved for optimal development of Th17 cells, including IL-6, TGF-β, IL-23, and IL-1β. This cell subset is characterized by the expression of orphan nuclear receptor RORγt together with the production of high levels of IL-17, IL-17F, IL-22, and IFN-γ[7,16-20]. Other factors can regulate differentiation of Th17 cells, such as prostaglandin E2, IL-21 (detailed in[20]). Since their identification, Th17 cells have been largely described for their critical role during the development of inflammation and autoimmunity[11]. Interestingly, Th22 cells were recently described as an additional effector subset during wound healing and tissue reparation[9,21]. These cells develop in response to tumor necrosis factor (TNF)-α and are characterized by the production of IL-22 but not IL-17[21].

Differentiation of Th0 towards Th17 *vs* Treg cells is another important checkpoint for immune response and tolerance and many studies addressed factors that may derive this differentiation step (Figure 2)[2,3,22,23]. Cells receiving strong antigenic signaling differentiate into Th17 cells while those receiving lower activation express the transcription factor Foxp3 and polarize into Treg cells[24]. In addition, development toward a Th17 or a Treg phenotype is dependent on the cytokinin environment, such as TGF-β concentration and presence of pro- *vs* anti-inflammatory cytokines[3,24].

Recently, hypoxia-inducible factor 1 (HIF1)-α and mammalian target of rapamycin (mTOR) were identified as factors positively regulating Th17 differentiation[22,23,25]. In turn, these pathways downregulate Treg cell polarization and constitute potent targets to upregulate Th17 cell development (see below). In addition to IL-17 and IL-17F, Th17 cells are potent producers of IL-22, IL-21, IL-6, TNF-α, CCL20 and IFN-γ, which cooperate together to define the duality of Th17 role: host defense *vs* inflammation[7,25]. The Th17/Treg ratio is now considered as a critical target for the modulation of inflammatory response and tolerance.

TH17 cell diversity

Th17 cells were recently shown to comprise distinct subsets defined by their functions and cytokine secretion profile[24,26]. In addition to initial "regulatory" Th17 cells with important role during immunity to extracellular pathogens[24,25], alternative "inflammatory" Th17 subsets have been identified during autoimmune diseases which require IL-23, IL-1β and IL-6 for their differentiation and were less dependent on TGF-β. Critical distinction between these populations is their cytokine production as regulatory Th17 cells secrete higher levels of IL-10 while inflammatory Th17 cells produce more IL-22, granulocyte macrophage colony-stimulating factor (GM-CSF) and IFN-γ which may explain their proinflammatory property. However, inflammatory Th17 cells seem to comprise various subpopulations that differ by their cytokine release and need further characterization.

IL-17

The characterization of IL-17 and its production by CD4$^+$ T cells distinct from Th1 and Th2 cells led to subsequent identification of Th17 cells[4,5] and better comprehension of T cell role during chronic inflammatory diseases. This cytokine is also produced by other adaptive immune cells including activated CD8$^+$ T cells under specific cytokinin conditions and are defined as Tc17 cells[27,28] with possible role during inflammatory reaction[29,30]. In addition, IL-17 secreting B lymphocytes were recently reported during immune response to parasite infection[31]. Many experimental inflammatory data

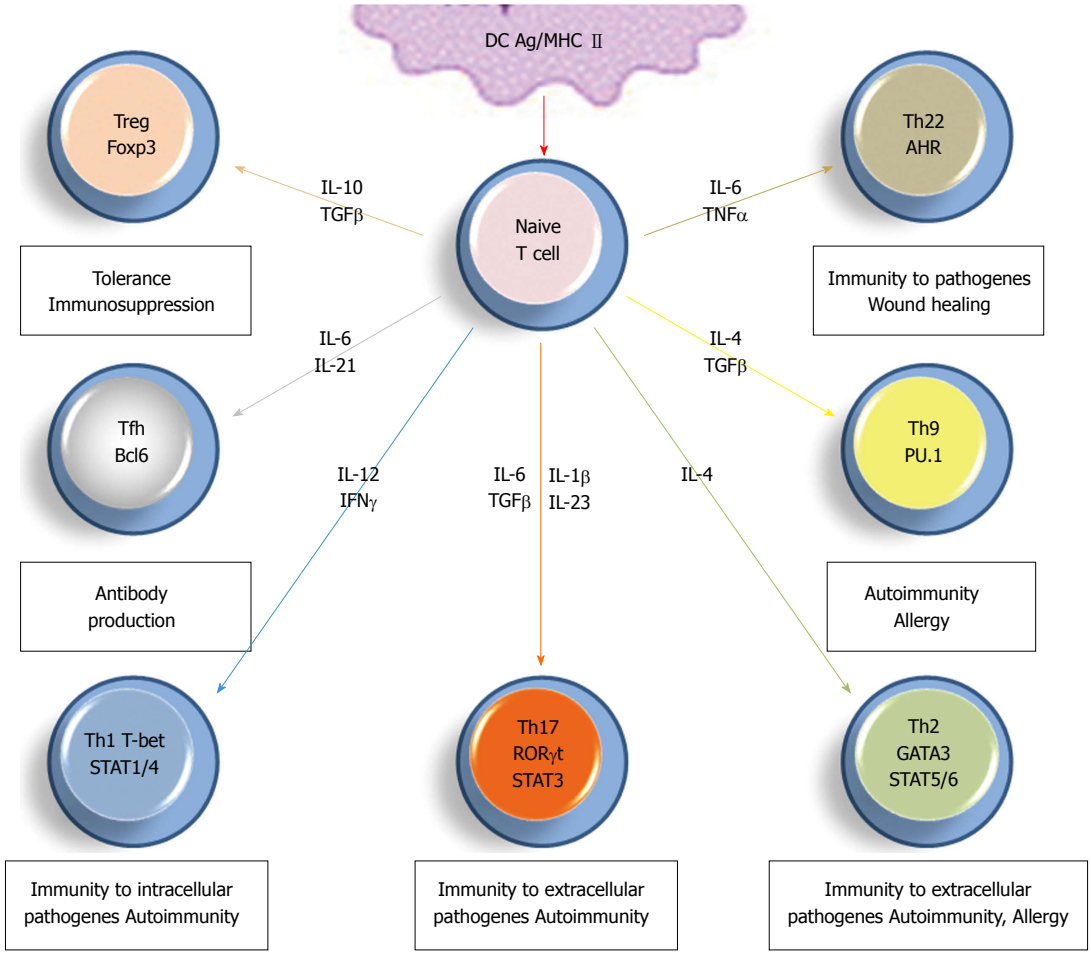

Figure 1 Diversity of CD4+ T helper cell subsets. STAT: Signal transducer and activator of transcription; IL: Interleukin; TGF: Transforming growth factor; TNF: Tumor necrosis factor; HIF1: Hypoxia-inducible factor 1.

enforced IL-17 role during autoimmune diseases[32,33]. Finally, several innate cell subsets also produce IL-17, such as γδT cells, innate lymphoid cells, mast cells and natural killer cells[34].

Th17 and rheumatoid arthritis

RA is chronic autoimmune disease affecting 1% of population and characterized by synovial inflammation correlated with leukocyte infiltration and overproduction of multiple inflammatory mediators[35]. Despite the presence of autoantibodies, chemokines, lipidic mediators and/or oxidative burst, decade use of anti-cytokine based therapeutics clearly enforced their role as key pathogenic factors during most steps of RA disease progression. Meanwhile, variations in patient response to available anti-RA therapeutics corroborate the fact that RA is heterogeneous and complex disease due to various immune pathways involved[36]. Although Th1 immunity during RA is established through multiple experimental data and patients' observations, accumulating evidence points out the contribution of Th17 cells and IL-17 during disease progression. Beside TNF-α and IL-1β, IL-17 seems to be a critical pathogenic factor in RA and is released by both Th17 and mast cells within inflamed joints[37,38]. Recruitment of Th17 *in situ* during RA appears to be facilitated by CCL20 expression by synoviocytes, the ligand of CCR6, a chemokine receptor known to be expressed by Th17 cells[38].

Compared to healthy individual, arthritic patients present significantly higher serum IL-17 and IL-22 levels, corroborating their clinical scores and cartilage degradation[39,40]. Accordingly, many mouse models of arthritis enforce Th17/IL-17 role during the pathogenesis of RA[41-43]. Interestingly, mice deficient in IL-1 receptor antagonist (IL-1Ra) have increased number of Th17 cells and spontaneous development of arthritis is abrogated in these animals following IL-17 neutralization[44,45]. Nevertheless, after the onset of arthritis, neutralization of IL-17 prevents disease worsening but does not reduce the arthritis score[44]. Beside IL-17, Th17 cells infiltrated the joints produce IL-22, IFN-γ and GM-CSF that are able to activate bone cells, synoviocytes, as well as cells infiltrated the joints such as macrophages. Activation of these cells results in the production of other pro-inflammatory cytokines, lysing enzymes and chemokine, resulting in increasing migration of immune cells *in situ*[46,47]. Activated macrophages secrete IL-6, IL-1β and IL-23, cytokines that potentiates Th17 cell development, thus enforcing chronic inflammatory response within RA inflammatory joints. Recent data in mice suggest that Th17 may also in-

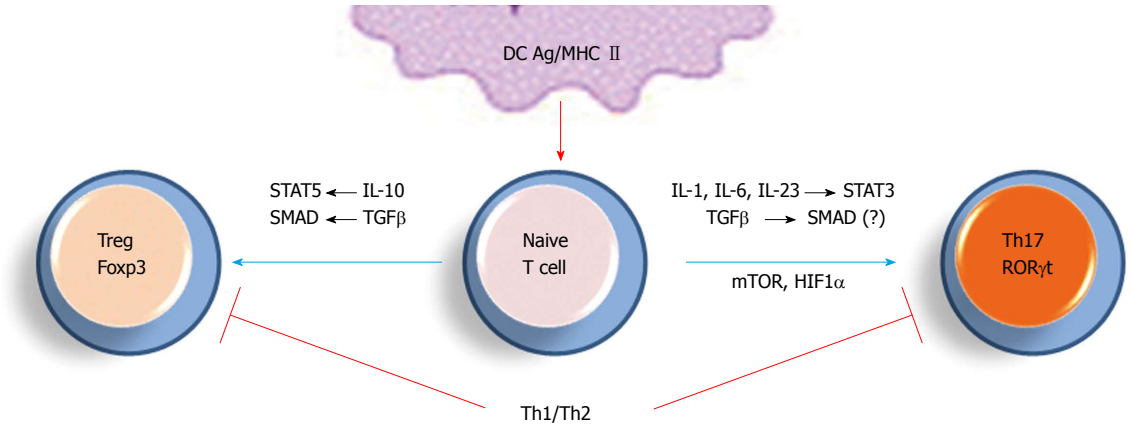

Figure 2 Differentiation of T helper 17/Treg cell subsets. STAT: Signal transducer and activator of transcription; IL: Interleukin; TGF: Transforming growth factor; TNF: Tumor necrosis factor; HIF1: Hypoxia-inducible factor 1.

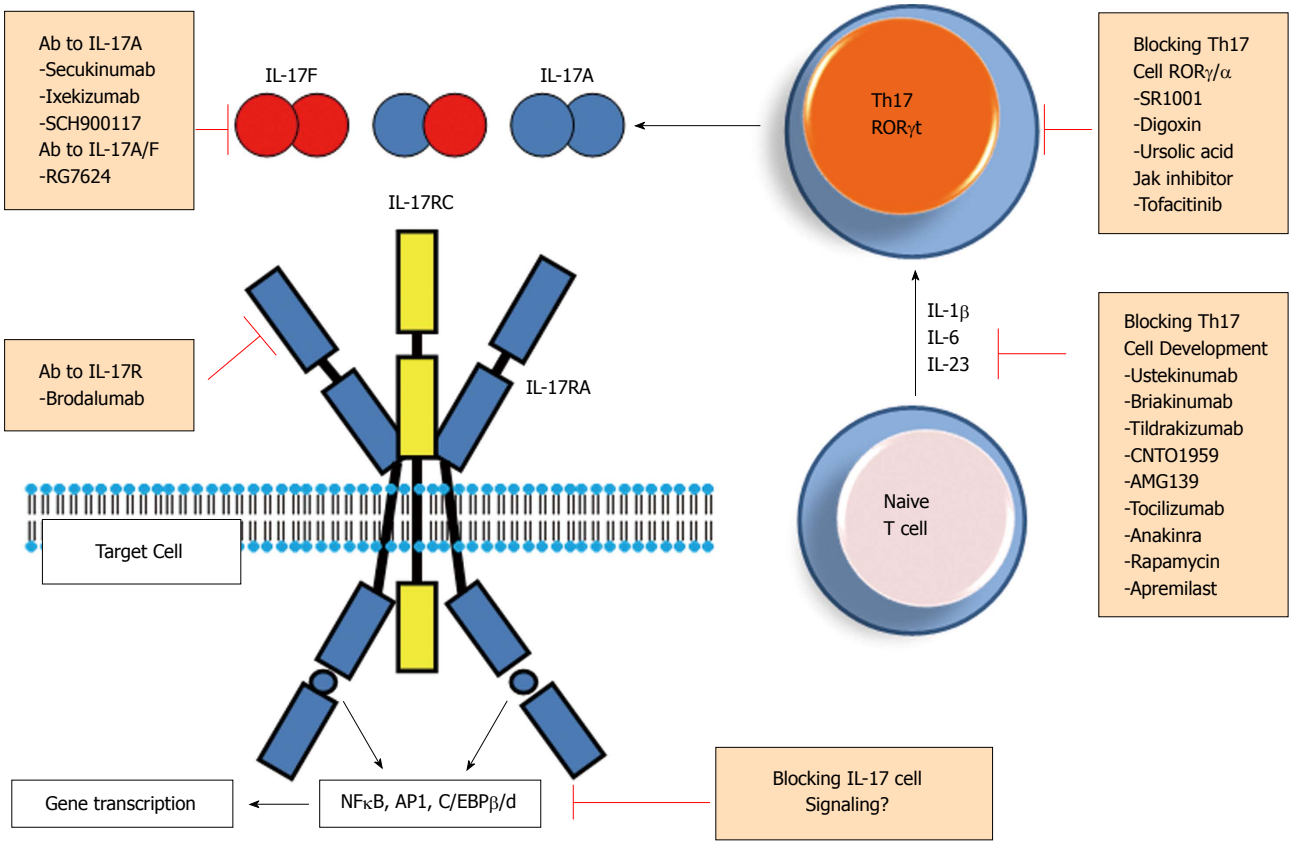

Figure 3 Strategies targeting the T helper 17 pathway. STAT: Signal transducer and activator of transcription; IL: Interleukin; TGF: Transforming growth factor; TNF: Tumor necrosis factor; HIF1: Hypoxia-inducible factor 1.

crease germinal center B cells to produce higher amounts of autoantibodies[48]. While γδT cells also contribute to IL-17 production, these cells seem to have minor role in RA[49,50]. Finally, while TNF-α would be involved during early RA progression, IL-17 would rather contribute to the chronicity and late pathogenic responses[51]. Together, data accumulated over the years suggest the involvement of the IL-17/Th17 pathway during all progression stages of autoimmune arthritis and related inflammation.

TH17/IL-17 AS THERAPEUTIC TARGET

Key role of IL-17/Th17 during the pathogenesis of RA and other major autoimmune inflammatory disorders, such as psoriasis, inflammatory bowel diseases and multiple sclerosis made this pathway a potent target for therapeutic intervention in these affections[52]. Various steps of Th17 cell differentiation or of the secretion of IL-17 and other Th17-related cytokines/factors are now being con-

sidered as possible targets to decrease Th17 cell related inflammatory response (Figure 3). Below, we summarize ongoing clinical and experimental attempts addressing this goal.

Blockade of Th17 cell differentiation

As IL-6, IL-23 and IL-1β are essential during Th17 polarization and functional maturation, it is believed that beneficial role of inhibitors of IL-1 (*e.g.*, Anakinra)[53] and IL-6 (*e.g.*, tocilizumab)[54] may be in part through their ability to target Th17 cell development (Figure 3). Monoclonal antibodies were developed to block p40 protein, a shared subunit between IL-23 and IL-12 (ustekinumab and briakinumab)[55,56]. Such antibodies inhibit biological activities of both IL-23 and IL-12 and hence prevent the development of Th1 and Th17 cells. Selective inhibition of IL-23 by anti-p19 neutralizing antibodies (such as Tildrakizumab, CNTO1959 and AMG139) is currently under various clinical trials (Figure 3)[56,57]. Involvement of phosphoinositide 3-kinase (PI3K)/AkT activation and subsequent mTOR pathway during optimal differentiation of Th17 cells may also be targeted by rapamycin and results in experimental autoimmune diseases are promising[58,59]. Another factor affecting Th17 cell differentiation from naive T cells is HIF-1α[22,23] but pharmaceutical inhibition of this factor appears to be more difficult, due to its' wide range of activities in normal cell physiology.

Blockade of Th17 cell functions

Several studies attempted to inhibit Th17 cell functions by blocking RORγt and/or RORα transcription factors[60-63] essential functional marker for these cells. Small synthetic ligands were identified and block specifically RORγt as shown with a RORγt-dependent galectin 4 -driven reporter system (Digoxin) http://www.nature.com.gate2.inist.fr/nrd/journal/v11/n10/full/nrd3794.html - B151[63], or inhibit both RORγt and RORα activities (SR1001)[61]. Ursolic acid also antagonizes RORγt activity[62] but the use of these molecules requires more *in vivo* experiments. More recently, tofactinib (Apremilast), a phosphodiesterase-4/JAK pathway inhibitor was shown to decrease IL-17 production from $CD4^+$ T cells[64]. Together, these findings pointed to various available targets to inhibit the differentiation/function of Th17 cells, upstream of IL-17 secretion.

Neutralizing IL-17

Various antibodies were generated to bind IL-17 and neutralize its activities, most are under clinical trials in RA or/and psoriatic patients including anti-IL-17A (Secukinumab, Ixekinumab, SCH900117, and RG4934)[52,56,65,66] or anti-IL-17A/F (RG7624) antibodies[67]. Another antibody was generated to inhibit IL-17 receptor (brodalumab)[52,67] and was recently shown to block both IL-17RA and IL-17RC subunits (Figure 3). Finally, as IL-17 synergizes with TNF-α to amplify the inflammatory response, inhibition of both cytokines is under clinical trial in RA[68]. Beside IL-17, a specific antibody to IL-22 was generated (Fezakinumab)[69] to inhibit this cytokine, but the trial was discontinued.

CONCLUSION

Among $CD4^+$ T lymphocytes, Th17 are important functional cells due to their role during infection and autoimmune diseases. Together with Th1 cells, their role during inflammatory pathogenic response in RA patients makes these cells an interesting target for the development of specific biotherapy or co-therapy to decrease both ongoing inflammatory response and disease chronicity.

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MINIREVIEWS

Hot topics in lupus pregnancy

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Abstract

Systemic lupus erythematosus (SLE) typically affects women in their childbearing age, who have the same fertility rates as the healthy population. The effect of pregnancy on the disease and the effect of SLE on pregnancy and the fetus are highly important issues for the attending physician. Whether lupus flares are more frequent during pregnancy remains controversial. Among the possible effects of SLE on pregnancy are a greater number of abortions, fetal loss, pre-term deliveries and perinatal mortality. The newborn may be affected by the onset of neonatal lupus erythematosus (neonatal LE), either as a skin or blood disease, or by the presence of congenital heart block. The frequent association between SLE and antiphospholipid syndrome represents another risk situation for the mother and the product of conception. Multiples drugs used in SLE patients should be evaluated. Those with teratogenic potential should be withdrawn before pregnancy, and when necessary, appropriate medications should be indicated to treat the mother without compromising the safety of the baby. In conclusion, pregnancies in lupus patients represent a challenge for the physician and must be closely followed up and treated if necessary, during all trimesters and in the puerperium period, to improve outcome.

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Key words: Systemic lupus erythematosus; Pregnancy; Pre-eclampsia; Lupus nephritis; Neonatal lupus erythematosus; Congenital heart block

Core tip: Systemic lupus erythematosus (SLE) typically affects women in their childbearing age. The effect of pregnancy on the disease and the effect of SLE on pregnancy and the fetus are highly important issues for the attending physician. The newborn may be affected by the onset of neonatal lupus erythematosus, either as a skin or blood disease, or by the presence of congenital heart block. The frequent association between SLE and antiphospholipid syndrome represents another risk situation. Optimization of pharmacological therapy before and during pregnancy should be done in order to reduce adverse events to the mother and the baby.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease that typically affects women in their childbearing age. The peak incidence of SLE occurs between the ages of 15 and 40 years, with an estimated female to male incidence of 9:1. Multiple reports have researched the impact of pregnancy on SLE with dissimilar results. While some authors hold that pregnancy is not a cause of disease exacerbations[1] other researchers have found exacerbations in 74% of cases[2]. There is no consensus on the management of pregnancy in SLE patients[3]; therefore pregnancy is a challenge for lupus patients and their physicians.

Although pregnancy in SLE currently has favorable

outcomes for the majority of women, the potential for maternal and fetal complications still exists[4]. Next we summarize the latest bibliographical data of SLE and pregnancy.

FERTILITY: IS FERTILITY IMPAIRED IN LUPUS PATIENTS?

Women with SLE have normal fertility, even if disease is active. However, fertility may be reduced in the presence of impaired renal function. Cyclophosphamide has previously been associated with ovarian failure. However, it has now been demonstrated that cumulative dose of cyclophosphamide on patients over 32 is the most important predictor of anovulation[5]. On the other hand, the use of azathioprine, cyclosporine and methotrexate is not associated with ovarian failure[6].

WHICH ARE THE BEST CHOICES FOR BIRTH CONTROL?

Patients with SLE should be encouraged to delay pregnancy until their disease is inactive for at least 6 mo, to avoid major complications and fetus exposure to potentially teratogenic medications.

Effective and safe birth control is essential to the care of these patients, especially in the group that have high risk of complications, where pregnancy is contraindicated (Table 1)[7].

Barrier methods are the most common form of contraception in these patients. However, they are not the most appropriate choice because they have a relatively high rate of failure compared to, the significantly lower failure rate of hormonal contraceptives. Oral contraceptives are safe for about two thirds of SLE patients, according to OC-SELENA trial which demonstrated that oral contraceptives do not appreciably increase the risk of a severe flare as compared with placebo[8]. The exception would be unstable lupus, hypercoagulability due to antiphospholipid antibodies or to nephrotic syndrome or past history of thrombosis. Although estrogen containing contraceptives are contraindicated for this risk group, other contraceptive methods can be recommended. Progestin-only methods, including the levonorgestrel-containing intrauterine devices (IUD) do not increase the risk of thrombosis in the general population.

The lowest failure rates are achieved with IUD, a method that offers effective, reversible contraception without increasing vascular risk. Besides, this method is considered safe for all women with SLE. Previous concerns about an increased risk of infection in immunocompromised patients appear unfounded[9].

HOW DOES PREGNANCY AFFECT LUPUS PATIENTS?

The influence of pregnancy on disease activity in women with SLE is variable. This variability may be due to the differences in study populations, the number of patients included in the series, the methodological differences in the study design, the existence or lack of a control group, and the definition of flare that is being used. In, general flares during pregnancy were observed in 40%-60% of patients in all trimesters and in the puerperium period and they were usually mild. Severe flares may occur in 15%-30% of the cases dependent on disease activity 6 to 12 mo prior to conception[10,11]. Several studies to date provide a consensus: pregnancy outcome is optimal when disease is in complete clinical remission for 6-12 mo[12,13]. Pregnancy should therefore be planned when SLE is in remission.

Disease flare can occur at any time during pregnancy and puerperium without any clear pattern. Minor organ manifestations are common, however major organs manifestations can also occur; the main risk is glomerulonephritis. Some clinical and laboratory features of normal pregnancy can simulate lupus activity (Table 2)[14].

Table 1 Contraindications to pregnancy in women with systemic lupus erythematosus

Severe pulmonary hypertension (estimated systolic PAP > 50 mmHg or symptomatic)
Severe restrictive lung disease (FVC < 1 L)
Heart failure
Chronic renal failure (Cr > 2.8 mg/dL)
Previous severe preeclampsia or HELLP syndrome despite therapy with aspirin and heparin
Stroke within the previous 6 mo
Severe lupus flare within the previous 6 mo

PAP: Pulmonary arterial pressure; FVC: Forced vital capacity.

FLARE INDEXES: WHICH MEASURES OF ACTIVITY ASSESSMENT COULD BE USED?

In the last 2 decades, several lupus activity scales have been adapted for pregnancy: Systemic Lupus Erythematosus in Pregnancy Activity Index (SLEPDAI), Modified Lupus Activity Measurement (m-SLAM) and Lupus Activity Index in Pregnancy (LAI-P). All of them take into account the influence of pregnancy on clinical manifestation and common biochemical tests. LAI-P also accounts for specific manifestations of Antiphospholipid Syndrome in order not to score them as due to SLE activity. SLEPDAI and LAI-P have a sensitivity of 93% and a specificity of 98%. However, daily assessment and management of individual pregnant women with lupus still relies on the clinical skills of attending physicians[15-18].

INFLUENCE OF SLE ON PREGNANCY: ARE OBSTETRIC COMPLICATIONS MORE COMMON IN LUPUS PREGNANCY?

Historically, lupus pregnancy was associated with a high

Table 2 Diferences between lupus flare and normal pregnancy

	Lupus flare	Normal pregnancy
Clinical features	Malar rash	Palmar and facial erythema
	Inflammatory arthritis	Arthralgia/Joint effusions
	Lymphadenopathy	Fatigue
	Fever	Hair loss
	Oral ulcerations	
	Raynaud phenomenon	
Laboratory features	ESR increased	ESR increased
	Leukopenia/lymphopenia	
	Anemia	Anemia due to hemodilution
	Complement levels drop	Complement levels increased
	dsDNA antibodies rising	dsDNA antibodies stable
	Hematuria	
	Proteinuria ⩾ 300 mg/dL	Proteinuria ⩽ 300 mg/dL

ESR: Erythrocyte sedimentation rate.

rate of obstetric and fetal complications. These include spontaneous abortion, late miscarriage, intrauterine growth retardation, preterm delivery and prematurity (Table 3). With the widespread use of careful monitoring and treatment schedules of these patients many improvements in both fetal and maternal pregnancy outcomes have occurred. The rates of fetal loss has declined significantly in pregnancies in patients with SLE, from 43% before 1975 to 17% in recent years, live birth rates of 85%-90% have been reported in recent studies[19].

Predictors of fetal loss include: active disease, lupus nephritis, presence of antiphospholipid antibodies (aPL), thrombocytopenia, proteinuria and hypertension[20]. In our series there were 61 live births, including one twin birth (85%), six still birth (8%) and 5 spontaneous abortions (7%)[21].

Preterm delivery is frequent and the strong predictors of preterm birth are lupus activity, hypertension and corticosteroid use[22].

In this study, forty six percent of 72 pregnancies ended in preterm deliveries. Significantly more women in the preterm delivery group were taking ⩾ 10 mg/d of prednisone compared to the full term delivery group[21].

Intrauterine growth retardation (IUGR) is reported in 10%-30% of pregnancies in patients with SLE. The risk is higher in presence of active disease and lupus nephritis[19].

ARE HYPERTENSIVE PREGNANCY COMPLICATIONS FREQUENT IN LUPUS PATIENTS?

Lupus pregnancy is associated with an increased risk of pre-eclampsia especially in the setting of lupus nephritis. Pre-eclampsia and eclampsia can both mimic lupus by presenting as edema, thrombocytopenia, hyperuricemia, anemia, hypertension, proteinuria, hematuria and seizures in eclampsia[23].

Table 3 Obstetric complications of systemic lupus erythematosus

Spontaneous abortion
Late miscarriage
Intrauterine growth retardation
Preterm delivery
Prematurity

Table 4 Differences between preeclampsia and active lupus nephritis

	Pre eclampsia	Lupus nephritis
Backgrounds	Chronic hypertension, antiphospholipid syndrome, diabetes mellitus, past preeclampsia	
Hypertension	Onset after 20 wk	Onset before 20 wk
Proteinuria	++	++
Urinary sediment	Inactive	Active (red cells, white cells and cellular casts)
Complement levels	Normal	↓↓
Anti DNA antibodies	Stable	↑↑
Uric acid levels	↑	
Urinary calcium excretion	↓	
Extrarenal manifestations		Present

Pre-eclampsia is more common in patients with antiphospholipid syndrome, lupus nephritis, diabetes mellitus or past pre-eclampsia[24].

Investigations of serum complements C3, anti DNA antibodies and urinary sediment can help to differentiate between both diseases (Table 4). In our study we have seen gestational hypertension in 15 pregnancies (21%) and preeclampsia in 8 pregnancies (11%). No eclampsia or HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) occurred[21].

LUPUS NEPHRITIS: HOW DOES LUPUS NEPHRITIS INFLUENCE PREGNANCY?

Approximately 50% of SLE patients will develop renal compromise[25] that may carry complication to the mother and/or fetus. High rates of pre-eclampsia are common in women with lupus nephritis ranging from 9% to 35%, specially in women diagnosed with lupus nephritis during pregnancy, unplanned pregnancies or with active disease before pregnancy[5]. Furthermore, the activity of lupus nephritis (LN) at conception has a high impact on premature birth[26] and fetal losses, which range between 25%-57% in women with active LN *vs* 8%-12.5% in those with stable renal disease[24]. Others potential pregnancy complications in patients with renal involvement are pre term delivery[27,28] and intrauterine growth retardation[26].

Table 5 Pregnancy morbidity of antiphospholipid syndrome

Classification criteria of APS in pregnancy
One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or (b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (1) eclampsia or severe preeclampsia defined according to standard definitions[11], or (2) recognized features of placental insufficiency-, or (c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.
Others obstetric manifestations of APS
Increased risks of intrauterine growth retardation
HELLP syndrome
Utero-placental insufficiency
Preeclampsia
Risk of thrombosis in the mother

APS: Antiphospholipid syndrome.

ANTIPHOSPHOLIPID SYNDROME: HOW CAN ANTIPHOSPHOLIPID SYNDROME COMPLICATE LUPUS PREGNANCY?

The antiphospholipid syndrome (APS) is defined by the presence of thrombosis and/or pregnancy morbidity in combination with the persistent presence of circulating aPL: lupus anticoagulant (LA), anticardiolipin antibodies (ACL) and/or anti-B2 glycoprotein I antibodies (anti-B2 GPI) in medium to high titers[29].

Several pregnancies morbidity are related to APS[30] (Table 5).

The treatment of pregnancies in women who are positive for aPL, depends on the presence of concomitant risk factors. In women positive for aPL but with no prior thrombotic event or pregnancy loss, low dose aspirin is recommended throughout the pregnancy. In those with aPL positivity and with recurrent early losses or one or more late fetal loss, without history of systemic thrombosis, aspirin in combination with prophylactic doses of heparin is indicated during pregnancy. Patients with prior systemic thrombosis in the presence of aPL should receive full therapeutic doses of heparin during pregnancy.

Low-molecular weight heparin (LMWH) has similar efficacy to unfractionated heparin with less adverse effects and easy monitoring. It requires more frequent dosing and twice-daily administration for all doses and it should be transitioned to unfractionated heparin near term to ensure fast reversal of anticoagulation at the time of delivery. Heparin treatment should be continued for 6 wk after delivery[31]. Corticosteroids, in combination with aspirin, were shown to have similar efficacy to heparin, but with higher maternal morbidity. IVIg was evaluated in two randomized trials and it was less efficient than the aspirin and heparin combination treatment in prevention of recurrent loss. Some women are refractory to aspirin and heparin combination and continue to have recurrent losses despite treatment. No consensus exists for the management of this group of patients. The addition of corticosteroids, IVIg, and plasmapheresis has been tried, but data are limited[19].

NEONATAL LUPUS ERYTHEMATOSUS: WHAT'S THE FREQUENCY OF NEONATAL LUPUS?

Neonatal lupus erythematosus (NLE) is a condition represented by cutaneous, cardiac, hepatic, hematologic, neurologic and splenic abnormalities, observed in newborn infants whose mothers have autoantibodies against Ro/SSA, La/SSB and, less frequently, U1-RNP[32].

These autoantibodies cross the placenta and cause neonatal lupus in 1% of newborns, and subsequent children have a 25% risk if the mother has had a previously affected baby[33].

All lupus patients contemplating pregnancy should have an anti-Ro/SSA, anti-La/SSB status determined, these antibodies are present in 30%-50% of SLE patients. The majority of the affected babies suffer a transient and often mild lupoid rash characterized as annular erythematous or polycystic plaques on the scalp, neck or face, typically periorbital; they resemble the lesions of subacute cutaneous lupus erythematosus. These lesions last for weeks or months and then resolve spontaneously consequent to the disappearance of maternal antibodies in the neonatal circulation[34].

Hepatobiliary involvement in NLE includes elevation of liver enzymes and/or conjugated hyperbilirubinemia. Some babies may have hepato-splenomegaly and less frequently, cholestatic hepatitis and hepatic failure.

Hemolytic anemia, thrombocytopenia and neutropenia may occur in the first 2 wk of life and they usually are asymptomatic. Hematologic symptoms disappear by the end of the second month. Other abnormalities like aseptic meningitis, myelopathy, hydrocephalus and macrocephaly have rarely been described[35].

The most common and well recognized cardiac manifestation of NLE is congenital heart block (CHB) that occurs in only 2% of infants born to mothers with anti-Ro/SSA or anti-La/SSB antibodies. The risk of CHB increases in infants born to mothers with a previous child having CHB and occurs in nearly 20% of the subsequent pregnancies.

This cardiac manifestation is irreversible and has significant mortality (approximately 20% in the neonatal period), and morbidity with more than 60% of the cases requiring permanent pacemakers and 10% developing severe cardiomyopathy[33].

The first fetal echocardiogram should be performed at 16 wk of gestation and then weekly for high risk infants (prior fetus with CHB) or every 2 wk in lower risk settings[23].

The goal of this monitoring would be to identify a biomarker of reversible injury such as PR interval prolongation > 150 ms, moderate/severe tricuspid regurgita-

Table 6 Medications use during systemic lupus erythematosus pregnancy

Medication	Permitted	Not allowed
Corticosteroids	Prednisolone, Dexamethasone, Betamethasone, Pulses methylprednisolone	
Antimalarials	Hydroxychloroquine	
Immunosuppressives	Cyclosporine Azathioprine Tacrolimus	Cyclophosphamide Methotrexate Leflunomide Mycophenolate mofetil
Anticoagulants	Unfractionated heparin Low-molecular-weight heparin	Warfarin Acenocumarol
Antiplatelets	Aspirin	Clopidogrel Ticlopidine
Non-steroidal anti-inflammatory drugs and analgesics	NSAIDs (until week 32) Acetaminophen	COX-2 inhibitors
Biologics		Rituximab Belimumab
Miscellaneous	Intravenous immunoglobulin	

NSAID: Non-steroidal non steroidal antiinflammatory drugs.

tion, and/or atrial echodensity[36].

Prenatal maintenance therapy with betamethasone or dexamethasone given to the mother starting early in pregnancy (before 16 wk' gestation), might reduce the risk of developing antibody-mediated congenital heart block in the offspring[37].

In contrast, recent data confirm the irreversibility of third degree block and progression of second to third degree block despite the use of dexamethasone. A potential benefit of this drug in reversing first or second degree block was observed in rare cases[38].

Moreover, in regard to the role of Toll- like receptors in the pathogenesis of cardiac-NLE, two studies, a case -control study and a multinational historical cohort study, suggest that hydroxychloroquine use in a mother with anti-SSA/Ro antibodies and a previous child with cardiac-NLE may reduce the risk of cardiac NLE recurrence in a subsequent pregnancy[39,40].

In our study, there was only one infant with CHB in an anti-Ro/SSA positive mother. Although intrauterine dexamethasone was administered, the infant did not survive[21].

WHICH DRUGS ARE ALLOWED IN LUPUS PREGNANCY?

SLE in women in their reproductive years may need potentially teratogenic drugs during pregnancy, puerperium and in the breastfeeding period, to control maternal disease and to ensure successful pregnancy outcome.

Because only those drugs considered safe can be studied in pregnant or lactating women, the number of controlled studies is small. Information on the safety of these drugs during these periods is derived only from experimental and preclinical studies (Table 6).

Non steroidal antiinflammatory drugs

Cox-1 and Cox-2 are involved in ovulation and implantation. Several case reports and small series have described transient infertility after treatment with suppress duplicate non steroidal antiinflammatory drugs (NSAID), such as indomethacin, diclofenac, piroxicam and naproxen. Also, some studies in animals and humans have shown that these drugs can inhibit the rupture of the luteinized follicle.

Non-selective Cox inhibitors are not teratogenic and can be continued during the first and second trimesters, but all NSAID (except aspirin add at less than 100 mg/d) after the 20th gestational week can cause constriction of the ductus arteriosus and impair fetal renal function. Consequently, they should be withdrawn at gestational week 32.

In relation to low dose aspirin (LDA) there is no consensus on when to stop it before delivery. Some advice cessation of the treatment one week before a planned delivery with epidural anesthesi. Other experts do not stop LDA in patients with APS.

Most NSAID are excreted in very small quantities into breast milk. The American Academy of Pediatrics considers ibuprofen, indomethacin, diclofenac, piroxicam, naproxen, mefenamic acid, tolmetin, and flufenamic acid to be compatible with breastfeeding.

At present there are no reliable data on selective Cox-2 inhibitors so they should be avoided in pregnancy[41].

Corticosteroids

11-β hydroxi steroid dehydrogenase in the placenta deactivates prednisone and prednisolone[42]. On the other hand fluorinated corticosteroids (betamethasone and dexamethasone), are less well metabolized by the placenta and should be avoided unless there is a need to induce fetal lung maturation or in an effort to treat in utero fetal heart block[36].

All corticosteroids increase the risk of premature rupture of membranes, hypertension, pre-eclampsia, diabetes mellitus and infection. Ideally, treatment should not exceed the recommended maximum dose of 15 mg a day[10].

An increased risk for clef palate has been associated with corticosteroid use during first trimester, although the risk is low[11].

Due to the side effects, prophylactic use of corticosteroids during pregnancy is not recommended[42].

Stress doses of hydrocortisone at delivery are recommended in patients on corticosteroids long term therapy.

Breast feeding is allowed with low to moderate doses of corticosteroids.

Antimalarial drugs

Hydroxychloroquine (HCQ) crosses the placenta with no significant difference in the mean concentration in maternal and cord blood. Discontinuation of this drug leads to increased risk of disease activity. The half-life of HCQ is approximately 2-3 mo, therefore pregnancies in which

this drug was stopped just prior to or after conception will still have exposure to it[42].

Other articles did not find an increase in congenital malformations or cardiac conduction disturbances in children exposed antenatally to this drug.

A recent multinational study showed that HCQ use in mothers with positive anti-SSA/Ro antibodies and a previous child with cardiac neonatal lupus may reduce the risk of cardiac neonatal lupus in a new pregnancy[40].

Breastfeeding is permitted with this drug.

Methotrexate

Methotrexate is contraindicated during pregnancy and in the breastfeeding period. There are known risks of fetal abnormalities in humans associated with methotrexate use. Therefore, all women of childbearing potential should be strongly counseled and advised to use reliable forms of contraception while taking methotrexate. If a woman inadvertently becomes pregnant, she should discontinue the medication immediately and be counseled concerning the risks of congenital abnormalities. Reports based on human cases describe a methotrexate embryopathy that includes growth deficiency, abnormalities in central nervous system, microcephaly, hypoplasia of skull bones, craniosynostosis, short limbs, hypodactyly, and syndactyly.

Therefore, this drug must be withdrawn three months before a planned pregnancy. Although the amount of methotrexate excreted in breast milk is low, it is unknown how this may affect a young infant and, therefore, methotrexate is considered to be unsafe during lactation[43,44].

Cyclophosphamide

Cyclophosphamide (CYC) is gonadotoxic in both women and men. Cryopreservation of sperm and sperm banking is the method of choice in men. Preservation of gonadal function in women is best done with a gonadotrophin-releasing hormone agonist. Its use in the first trimester of pregnancy is associated with fetal malformations and growth retardation, and suppression of fetal hematopoiesis if it is used during the second and third trimester[45].

This drug is excreted into breast milk. Suppression of hematopoiesis in breastfed infants has been reported, so it is contraindicated during breast feeding period. As MTX, it must be withdrawn 3 mo before a planned pregnancy[41].

Azathioprine

Azathioprine (AZA) does not adversely affect the fertility of both women and men. It can be used during pregnancy at a daily dose not exceeding 2 mg/kg per day because higher doses have risk of depressed hematopoiesis in infants.

Nursing is not recommended by the American Academy of Pediatrics[10].

Cyclosporin A

Successful use of Cyclosporin A (CsA) in pregnancy has been reported mainly in transplant recipients. It can be used in pregnancy at the lowest effective dose, with close control of maternal blood pressure and renal function during therapy. Breastfeeding is not recommend because small amounts of CsA are excreted in breast milk[41].

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is contraindicated during pregnancy. It is associated with craniofacial malformations, ocular anomalies, limbs abnormalities and renal, cardiovascular and nervous system malformations. The drug should be stopped at least 12 wk before a planned pregnancy. Breastfeeding is not allowed[10].

Leflunomide

Leflunomide is contraindicated during pregnancy and breastfeeding. It should be discontinued 2 years before conception or a washout procedure with cholestyramine should be used[10].

Tacrolimus

There is an increased risk of gestational diabetes and hypertension in women taking tacrolimus. It may be maintained during pregnancy at the lowest possible dose. Nursing is possible[5].

Intravenous immunoglobulin

It can be used in pregnancy and in the breastfeeding period, no fetal adverse effects have been reported[20].

Rituximab

Rituximab crosses the placenta. It is not clear whether preconceptional or first trimester exposure to rituximab would expose the fetus to any risk. However, second and third trimester exposure causes B-cell depletion in the fetus with unknown long-term effects in the child. With a maximal elimination half-life of 36 d, discontinuation of rituximab for a period five times the half-life (6 mo) before conception may be adequate to not expose the baby to deleterious effects[46].

Belimumab

At present there are no data about the safety of Belimumab use during pregnancy.

Thromboprophylaxis

Low-molecular-weight heparin (LMWH) and unfractionated heparin are safe in pregnancy and are considered in pregnant patients with lupus nephritis with serum albumin $\leqslant$ 30 g/L or with proteinuria $\geqslant$ 3g/24 h[5].

ANTIHYPERTENSIVE DRUG

Arterial hypertension can develop during pregnancy, or a known history of hypertension pre-pregnancy can be present in a SLE patient with renal involvement.

Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), are popular for the

treatment of hypertension in SLE patients and are widely used because they antiproteinuric effects. However, ACE inhibitors and ARBs should be stopped immediately after pregnancy is confirmed because these medications are associated with renal agenesis and fetal demise.

All antihypertensive agents cross the placental barrier and are present in varying concentrations in the fetal circulation.

Methyldopa is the first line agent for treating hypertension in pregnancy. It has been the most frequently assessed antihypertensive in randomized trials and has the longest safety track record.

Beta Adrenergic Blockers, as Labetalol or Metoprolol, should be used when monotherapy with Methyldopa is insufficient or when women are unable to tolerate Methyldopa.

Calcium channel blockers, such as nifedipine or isradipine are second line agents; they can be administered in hypertensive emergencies or in hypertension caused by pre-eclampsia.

Besides, nifedipine may be considered in patients with severe Raynaud phenomenon.

Diuretics should be avoided for treatment of hypertension because they may decrease placental blood flow.

Post partum hypertension is common. Blood pressure typically rises after delivery over the first five days. Most antihypertensive agents used in routine practice are compatible with breastfeeding, but safety data for doxazosin, amlodipine, and ARBs are lacking.

Methyldopa should be avoided post partum because of the risk of postnatal depression.

The first line agent is labetalol, plus nifedipine or an ACE inhibitor if another agent is required. Diuretics are usually avoided if the woman wishes to breastfeed because of increased thirst[47,48].

CONCLUSION

Pregnancy in a lupus patient continues to be a mayor challenge for the physician and it should be considered as a high-risk situation. However, if it is planned when the disease is stable and under close supervision by a multidisciplinary team, we could expect a good outcome for the mother and her baby.

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MINIREVIEWS

Lymphedema and rheumatological disorders

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Abstract

In the literature, although the prevalence of lymphedema is low in inflammatory rheumatological diseases, rigorous approaches to diagnosis and treatment have led to significant improvement in patients' quality of life. Lymphedema is observed more frequently in patients with rheumatoid arthritis with respect to case presentations, but it is also observed in psoriatic arthritis, ankylosing spondylitis, systemic sclerosis, and childhood inflammatory rheumatological diseases. Other rheumatological diseases and tumor-related secondary causes should also be kept in mind in the diagnosis of lymphedema. Complex decongestive therapy-skin care, manual lymph drainage, compression and exercise are the primary treatment approaches. Both basic drugs and tumor necrosis factor-α inhibitors have been tried in addition to complex decongestive physiotherapy programs. However, the success of alternative medical treatments is controversial in the literature. It may be useful to include the disease in post-diagnosis complex decongestive physiotherapy program and to use the drugs mentioned in the literature. However, more data are needed to reach conclusive results.

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Key words: Lymphedema; Rheumatoid arthritis; Psoriatic arthritis; Ankylosing spondylitis; Systemic sclerosis

Core tip: Coexistence of inflammatory rheumatological diseases and lymphedema is an under-recognized subject. Drawing clinicians' attention to this issue is important for improving patients' quality of life. In patients with inflammatory rheumatological disease and lymphedema, although the complex decongestive therapy method is the primary approach, tumor necrosis factor-α inhibitors mentioned in the literature, whose efficacy requires explanation, may also be tried.

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INTRODUCTION

Lymphedema (LE) may be defined as an accumulation of protein-rich interstitial liquid as a result of congenital or acquired disruption of the lymphatic circulation. It occurs as a consequence of increased lymphatic load and/or reduced lymphatic transport. LE is a chronic, progressive condition that impairs mobility and joint movement: the swollen areas increase in size and weight, often causing postural alterations and pain as the individual struggles to perform daily living activities. It eventually leads to impairment of physical and psychosocial functions, accompanied by a change in body image and thus affects quality of life[1].

In the literature, although the coexistence of inflammatory rheumatological diseases and lymphedema is rare, attention is drawn to the difficulties in its diagnosis and treatment. The most frequent inflammatory rheumatological disease that accompanies lymphedema is reported to be rheumatoid arthritis (RA)[2-11]. However, other cases have been reported where LE is accompanied by psoriatic arthritis (PsA)[4,12-15], ankylosing spondylitis (AS)[16], systemic sclerosis (SS)[17,18] and childhood inflammatory rheumatologic diseases[19-21], in addition to RA[22].

PATHOGENESIS

Lymphedema associated with RA was first described by Kalliomaki and Vastamaki in 1968[12], and it appears to be a relatively rare complication of RA. Several reports indicate that lymphedema as a complication of RA is not restricted to seropositive arthritis, but also occurs in other forms of inflammatory arthropathy[12,16,18,20]. Few cases of lymphedema associated with PsA have been described[12-15]. As in patients with RA and lymphedema, the etiology of edema associated with PsA remains puzzling.

Associated arterial and venous disease can be found in approximately half of patients in SS[17,18]. Leg ulcers have been described in SS, often revealing a multifactorial etiology. In scleroderma, skin biopsies showed fibrosis of the lower two-thirds of the dermis and the subcutaneous fibrous trabeculae. Its presence in sclerodermatous skin has also been described and may partially account for the early edematous phase of the disease. One study using fluorescence microlymphography (which allows visualization of the superficial cutaneous lymphatic capillary network) found that lymphedema in SS could, at least in part, be a result of lymphatic microangiopathy[18]. By contrast, significant chronic lymphedema, leading to the development of elephantiasis nostras verrucosa, is extremely rare[18].

In those cases of PsA and lymphedema in which lymphatic function was examined, quantitative lymphoscintigraphy disclosed abnormal lymphatic drainage of the affected limb. There are several reports that suggest lymphatic vessels are altered in both inflammatory arthritis and psoriasis. No lymphatic vessel staining in the manner of normal lymphatics was found in rheumatoid arthritic synovium. Based on morphological examination of psoriasis skin lesions, several authors have described abnormalities of the lymphatics, such as dilatation, lack of fenestration or dermal distal blind loops. Other authors were unable to confirm such findings. Patients with chronic plaque psoriasis revealed a greater network of lymphatics in perilesional skin compared with lesional skin, as demonstrated by fluorescence microlymphography[12]. To determine whether inflammatory arthritis itself leads to impaired lymphatic function, Kiely *et al*[23] examined 10 patients with inflammatory arthritis (RA or PsA) and edema and 18 patients with inflammatory arthritis without edema using lymphoscintigraphy. Inflammatory arthritis alone was not associated with impaired lymphatic flow, suggesting the presence of additional unrelated factors for the development of lymphedema in patients with inflammatory arthropathy.

We are unaware of any studies addressing the macromolecular composition of the interstitial fluid from swollen extremities of patients with lymphedema and PsA. In RA, conflicting data have been reported regarding the protein content of the edematous fluid. In at least some of these reports, protein levels of the interstitial fluid of patients with edema and RA were compared with the protein contents of the interstitial fluid of patients with congestive heart failure and edema. Future studies on directly testable microvascular parameters, such as interstitial fluid pressure, interstitial colloid osmotic pressure and interstitial plasma protein content in swollen limbs of patients with PsA, as well as the careful design of proper controls may shed more light on the pathophysiology of PsA and lymphedema[12].

Some cases have been reported of lymphedema development in patients with AS[16] and juvenile rheumatoid/idiopathic arthritis[19-21].

In addition, scleroderma-like skin changes during lymphedema development induced by taxanes (docetaxel) treatment have been observed[17]. Improvement was reported shortly after the discontinuation of medication. Histological examination of skin biopsies showed diffuse infiltration of histiocytes and macrophages in the superficial dermis associated with lymphangiectasia without vasculitis. Although its mechanism is unknown, an autoimmune or paraneoplastic origin has been considered[17]. It is difficult to comment on the relationship between docetaxel and early lymphedema-associated scleroderma-like skin changes, yet it should be taken into consideration.

The etiology is unknown in inflammatory arthropathy. This uncertainty in etiology and pathogenesis may be explained by the lack of data on lymphedema in inflammatory rheumatological pathologies. The available data are based on limited information mostly from case presentations; therefore, it is limited mostly to clinical practice. Several hypotheses have been suggested for its pathogenesis in patients with inflammatory rheumatological disease, such as lymphangitis, lymphatic obstruction caused by fibrin, capillary permeability increase, fluid retention associated with immobilization, venous obstruction, lymph vessel obstruction, lymphatic obstruction associated with coagulation system abnormalities, abnormal fibrinolysis and potential fibrosis of the superficial lymph vessels[2-10]. Some cases presented with an increase in plasma fibrinogen degradation products or hypoalbuminemia[9]. Diffusion of inflammatory processes into lymphatic vessels is thought to be a possible cause of chronic lymphangitis and edema[24].

In any of these diseases, there was no correlation with positivity for the rheumatoid factor or with the severity of the disease[9-12].

CLINIC PRESENTATION AND DIAGNOSIS

The duration of lymphedema after the onset of RA varied from the simultaneous onset to 37 years (mean duration: 7.7 years). The most affected sites were the upper limbs, especially the hands. Only six cases showed lower limb involvement. Positivity for the rheumatoid factor was noted in 61.3% of the patients[9]. The majority of previous reports described the lymphedema as persistent. In some patients with RA, an extension of the inflammatory process to include lymphatic vessels may cause the chronic lymphangitis responsible for the

edema[6]. This would interfere with normal lymph flow and lead to local tissue edema. It is possible that some treatments may reverse lymphangitis before permanent damage to structure or function can occur[15]. In PsA, lymphedema exclusively affects the upper limbs, with the right more frequently affected than the left. In most of these patients the metacarpophalangeal and interphalangeal joints, followed by the wrist and carpal joints, were involved[12].

The diagnosis is clinical, as one or more limbs have been observed to undergo painless swelling. Ultrasonography, Doppler ultrasonography, magnetic resonance imaging (MRI), lymphoscintigraphy and histopathological examination are used to confirm the diagnosis of lymphedema[13,14]. Ultrasonography helps the diagnosis by imaging of the lymph nodes, diagnosing secondary lymphostatic edema (tumor, metastasis), distinguishing adipose tissue (distinguishing lipedema), and imaging of joint and/or soft tissue (Baker's cyst rupture). Doppler ultrasonography is an illuminating tool, especially in terms of venous insufficiency and thrombosis. Computed tomography and magnetic resonance imaging are very important in the diagnosis of tumors and metastases. In addition, MRI may be used to identify and determine the location of circumscribed fluid accumulations. These analyses are particularly helpful for differential diagnosis. Qualitative lymphoscintigraphy discloses abnormal lymphatic drainage of the affected limb[11].

Lymphedema due to RA or PsA must be distinguished from a number of other conditions, including remitting seronegative symmetrical synovitis with pitting edema syndrome. Distal extremity swelling with pitting edema has also been described in polymyalgia rheumatica and giant cell arteritis. Primary lymphedema usually affects women, has an earlier onset and involves the lower extremities in the majority of cases. All forms of secondary lymphedema, including those caused by lymphatic compression or obstruction by tumors, infections (*e.g.*, filariasis) or artifacts (SecreÂtan's syndrome and Charcot's oedeme bleu) must be distinguished from lymphedema associated with PsA[2-10,12]. In differential diagnosis, venous stasis, deep vein thrombosis, congestive heart failure, vasculitis, hypoalbuminemia and nephrotic syndrome should be considered[23,25].

Rarely, rheumatological disorders can cause chronic lower extremity swelling in children. Lymphedema and other conditions are ruled out by lymphoscintigraphy and magnetic resonance imaging. If there is no history of trauma and no other potential cause of the swelling can be identified, children are referred for rheumatological consultation. A patient thought to have a condition other than lymphedema on history and physical examination usually undergoes MRI evaluation to confirm the suspected diagnosis and/or to define the extent of the disease. MRI also is commonly used as a secondary imaging study if lymphoscintigraphy is negative. Correct diagnosis is important, because the natural history and management of lymphedema are very different to other lower extremity diseases in children[19-21].

TREATMENT

Treatment for lymphedema is inefficient and is usually limited to symptomatic treatment. The intervention for lymphedema-complex decongestive therapy-CDT-consists of four main components: skin care, manual lymph drainage, compression and exercise, and remains the cornerstone of therapy in all patients suffering from lymphedema associated with inflammatory rheumatic diseases[1]. Skin care (moisturizing the skin; protection from infection and trauma), manual lymph drainage, short stretch bandage technique and exercise steps are applied in an intensive treatment program until the difference in arm circumference is reduced in patients. Manual lymph drainage is a sensitive massage technique applied using special techniques for lymph circulation stimulation, taking body lymph circulation into consideration. The person who applies this technique must receive special training. Short stretch bandage compression, as the name suggests, is a multi-layered bandage applied using short stretch bandage materials and special techniques. When the difference in arm circumference is reduced and when this decrease is stabilized, we proceed with maintenance treatment and the patient is given a special lymphedema compression garment. Skin care, manual lymph drainage and exercise steps are also continued during this process. Patient education (diet and protection) is one of the most important treatment steps. Although it is a challenging treatment, patient compliance to this treatment is generally favorable.

In most cases of RA or PsA, introduction of disease modifying drugs does not improve the edema. In some cases, intra-articular injection of corticosteroids into the joint proximal to the swollen area resulted in prompt resolution of the edema, whereas in other patients, intra-articular corticosteroids had little effect[12].

The literature includes publications indicating that tumor necrosis factor (TNF)-α inhibitory drugs used in the treatment of rheumatological diseases may be effective for lymphedema treatment[15,16,26]. Ostrov[11] reported that etanercept dramatically reduced the lymphedema in a patient with RA. Almodóvar *et al*[16] described the first case of a patient diagnosed with ankylosing spondylitis that was complicated with lymphedema who, after receiving treatment with infliximab, showed complete disappearance of the lymphedema. The mechanism by which TNF-α inhibitor therapy acts on lymphedema is not known, but the drugs are believed to act on the inflammatory response of the lymphatic vessels. Assuming that synovitis causes adjacent lymphatic inflammation and, ultimately, fibrosis, maximal control of active rheumatoid synovitis could abrogate this reaction. Therefore, TNF-α inhibitor therapy can be considered for the treatment of extra-articular manifestations in rheumatic diseases, such as lymphedema.

On the other hand, the temporal relationship suggest-

ed a link between the initiation of TNF-α inhibitors and the development of lymphedema[25]. Many authors have reported paradoxical effects of TNF-α inhibitors, such as new onset or exacerbation of psoriasis or psoriasiform skins. This is a class effect, as it has been associated with all the three TNF-α inhibitors. In some cases, the lesions completely resolved after the drug was discontinued, but returned on re-challenge either with the same agent or a different TNF-α inhibitor, whereas, in other cases, the lesions subsided after topical treatment. The underlying mechanism for these paradoxical effects is not well understood. Anti-TNF-α-TNF-α immune complexes may be deposited in small capillaries, triggering a type Ⅲ hypersensitivity reaction. Another theory is that TNF-α blockade may interfere with the maintenance of tolerance by inhibiting apoptosis[25]. Lymphedema after initiation of TNF-α inhibitors remains a diagnosis of exclusion. A temporal relationship points toward a possible linkage; however, the actual pathophysiology remains unclear. In inflammatory rheumatological conditions, disease modifying drugs are not very effective; however, some favorable results have been reported for TNF-α inhibitors. These data, on the other hand, are very confusing. Based on current data, it is not possible to say that TNF-α inhibitors are effective or ineffective. When this kind of case is encountered, complex decongestive therapy (CDT) treatment can be initiated and other drugs may be tried in addition to the principal treatment, depending on the patient's response. There is no sufficient explanation of how CDT works in these case presentations; therefore, it is difficult to say if the treatment response is associated with CDT or with the drugs. It may be beneficial to provide more explanatory information on treatment in future case presentations.

In a conclusion, lymphedema may be observed, although rarely, in inflammatory rheumatological diseases. The pathology of this occurrence, which presents as extra-articular involvement of the disease, is not fully established; therefore, the likelihood of successful treatment is low. The efficacy of TNF-α inhibitor drugs reported in case studies also seems to be contradictory. Based on these results, it may be useful to include the disease in post-diagnosis complex decongestive treatment program and to use the drugs mentioned in the literature. However, more data are needed to reach conclusive results.

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Dysphagia in rheumatological disorders

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Abstract

Dysphagia can be seen in rheumatological diseases. Due to life-threatening complications, early diagnosis and treatment of dysphagia is important. However, sufficient data is not available for the diagnosis and treatment of dysphagia especially in the group of rheumatological diseases. In this paper, the presentation of dysphagia in rheumatological diseases will be reviewed.

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Key words: Dysphagia; Swallowing; Inflammatory rheumatological disease; Non-inflammatory rheumatological disease; Rehabilitation

Core tip: Although dysphagia symptoms are common in rheumatological diseases, these conditions are often overlooked. Both the diagnosis and treatment of them is an issue to be considered carefully as they will lead to an apparent improvement in the patient's quality of life. Health professionals should be made aware of this issue.

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INTRODUCTION

Swallowing is a complex function enabling forwarding of the material and saliva in the mouth into the stomach. Dysphagia is associated with impaired swallowing function and can be defined as the difficulty or failure in conveying foods or liquids from the mouth to the stomach. Swallowing problems may develop in connection with a large variety of diseases in all age groups from a newborn to an elderly[1]. Swallowing problems are encountered in inflammatory or non-inflammatory rheumatological diseases due to the disease itself or the treatment administered[1,2]. Aspiration, pneumonia, malnutrition, increased mortality, prolonged hospitalization, advanced disability, declined quality of life and isolation from the society may accompany the difficulty in swallowing. Early diagnosis and treatment of dysphagia is important due to such life-threatening complications. In this paper, the presentation of dysphagia in rheumatological diseases will be reviewed.

INFLAMMATORY RHEUMATICAL DISEASES

Scleroderma

It has been reported that 87% of patients with progressive systemic sclerosis complained from dysphagia. Even during the first examination, 60% of patients have complained about dysphagia[3-6]. Early diagnosis and treatment of dysphagia in this patient group is important in terms of patient care.

Perioral skin and temporomandibular joint limitation may lead to difficulty in opening the mouth and glossal papillae, and mucous membrane atrophy to impaired taste and eating problems, which in turn results in serious weight loss. Esophagus dysfunction in this disease, on the other hand, has a complex, multifactorial characteristic which is variable according to the stage of the disease[3-6].

Impairment of the motor function of the esophagus has been linked to more severe reflux and possible recurrent episodes of micro aspiration and lung damage. The

degree of mucosal damage diagnosed by endoscopy was also worse in patients with aperistalsis. In the scleroderma patients, abnormal reflux was found in 91%. Presence of chronic reflux may result in Barrett's metaplasia, chronic pharyngitis-laryngitis and aspiration pneumonia in these patients. It may also lead to muscle atrophy and fibrosis in 2/3 portion of the lower esophagus as well as to motility damage[7]. The findings obtained include decreased resting lower esophageal sphincter (LES) pressure, impaired LES relaxation, and increased non-peristaltic contraction alongside decreased esophageal peristaltic contraction amplitude. Cholinergic function abnormalities may also be seen at various severities depending on the stage of the disease. There are data indicating a relationship between the dysmotility in esophagus and the Raynaud phenomenon. Esophagus involvement shows itself also in the CREST syndrome with heartburn, regurgitation and chronic intermittent dysphagia to both liquid and solid foods. It was reported that eosinophilic fasciitis may cause esophageal dysfunction in cases involving systemic sclerosis[6].

Sjögren's syndrome

Swallowing difficulties are frequently (32%-85%) encountered complaints in the primary Sjögren syndrome (SS). Exocrine gland infiltration causes dysphagia symptoms in these patients. The manifestations from the gastrointestinal system in patients with SS include mucosal dryness, accelerated dental decay, and enlargement of the major salivary glands, as well as dysphagia, nausea, epigastric pain, and dyspepsia. The oral-pharyngeal phase and esophageal phase of swallowing is being affected. It is difficult to establish a relationship between the severity of symptoms and the severity of disease involvement[2,4-6].

The data obtained in the long term were meant to reveal the esophageal disorders in SS[8]. Patients consult us with esophagus atrophy and motor coordination problem as a result of an inflammation of the esophageal exocrine gland. Such patients apparently have abnormal esophagus motility. They seem to have a LES pressure higher than that in healthy people, an upper esophagus sphincter (UES) impairment and a decreased ability of contraction in the upper 1/3 of esophagus. Peristaltic contraction velocity decreases and its duration increases in the lower and middle parts of esophagus[8-10].

It has been reported that multi-factorial mechanisms lead to dysphagia in SS[6,11]. The results were tried to be explained by lack of saliva, esophageal dysmotility (36%-90%), esophageal web, achalasia, exocrine gland involvement, low grade myositis, and parasympathetic function damage. The relationship between the severities of xerostomia and dysphagia is controversial[2,4-6,8].

Idiopathic inflammatory myopathies

Dermatomyositis (DM) and polymyositis (PM) are classified as idiopathic inflammatory myopathies. Dysphagia can be a serious problem in these patients. Dysphagia in this patient group is associated with the severity of the disease and is also an indicator of a poor prognosis. Involvement of the striated muscles of the oropharynx and upper esophagus occurs in 10%-15% of patients, and may lead to dysphagia (10%-15%), regurgitation, and aspiration pneumonia. In addition, there may be ventilatory dysfunction due to involvement of the diaphragm and intercostal muscles. Dysphonia with a nasal speech quality may be noted[12]. In PM/DM patients, the triggering of the swallowing reflex for the voluntarily initiated swallow was normal while the pharyngeal phase of swallowing was significantly prolonged. The cricopharyngeal sphincter muscle electromyography (EMG) demonstrated severe abnormalities in halves of the patients investigated. These findings demonstrated the weakness of the striated oropharyngeal muscles. Cricopharyngeal (CP) sphincter muscle was affected less frequently and showed either hyperreflexic or hyporeflexic states during swallowing. It is concluded that the pharyngeal stage of oropharyngeal swallowing is mainly involved in patients with PM/DM[13]. Decreased pharyngeal muscle strength, palate elevation disorder, tongue weakness, cricopharyngeal muscle dysfunction, and sphincter closing problem are among the findings seen in this group of patients. The oropharyngeal swallowing problem was in 20% of the patients, esophagus involvement was in 1/3 of proximal part and there was esophagus dysmotility. There was a slowdown in the speed of gastric motility. Malignity of gastrointestinal system and nasopharynx can also be seen[6].

Pharyngeal involvement in juvenile DM was also found to be associated with poor prognosis. Weakness in oropharyngeal, laryngeal and esophageal muscles cause swallowing dysfunction[14]. In the absence of a more accurate assessment method to determine which children with active JDM are most at risk of swallow dysfunction and aspiration, all children with active dermatomyositis should be referred for speech and language assessment and videofluoroscopic swallow study (VFSS)[14].

Dysphagia is more common in inclusion body myositis (IBM) than in the other inflammatory myopathies and is reported to be occurring in 38%-84% of patients. Moreover, its outcome is worse in patients with IBM than in those with either poly- or dermatomyositis and its contribution to aspiration pneumonia associated respiratory failure may be the most common cause of death in people with IBM[15]. Dysphagia was frequently the presenting clinical symptom in patients who had IBM-associated dysphagia, observed more often in women and was usually refractory to medical and nonsurgical treatment[15].

Common dysphagia symptoms were sensation of food sticking in the throat and coughing during meals. The patients noted difficulty with dry foods, solids, and thin liquids most frequently. Clinical oral examination findings typically showed normal lingual range of motion, strength, and coordination.

The most common videofluoroscopic abnormalities are residual pharyngeal pooling, tongue base weakness, airway penetration, reduced pharyngeal constrictor con-

traction, CP muscle dysfunction described as a prominent CP muscle with poor relaxation and narrowing in the upper esophagus, and impaired laryngeal elevation. Aspiration was revealed in eight patients (35%). Prominent, tight CP muscle was noted in all nine patients who underwent a barium swallow. Common pharyngoesophageal manometry findings included low amplitude pharyngeal constrictor contraction (75%), normal resting tone and relaxation of the UES (82%), and diminished inferior esophageal sphincter pressure (42%)[15].

Systemic lupus erythematosus

In the systemic lupus erythematosus (SLE) patient group, we often encounter gastrointestinal complaints associated with the disease itself or the treatments given. In this patient group where systemic symptoms are in the foreground, mucosal ulcer (50%), decreased salivation, esophagus ulcer-perforation, decreased esophageal motility (72%), isolated abnormal peristalsis in esophagus, stricture, and reflux may be seen. The complaints are mild and vary in line with the disease activity. These findings are thought to emerge as a result of muscle inflammation and/or vasculitis-related damage. If vasculitis is present, more severe complaints and symptoms may be seen. Involvement can occur in any place in the gastrointestinal system. The region that is involved most frequently is the oral cavity. Erythematous lesions or discoid ulcers occurring in the hard palate, buccal mucosa or vermilion border regions cause dysphagia and odynophagia. The upper 1/3 region of esophagus is affected more. Abnormal peristalsis in proximal or distal esophagus is one of the leading pathologies. LES involvement is not seen much in this patient group[2,4-6].

Rheumatoid arthritis

One third of the patients in this rheumatologic disease group mention about the dysphagia symptoms. Temporomandibular joint involvement and Sicca syndrome cause impaired chewing function and difficulty in swallowing. Esophageal involvement is associated with pharmaceutical therapies that last much longer than the disease itself. Atlantoaxial subluxation and vasculitis (1%) are rare but may lead to esophageal problems (dysmotility, fibrosis, stricture and ulceration)[2,4-6]. Rheumatoid nodule or laryngeal synovitis may also create a dysphagia symptom[16]. Accumulations of esophagus amyloid and pseudo-achalasia may appear as complications in RA patients.

Eosinophilic infiltration of gastrointestinal tract (esophageal and pharyngeal) in RA appears as a rare and interesting involvement. Eosinophilia in RA patients can be associated with allergies, drugs (gold, penicillamine, sulfasalazine, methotrexate), disease activity, rheumatoid vasculitis and parasitic infections[17].

Children with Juvenile rheumatoid arthritis (JRA) rarely report temporomandibular joint pain, which may be due to pain avoidance mechanisms resulting in compromised masticatory function. Micrognathia, loss of a mandibular condyle and jaw retrusion seem to be associated with dysphagia symptoms in the child patient group. Other findings also encountered include decrease/impairment in esophagus distal peristalsis (30%-58%), decrease in LES tonus, esophageal ulcers (Felty's send). A complaint of reflux may arise in connection with these findings[18].

Other

Dysphagia symptoms that are pill-induced or associated with the presence of esophagitis are rarely seen in the *Seronegative arthropathy* group. Annulus fibrosis and longitudinal ligament bone formation may lead to dysphagia symptoms in patients with ankylosing spondylitis.

Sarcoidosis can affect the oesophagus in different ways. Stenosis of the distal oesophagus due to direct granulomatous involvement, or extrinsic compression by enlarged hilar and mediastinal lymph nodes, may both cause dysphagia. Sarcoid infiltration of the distal oesophagus can give rise to achalasia, and granulomatous myositis of the cricopharyngeal muscle causing dysphagia has also been reported. Barrett's oesophagus can also occur in sarcoidosis.

Since *vasculitis* can produce any type of a vessel involvement in any organ, gastrointestinal-esophageal involvement is also a diagnosis that should be considered in vasculitis such as Behçet's disease. Oral and esophageal ulcers may cause dysphagia symptoms. Esophageal manometry was found abnormal in a third of the cases. Mucosal lesions, odynophagia associated with esophagus involvement, bleeding, and ulcerations may occur in other types of vasculitis such as Wegener granulomatosis[2,4-6].

In inflammatory rheumatologic diseases, abnormal motility of esophagus may be associated with the worsening of pulmonary functions and the severity of reflux[7].

NON-INFLAMMATORY RHEUMATIC DISEASES

Due to the close relationship between esophagus and cervical spine, the presence of broad anterior osteophyte (spondylosis or DISH) causes dysphagia symptoms. Dysphagia is probably the most common cervical manifestation associated with DISH and was reported by various specialties. DISH was the cause of dysphagia in 17%-28% of patients over 60 years of age referred for dysphagia evaluation. Obstruction frequently occurs at C5-6 and more rarely at C4-5, C2-3 and C3-4. This location is particularly vulnerable to local pressure because the osteophytes compress the relatively immobile portion of the esophagus at the level of the cricoid cartilage. Larynx and hyoid elevation becomes a problem for epiglottic movement and bolus movement. Conditions other then cervical osteophytes may induce dysphagia, such as strictures, oesophagitis, cardiospasm, diverticula, motility disorders, benign or malignant tumors, and other C-spine disorders[19].

Skeletal deformity/basilar invagination may lead to oropharyngeal dysphagia symptoms in Paget's disease al-

though very rarely.

COMPLICATIONS OF MEDICAL TREATMENT IN RHEUMATIC DISEASES

Not only rheumatic diseases themselves but the drugs used in treating these diseases may also cause impairment in swallowing functions. Gold, penicillamine, sulfasalazine, methotrexate and other cytotoxic drugs can cause stomatitis and oral ulcers. Similarly, non-steroidal anti-inflammatory drugs, corticosteroids and bisphosphonates can cause mucosal erosion, oesophagitis and oesophageal ulceration[2,20]. Psychological and behavioural adverse events of low- to medium-dose glucocorticoids during ⩾ 1 mo for inflammatory diseases were most frequently reported, followed by gastrointestinal events such as dysphagia. Whereas "pill oesophagitis" may cause identical symptoms to gastroesophageal reflux disease with retrosternal chest pain and possibly dysphagia, odynophagia is usually the dominant complaint[3]. Steroid therapy and other immunosuppressive agents may also impair deglutition by predisposing to candidiasis of the upper intestinal tract[2,20].

ASSESSMENT

A good assessment is a must for the success of the treatment in patients with dysphagia. Speech language therapists assume a big task in the assessment and treatment of swallowing disorders. A physiatrist and/or a radiology specialist may be helpful in performing the assessment. However, assessment of a patient should be conducted in a multidisciplinary way[1].

At the stage of assessing patients, whether or not there is a swallowing disorder, possible local and anatomic causes of dysphagia (oropharyngeal, esophageal), airway protection capability (*e.g.*, aspiration risk), oral feeding functionality, alternative methods for regulating eating, an additional specific diagnostic test and need for consultation should all be considered. Anamnesis, queries about the drugs (sedative, antispastic, anticholinergic, *etc.*) and disease, background, family history, physical examination and imaging methods are used in an effort to arrive at a diagnosis. Failure or delay when initiating oropharyngeal swallowing, postnasal regurgitation or nasal regurgitation, cough indicating aspiration, apnea, presence of residue in the mouth and swallowing that necessitates repetition to clear the mass from hypopharynx may serve as guidelines for an oropharyngeal swallowing problem. A sensation of sticking behind the sternum during swallowing, painful swallowing, heartburn, and lack of pharyngeal symptoms also require investigation in terms of esophageal dysphagia. Weight loss and prolonged eating time are also important symptoms. A history of pulmonary infection undergone by the patient may be enlightening.

Some of the patients who were diagnosed with gastroesophageal reflux consult polyclinics with a complaint of dysphagia. Assessments of these patients do not reveal any significant pathology other than symptoms of reflux. They also need to be assessed in terms of esophagus motility problems.

During the physical examination, oropharyngeal condition, pulmonary system, musculoskeletal system, mental condition, speech and voice quality, cranial and reflex examination (gag reflex, cough reflex, swallowing reflex, touch and taste stimulation and pathologic reflex) and motor control are assessed. Biochemical parameters concerning nutrition should also be reviewed.

Diagnostic tests are started with a clinical or bedside swallowing assessment. The bedside assessment starts with a water and ice assessment. Various volumes of water (3, 5 and 10 mL of water) and food with various viscosities (nectar-like, honey-like, cracker, *etc.*) are tested. After swallowing, a change in the patient's color, wet voice, presence of food residues, and coughing can be enlightening for us in terms of aspiration. A bedside assessment gives us limited information on the function and mechanism of swallowing; its reliability is moderate. The VFSS is accepted as the gold standard. Clinical indicators do not reveal aspiration in inflammatory rheumatologic diseases particularly in children. Thus, although it is an unpleasant test in terms of radiation, money and time, VFSS still remains to be the most viable method today.

The fiberoptic endoscopic evaluation of swallowing (FEES) also gives fairly reliable information other than its assessment insufficiency at the oral phase. If a problem is being suspected particularly in oropharyngeal swallowing, these tests will help us for making a diagnosis[21].

A barium esophagram is important for the diagnosis of osteophyte, dilatation, stricture, Zenker's diverticulum, achalasia and presence of a lump. Esophageal dysfunction is frequently seen in autoimmune and inflammatory rheumatologic diseases. Esophageal manometric examination is a specific and sensitive method to assess the dysmotility of esophagus. The sensitivity of VFSS and FEES examinations is lower in this patient group. Esophagitis, Barrett's esophagus and presence of stricture can be revealed with a gastric endoscopy and gastroesophageal reflux disease with a 24-h ph-meter examination. Esophagus scintigraphy may be useful in these patients for assessment of esophagus dysmotility, esophageal emptying and reflux.

GENERAL PRINCIPLES IN TREATMENT

The treatment objective in these patients is to reduce the risk of aspiration, to ensure daily calorie intake, to increase oral feeding varieties for both nutrition and patient satisfaction and to raise quality of life. It is decided after the examinations whether the patient's way of food intake will be oral, through a nasogastric tube (NGT) or through percutaneous endoscopic gastrostomy (PEG)/jejunostomy (PEJ). In all viscosities, if there is more than 10% aspiration, the patient should not be fed orally. If the patient cannot eat safely and effectively, methods of

feeding through a tube will be tried. This is not a treatment method, but a strategy devised to protect the patient from negative clinical conditions (dehydration, malnutrition, aspiration). It should be made certain whether or not the patient is taking his/her daily calorie requirement. It may be difficult to ensure that he/she is taking sufficient calories depending on the duration of eating food (cognitive defect). As a general approach, if a short-term non-oral feeding is targeted, NGT will be chosen, if non-oral feeding for a longer period than 2-3 wk is considered, PEG or PEJ will usually be used. However, the healthcare staff that monitors the patient and the patient should make this decision together.

Treatment of dysphagia in inflammatory rheumatologic diseases is a difficult task. Although there is recovery in parallel with disease activity in some groups, it is hard to achieve this success at all times. Over three fourths of the patients received aggressive immunosuppression, but the benefit seems to be ineffective consistent with literature. The effect of the drugs used for treating the disease on dysphagia varies. While response to the treatment is limited in scleroderma, the decline in the severity of the disease in SLE patients results in an improvement also in dysphagia symptoms. The success of IVIG and steroid therapies is variable. The effect of TNF-alpha inhibitor drugs is unknown. If it is thought that the dysphagia is associated with the medication used by the patient, pharmaceutical rearrangements should be made. The treatment of gastroesophageal reflux may be useful in terms of securing oral hygiene, candida treatment, LES pressure-related approaches, dysphagia symptoms, and complications. Fortunately, although dysphagia symptoms are frequent, severe dysphagia and its complications are seen rarely. A multidisciplinary approach increases success in treatment.

In addition to the management of underlying disease, the treatment includes special dietary regimen, rehabilitation and even interventional surgical procedures, if necessary. Treatment options included swallowing strategies (exercise, special techniques, diet modifications), CP myotomy (Zenker's diverticulum, achalasia), pharyngoesophageal dilation, electrical stimulation to swallowing muscles, and botulinum toxin injection for the treatment of UES (in the presence of sphincter relaxation problem). It is decided after the assessment as to what treatment(s) is appropriate. The treatments may be grouped basically as compensatory and therapeutic approaches. Compensatory approaches are applied to control the way through which food will travel, to remove the symptoms and to prevent aspiration. Compensatory approaches include postural technique (eating positions), oral-sensory motor improvement techniques, and adjustment of the volume and viscosity of the bolus. Swallowing compensation and feeding techniques were recommended to over half of the patients, but their effectiveness remains uncertain in these diseases. The limited data available on this issue make it difficult for us to decide as to what treatment is more effective. Therapy procedures include special swallowing maneuvers (supraglottic, super-supraglottic, effortful swallowing, Mendelshon maneuver), bolus control exercises, jaw-tongue-lip-pharyngeal joint range of motion exercises, jaw, tongue and lip strengthening exercises, Shaker exercises, Masako maneuver, and breathing exercises. Adaptive devices and instruments are also used for eating safety and control. When assessing patients, an appropriate treatment plan is prepared by trying different maneuvers, viscosities and volumes at the same time.

In conclusion, swallowing problems in rheumatologic diseases appear to be a not very well known condition. Studies with long follow-up periods to be included in the literature in the future will provide us with more information. With the present data, it is quite difficult to comment on either the diagnosis or the treatment. It is important that healthcare staff is made aware of the fact that patients with dysphagia should be directed to rehabilitation units. In this way, a noticeable improvement can be achieved in patients' quality of life through small touches.

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