Ankylosing spondylitis and uveitis: overview

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ABSTRACT

The present article reviews the epidemiology, pathogenesis, clinical features, diagnosis, and treatment of ankylosing spondylitis and its association with ocular changes. The authors used the PubMed (MEDLINE), LILACS, and Ophthalmology Library databases. Ankylosing spondylitis is a chronic inflammatory disease that usually affects the axial skeleton and can progress to stiffness and progressive functional limitation. Ankylosing spondylitis usually begins around the second to third decade of life, preferentially in HLA-B27-positive white males. Its etiology and pathogenesis are not completely understood, and its diagnosis is difficult. Clinical control and treatment are frequently satisfactory. Acute anterior uveíte is the most common extra-articular manifestation, occurring in 20%–30% of the patients with ankylosing spondylitis. Approximately half of the acute anterior uveíte cases are associated with the presence of the HLA-B27 antigen. It can be the first manifestation of an undiagnosed rheumatic disease, usually having a good prognosis and appropriate response to treatment. In conclusion, for better assessment and treatment of patients with uveitis, ophthalmologists and rheumatologists should work together.

Keywords: ankylosing spondylitis; anterior uveitis; HLA-B27; tumor necrosis factor alpha.

INTRODUCTION

Ankylosing spondylitis (AS) is the prototype of a group of inflammatory diseases formerly known as spondyloarthropathies, and currently called spondyloarthritides, which share epidemiological, clinical, anatomopathological, radiological, and immunogenetic features. Spondyloarthritides comprise AS, reactive arthritis (formerly known as Reiter's syndrome), psoriatic arthritis, inflammatory bowel disease-related spondyloarthritis, and undifferentiated spondyloarthritis.[1]

AS is a chronic, progressive inflammatory disease that affects primarily the sacroiliac joints and the axial skeleton (spine) and, less frequently, peripheral joints and other extra-articular organs such as the eyes, skin, and cardiovascular system. The major functional losses occur during the first 10 years of disease. It usually begins in the second or third decade of life, preferentially in HLA-B27-positive Caucasian males.[1]

Its etiology and pathogenesis are not completely understood, but the most prevalent hypothesis involves immune mediation as its major mechanism, including several cytokines, such as tumor necrosis factor (TNF), interaction between T cell response, genetic factors, environmental factors, and bacterial antigens. There is a strong association between AS and HLA-B27, with approximately 92% of the Caucasian patients with AS being HLA-B27-positive. That prevalence is lower in other ethnical groups.[2,3]

The use of non-steroidal anti-inflammatory drugs (NSAIDs) and practice of physical exercise constitute the treatment of choice, although they are considered palliative measures that neither change the course of disease nor prevent structural damage. When symptoms are refractory to NSAIDs, corticosteroids can be used in specific cases, as well as several antirheumatic drugs such as sulfasalazine, methotrexate, and, more recently, anti-TNF, which seem to change the course of disease.

Regarding extra-articular manifestations, the most frequent is anterior uveitis, observed in up to 40% of the patients on long-term follow-up, usually associated with HLA-B27 positivity and rarely resulting in sequelae.[2–5] Anterior uveitis

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includes terms such as iritis (inflammation of the eye's iris, with inflammatory cells in the anterior chamber and no involvement of the anterior vitreous), iridocyclitis (primary inflammation of the iris and secondary inflammation of the ciliary body; inflammatory cells present in both the anterior chamber and anterior vitreous), and cyclitis (inflammation of mainly the ciliary body).

Uveitis related to HLA-B27 are characterized by acute, unilateral recurring (affects each eye at a time) iridocyclitis of sudden onset, with a moderate to severe amount of fibrin and cells in the anterior chamber. It usually responds to topical corticosteroid treatment and mydriatic drugs prescribed to prevent posterior synechia.

This study reviews the epidemiology, pathogenesis, clinical findings, diagnosis, and treatment of the important association between AS and ocular involvement, showing the need for close collaboration of rheumatologists and ophthalmologists in managing the disease. The authors used the PubMed (MEDLINE), LILACS, and Ophthalmology Library databases.

EPIDEMIOLOGY

AS usually begins in the second or third decade of life, affecting mainly men, at the 3:1 ratio.[5,6] The disease pattern varies according to gender, being more severe in men[7] and having a late onset in women,[7] who have a more significant extraspinal involvement.[8,9]

The prevalence of AS is 0.1%–1.4%, varying according to both geography and ethnical groups; however, there is a strong correlation between the prevalence of HLA-B27 and that of spondyloarthritides in a certain population.[10] Positivity for HLA-B27 in patients with AS can vary from 80% to 98%, being greater in non-mixed Caucasian populations of North Europe.[11] Because HLA-B27 is extremely rare in African black populations, AS is rare in those populations; in Brazil, a country with intense ethnical miscegenation, AS and other spondyloarthritides are usually found in mulattos (due to the influence of the Caucasian genetic ancestry), being extremely rare in non-mixed blacks.[12]

Patients with severe and prolonged AS develop extra-articular manifestations, such as defects in cardiac conduction, aortic regurgitation, pulmonary fibrosis, neurological sequelae, and amyloidosis.[1,3] Acute anterior uveitis (AAU) occurs in approximately 20%–30% of the patients with AS, being considered the most common extra-articular manifestation.[2,5] It relates to neither joint disease exacerbation nor severity.[13]

PATHOGENESIS

The exact cause of AS remains unknown, but the combination of genetic and environmental factors seems to be important in its pathogenesis.

Genetic predisposition and immune mechanism

Studies have shown the involvement of immunity in the inflammatory process of AS, with increased serum levels of IgA and relationship with HLA-B27. There is a strong association of AS with the major histocompatibility complex (MHC) class I HLA-B27 molecule and the response of T cells as the key to pathogenesis. Although no specific and single agent has been identified as the cause of the disease, the interrelation between AS and inflammatory bowel disease suggests that bacterial enteritis (*Klebsiella*, *Chlamydia*, *Campylobacter*, *Shigella*, and *K. pneumoniae*) might trigger an immune response to the prolonged exposure to intestinal bacteria. That cytolytic response would lead to tissue damage and inflammation spreading.[14–16]

Based on histopathological data, there is evidence that entheseal fibrocartilage (attachment of a tendon to bone) is the first and major target in immune response. Theoretically, immunocompetent cells could have access to fibrocartilaginous antigens derived from bone marrow blood vessels.[17] Genes other than HLA are believed to be involved, such as HLA-B60, HLA-B61, HLA-DR8, HLA-DRB1, and MICA.[11] In addition to the presence of HLA-B27 in the short arm of chromosome 6, susceptible regions were identified in chromosomes 1p, 2q, 6p, 9q, 10q, 16q, and 19q.[16,18–20]

Positivity to the HLA-B27 antigen also seems to imply higher levels of TNF in the aqueous humor of patients with active uveitis.[19] A recent study has shown a female protective factor attributed to estrogens, which induces the constitutive synthesis of nitric oxide, the reduction in the expression of adhesion molecules (E-selectin) and the modulation of genes that promote the appearance of pro-inflammatory cytokines, such as interleukins IL-1, IL-6 and TNF-α.[21]

Environmental factors

The fact that only a small proportion of HLA-B27-positive patients develop the disease can be explained by the existence of different types of alleles, showing the importance of environmental factors.[19]

Studies have reported that HLA-B27-positive transgenic rats develop a disease similar to spondyloarthritis, with manifestations such as sacroiliitis, enthesitis, arthritis, ocular inflammation, and bowel inflammation. The rats non-exposed

to environmental germs do not develop the disease. Once introduced into regular environments and exposed to bacteria, they develop spondyloarthritis findings.

HLA-B27 AND AAU ASSOCIATION

The MHC is responsible for encoding molecules that present antigens to the immune system. In human beings, the major histocompatibility complex is called human leukocyte antigen system (HLA). Because of easy access, leukocytes are the cells most often used to study the HLA, being present in the surface of most nucleated cells. It has been determined that some human diseases are associated with the presence or absence of certain HLA antigens. Five series of HLA have been identified. The following *loci* have been identified in chromosome 6: A, B, C, D, or DR (D-related).[18]

Although the mechanism by which HLA-B27 predisposes to the appearance of diseases has not been completely elucidated, infections are believed to be among the triggering factors of uveitis in HLA-B27-positive patients.[13]

The HLA-B27 antigen is considered a genetic marker associated with spondyloarthritis. Its incidence varies according to the methodology used (microcytotoxicity, flow cytometry, and C-reactive protein), the population studied,[11,22] the type of disease (95% in Caucasians with AS)[23], and, occasionally, microbial agents.[23]

The association between HLA-B27 and AAU was first reported by Brewerton et al. em 1973,[24] being currently well established as a distinct nosological entity, with peculiar characteristics, such as earlier onset, unilateral involvement, and greater frequency of relapse, diversity, severity, complications, and possibility of low visual acuity[19] as compared with those of HLA-B27-negative patients. Approximately 30%–50% of the cases of AAU are associated with the presence of the HLA-B27antigen,[25,26] and, in approximately 90% of those cases, AS can be diagnosed.

Carvalho et al.,[27] studying 100 patients with non-granulomatous uveitis, have reported that 38 patients had a disease of the spondyloarthritis group as the underlying disease, and that HLA-B27-positive individuals had a 3.8-fold greater chance of developing uveitis than the HLA-B27-negative ones. In Brazil, Moraes, in 1996, found a 66.6% correlation between anterior uveitis and HLA-B27 as compared to 3.5% in the control group.[28]

DIAGNOSIS AND CLINICAL FINDINGS

The diagnosis is established by the combination of clinical findings and the radiological evidence of sacroiliitis defined by the modified 1984 New York criteria.[29]

Making an early diagnosis of AS was difficult, because disease onset is insidious and sacroiliitis is not evident on plain X-ray until the disease is at an advanced stage. Thus, the time interval between symptom onset and AS diagnosis could be as long as 5–10 years. Currently, the diagnosis is established earlier because some risk factors, such as absence of rheumatoid factor, HLA-B27 seropositivity, family history, male gender, disease onset prior to the age of 40 years, and frequent gastroenteritis[30] are considered. In addition to those probable factors, magnetic resonance (MR) is used to ensure the axial and peripheral nature of the disease; however, because of its cost, MR has not become routine.

The modified 1984 New York criteria are as follows: 1) clinical criteria: pain, of insidious onset, in lumbar spine and morning stiffness for more than three months, improved by exercise but not relieved by rest; limitation of lumbar spine motion in both the sagittal and frontal planes; limitation of chest expansion relative to normal values for age and gender; and 2) radiological criterion: bilateral grade 2–4 or unilateral grade 3–4 sacroiliitis on X-ray.[29]

Definite AS is diagnosed if the radiological criterion is present plus at least one clinical criterion. In the absence of radiological findings, individual probability can be calculated depending on typical AS manifestations. Thus, probable AS is considered if three clinical criteria are present alone, or if the radiological criterion is present with no clinical signs or symptoms.[29]

According to the Brazilian Consensus of Spondyloarthropathies,[30] the modified New York criteria and the European Spondyloarthropathy Study Group (ESSG) criteria (Table 1)

Table 1
Criteria

New York criteria (1984)	ESSG criteria (1991)
- Low back pain - Limitation of lumbar spine motion in both the sagittal and frontal planes - Limitation of chest expansion - Bilateral grade 2–4 sacroiliitis - Unilateral grade 3–4 sacroiliitis	- Inflammatory spinal pain OR synovitis (asymmetric, lower extremities) AND at least one of the criteria below: - Positive family history (AS, psoriasis, anterior uveitis, inflammatory bowel disease) - Cutaneous psoriasis - Urethritis or acute diarrhea within four weeks before onset of arthritis - Pain alternating between the two buttocks - Enthesopathy (insertion of the Achilles tendon or plantar fascia) - Sacroiliitis (bilateral grade 2–4 or unilateral grade 3–4)

ESSG: European Spondyloarthropathy Study Group; AS: ankylosing spondylitis.
New York criteria: AS is defined when the fourth or fifth criterion is present plus some clinical criteria.[30]
ESSG criteria: AS is diagnosed in the presence of at least one major and one minor criterion.[31]

continue to be widely used. It is worth noting that, similarly to most classifications, such criteria are useful for population studies and to assess individual patients, but the diagnosis of spondyloarthritis should not be ruled out if the criteria are not met.[31]

New criteria were discussed on the 73rd Annual Scientific Meeting of the American College of Rheumatology in 2009 and are the first to include MR to aid with the diagnosis of axial spondyloarthritides – providing a better analysis of the inflammatory process before it becomes a lesion anatomically visualized on conventional X-ray – and also with the patients' follow-up. However, rheumatologists should improve their knowledge about the different lesions observed on MR of the axial skeleton and sacroiliac joint and should know how to differentiate them from non-inflammatory causes.[31]

The laboratory findings are unspecific, consisting in changes common to chronic diseases, being as follows: normochromic and normocytic anemia; mild leukocytosis; increased erythrocyte sedimentation rate (ESR); increased C-reactive protein; and elevations in alkaline phosphatase and IgA.[30]

The HLA-B27 test is useful only as an adjuvant to diagnosis. Its presence is neither necessary nor sufficient to establish the diagnosis, but it is useful to support the calculation of the probability of developing AS. Thus, the HLA-B27 test should be considered, especially in patients with inflammatory spinal pain, because such patients have greater probability of a definite diagnosis of AS.[32]

The AS manifestations are as follows:

1) Systemic

The classic presentation begins with insidious inflammatory spinal pain and morning stiffness, relieved by exercise, and worsened with rest or inactivity. Other manifestations of seronegative spondyloarthritides include asthenia, fatigue, mild weight loss, and elevated body temperature.[1–3,30]

The spinal disease begins at the sacroiliac joint (bilateral lumbosacral region), and most patients have mild or intermediate chronic disease with remission periods. The spinal pain rarely persists active, and the disease progresses upwards along the spine. Patients with AS can have peripheral arthritis and peripheral enthesitis (inflammation of the attachment of a tendon to bone), which occur in 33% of the patients, are painful, commonly involving the insertion of the calcanean tendon and the plantar fascia in the calcaneus. All those symptoms can occur alone. Later, the following can be found: a reduction and even straightening of lumbar lordosis; atrophy of the buttocks; accentuation of thoracic kyphosis; destructive arthropathy of the hip or shoulders, resulting in flexion limitations and deformities; and straightening of the cervical spine, projecting the head forwards.[1–3,30]

Extra-articular involvements usually occur in subsequent progressive stages, and joint disease control has no relation to the appearance or severity of visceral changes. The longer the disease course, the greater the chances of visceral involvement.[13]

The major cardiorespiratory manifestations are cardiac conduction disorders, aortic regurgitation, pericarditis, and apical pulmonary fibrosis. Renal involvement, represented by IgA nephropathy and amyloidosis, can occur. Regarding gastrointestinal involvement, asymptomatic inflammation of the proximal colon and terminal ileum can be seen. Regarding neurological involvement, the following can occur: peripheral neuropathy; cauda equina syndrome in patients with long-term severe disease; cervical myelopathy due to atlantoaxial joint subluxation; and mucocutaneous lesions.[1–3,30]

Radiology is important to establish the diagnosis, and the radiological changes reflect disease progression. The most frequent radiological changes occur in the axial skeleton; however, those occurring in the sacroiliac joints are characteristic of the diagnosis. In the progressive form, we can find blurring of the joint edges, joint pseudoenlargement, subchondral bone sclerosis, erosions of the joint edges, formation of bone bars, narrowing of joint spaces, and joint fusion. In the spine, especially in lumbar spine, the following can be found: erosions of the vertebral bodies' angles; osteitis; square appearance of the vertebral bodies; syndesmophyte formation; calcifications of the intervertebral discs; and narrowing of joint spaces, culminating in fusion of the interapophyseal joints, producing the "bamboo spine" (Figure 1).

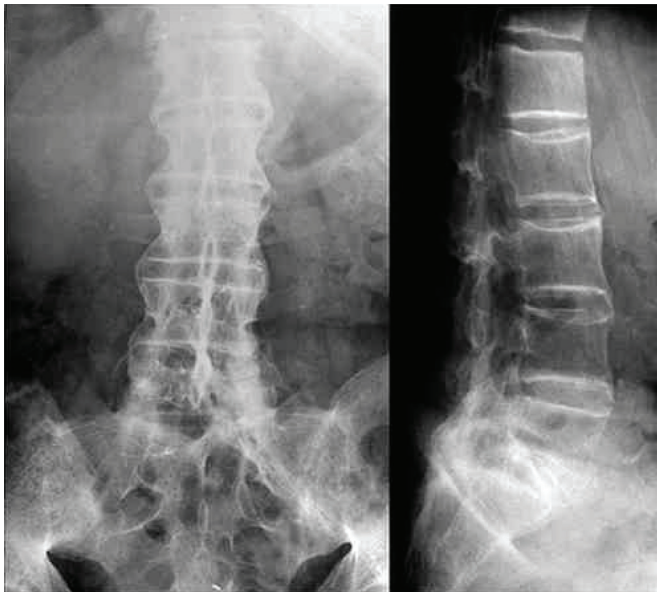

Figure 1
Final stage of a patient with AS showing syndesmophytes in lumbar spine, resulting in bamboo spine.
Source: http://quemdividemultiplica.blogspot.com/2010/02/espondilite-anquilosante.html.

On X-ray, the Ferguson view and oblique view provide better visualization of the sacroiliac joints. Computed tomography and MR can detect lesions of early AS with greater consistency than radiography, because they detect early sacroiliitis, erosions and enthesitis, and are useful to monitor the progression of the sclerosis of the sacroiliac joint.[1–3,31] Thus, MR has been introduced as a tool for the early detection of osteoarticular inflammation ("pre-radiographic" phase) and for patients' follow-up, as a way to prevent the radiological progression of the disease, especially of bone neoformation, thus determining the best treatment for suppressing inflammation at an early phase, before cartilage damage and bone erosions occur.[31]

2) Ocular

Most patients with acute uveitis seek emergency services, where uveitis is classified according to the International Uveitis Study Group classification (location, clinical course, laterality), and the possibility of primary ophthalmologic disease is ruled out. Then, the standard protocol for the first episode of uveitis is applied, consisting of blood count, biochemistry, ESR, urinalysis, serology for syphilis, and chest X-rays (the last two are performed because of the lack of a characteristic pattern of syphilis and sarcoidosis).[33]

In the presence of recurring non-granulomatous uveitis, which is the most frequent type in patients with AS, MR of the sacroiliac region should be requested, and, if possible, HLA-B27. All patients with recurring AAU of non-ophthalmologic etiology should be referred to the rheumatologist for complementary investigation with diagnostic purpose.

AUU is both the most common extra-articular manifestation and the most frequent ocular involvement. Its accumulated prevalence in the population is approximately 0.1%, representing 30%–70% of all types of uveitis.[19,23,24] In approximately 25% of the anterior uveitis cases, no associated systemic disease can be evidenced, and 50% of them have the HLA-B27 histocompatibility allele.[34]

AUU is an acute inflammation of the anterior segment of the eye, defined as recurring non-granulomatous iritis or iridocyclitis of sudden onset, with duration shorter than three months, which can become chronic with innumerous sequelae.[35] The patient complains of ocular hyperemia, pain, photophobia, lacrimation and visual blurring. Keratic precipitates on the cornea, never of the mutton-fat type, flare, and a large amount of cells in the anterior chamber can be seen. If treatment is not initiated, the iris can develop edema with posterior synechiae (Figure 2). Another characteristic of the AAU associated with AS is the lack of the simultaneous involvement of both eyes, which can be alternate.[34]

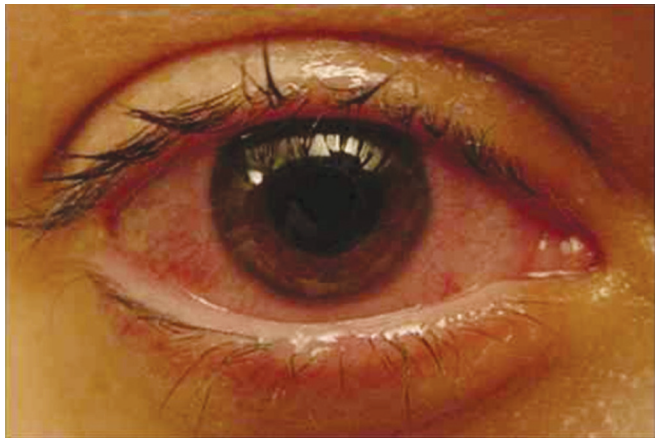

Figure 2
Anterior uveitis.

In cases of severe anterior uveitis, even when inflammation has already been treated, an irreversible and chronic break in the blood aqueous barrier can occur, with an elevation in protein levels;[36] it should not be considered a parameter of relapse or therapeutic failure.

When the uveitis has a chronic course, the following complications can occur, mainly in HLA-B27-positive patients: seclusion and pupillary occlusion; low visual acuity; cataract; secondary glaucoma; cystoid macular edema (CME); macular hole; and folds of the internal limiting membrane of the retina in the macular area.[37] Anterior uveitis of prolonged and uncontrollable course is a risk factor for the extension of inflammation to the posterior segment of the eye, and the following have been reported: vitreitis; papillitis; retinal vasculitis; CME; epiretinal membrane; and pars plana exudate.[38]

Mechanical ptosis, superficial keratitis, episcleritis, scleritis, and corneal ulcer are other possible ocular manifestations.[37,38]

TREATMENT AND PROGNOSIS

The treatment of AS is aimed at relieving pain and inflammation and at maintaining the best possible posture and joint function, to prevent or minimize sequelae, with consequent improvement in the patients' quality of life. It involves educational, pharmacological, physical or rehabilitation, radiotherapy and surgical measures, and, thus, should be multidisciplinary and multiprofessional.

The treatment of choice currently used for symptomatic patients consists in using NSAIDs along with physical therapy, although those are palliative measures and do not change disease course. Most patients use NSAIDs most of their treatment time, and more than one third requires another generation of

NSAIDs.[1–3] In case of refractoriness or intolerance to NSAID treatment, oral corticosteroid, sulfasalazine, methotrexate or biologics should be instituted.

Corticosteroids are occasionally useful to control symptoms for a short period, since they do not change the disease course and increase the tendency towards osteoporosis.

The use of slow-acting drugs, inducers of remission, for treating axial disease in AS has been discouraging, although some results have been obtained with the peripheral disease. Sulfasalazine is often used to treat AS, especially in the presence of peripheral joint involvement, and to prevent recurrent episodes of uveitis.[39] Methotrexate has been used in severe cases of active AS non-responsive to NSAIDs and sulfasalazine, and has shown better results in patients with peripheral involvement.[40]

The disease-modifying antirheumatic drugs that block TNF-alpha, when coupling to TNF, prevent it from binding to lymphocyte Fc receptors and their consequent changes in cellular immunity. They are infliximab, etanercept and adalimumab. Studies have shown that those agents have short-, mid- and long-term sustained efficacy and should be used as monotherapy. They start acting rapidly and have proved to reduce spinal inflammatory activity.[41–43]

The choice of treatment depends on the severity of inflammatory findings and the response to medications. Uveitis usually responds well to topical corticosteroids, which control inflammation – and should be associated with a mydriatic drug to prevent posterior synechiae − and decrease ciliary muscle spasm, thus reducing pain. Lack of response to topical corticosteroids and progression to chronic inflammation have been reported in only 13%–19% of the HLA-B27-positive uveitis cases, when periocular corticosteroid injection is preferred to systemic corticosteroids.[44]

Sulfasalazine, a conjugate of sulfapyridine and 5-aminosalicylate, has a local anti-inflammatory action, inhibiting the synthesis of prostaglandins. It is a good indication in cases of recurring AAU in AS, because most crises occur during the period of disease activity, and sulfasalazine is a good drug to treat AS, mainly in patients with the peripheral component.[39] Methotrexate is an antimetabolic agent, whose major mechanism of action is the competitive inhibition of the enzyme dihydrofolate reductase, which plays a central role in folic acid reduction, thus interfering in cell reproduction. Methotrexate is a base drug commonly used in AS, but it neither associates with a reduction in the number of uveitis crises nor modifies disease course.[40]

Although HLA-B27-positive anterior uveitis is the most common form of intraocular inflammation, satisfactory therapeutic strategies to prevent its recurrence could not be established.

The great perspectives on the treatment of AS are biologic drugs, which are claimed to provide for the first time more than only pain relief. The TNF inhibitors, such as infliximab, etanercept and adalimumab, act specifically in the disease inflammatory process, and should influence its progression. There are promising results in cases of refractory uveitis, mainly in cases of inflammation in the posterior segment, contributing to visual recovery.[41,43]

A recent study has shown an incidence of anterior uveitis in AS of 6.8 per 100 patient-years in the group treated with TNF inhibitors as compared with 15.6 per 100 patient-years in the control group treated with placebo. Thus patients with AS treated with anti-TNF agents show a significant decrease in the number of anterior uveitis flares;[42] however, their indication should be limited due to the reports of severe side effects, such as exacerbation of demyelinating diseases, bilateral anterior neuropathy, tuberculosis, histoplasmosis and sudden death in patients with congestive heart failure.

Complications of AS are consequent to joint and spine disease or extra-articular manifestations. A minority of patients develop vertebral fusion, which results in severe kyphosis and limited spine mobility, including the cervical region. Fusion increases susceptibility to fracture, even resulting from small traumas. Occasionally, the hip and shoulder joints develop arthropathy, requiring total joint replacement.[1–3,30]

According to most studies, the prognosis of AAU in patients with AS is usually excellent with only topical treatment, and only patients with involvement of the posterior pole or high tendency towards recurrence or chronicity would benefit from immunosuppressive drugs.[30,31] It is worth noting that CME is not a signal of involvement of the posterior pole, and, thus, does not imply the necessary use of immunosuppressive drugs.

Systemic AS also has a good prognosis, as long as the disease management comprises a global approach. A long treatment with anti-inflammatory drugs is usually required. Some indicators of poor prognosis of the disease are as follows: involvement of peripheral joints; disease onset during youth; and poor response to NSAIDs.[1–3,30]

CONCLUSION

Because uveitis can be the initial manifestation of spondyloarthritides, and especially a key symptom for the diagnosis of AS, the joint work of ophthalmologists and rheumatologists is fundamental to the earlier diagnosis and effective treatment

of those patients, and to the management of cases requiring immunosuppressive drugs.

It is worth emphasizing the need for the accurate rheumatological investigation of HLA-B27-soropositive young males with idiopathic and recurring AAU, and it should be periodically repeated, because the installation of systemic clinical findings of AS is frequent on a second occasion, sometimes even a few years after.[44]

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