

Ankylosing spondylitis and other spondyloarthropathies: extra-articular manifestations and their management

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The spondyloarthropathies (SpA) are a group of rheumatic inflammatory inter-related diseases that share common etiopathogenesis, clinical, genetic and radiological features, in which ankylosing spondylitis is the prototype of the family. All SpA are, to some extent, associated with human leukocyte antigen-B27, but the frequency varies among the several diseases. Extra-articular involvement is a frequent feature of the SpA. By the way they relate with the SpA concept, two different categories of extra-articular manifestations may be identified. First, is the extra-articular manifestation concept-associated, which has eye, bowel and skin involvement. This category may be present in all groups of the SpA family; they share common etiopathogenesis with the disease itself and can be present at any moment during disease evolution. Second, is the extra-articular manifestations non-concept associated, which involve cardiac, pulmonary, renal and neurologic manifestations, as well as osteoporosis and amyloidosis. This category is most frequently described in relation to ankylosing spondylitis, and often occurs in long-standing uncontrolled disease. In this article, we review the clinical features and therapeutic approach to the main extra-articular involvement of the SpA, paying special attention to ankylosing spondylitis.

The spondyloarthropathies (SpA) are a heterogeneous group of rheumatic inflammatory interrelated diseases that share common etiopathogenesis, clinical, genetic and radiological features, with frequent association with overlapping extra-articular features [1]. At least five entities comprise this group, as follows:

- Ankylosing spondylitis (AS) is the prototype of this family, characterized by predominant axial skeletal involvement and advanced radiographic sacroiliitis;
- Reactive arthritis (ReA);
- A subset of psoriatic arthritis (PsA);
- Arthritis associated with inflammatory bowel disease (IBD);
- Undifferentiated SpA (UndSpA).

They have as a common denominator their strong, but variable among them, association to human leukocyte antigen (*HLA*)-B27. At onset, SpA present four syndromes that are expressed to different degrees in each of them:

- Axial syndrome (the most important hallmark is the involvement of the axial skeleton with

spondylitis and/or sacroiliitis). This is clinically characterized by inflammatory back pain and stiffness, the latter being due to both inflammation and progressive bony ankylosis of the spine;

- Peripheral syndrome (generally asymmetrical oligoarthritis predominantly of the lower limbs);
- Enthesitic syndrome;
- Extraskeletal syndrome (SpA is associated with several extra-articular manifestations, including inflammatory intestinal lesions, acute uveitis and skin lesions) [2].

It is especially relevant that we acknowledge that in the same patient we can find any of the four syndromes, or all of them in diverse combinations.

Ankylosing spondylitis is a chronic systemic inflammatory disorder, with an estimated prevalence of 0.2–1.2%, involving the sacroiliac (SI) joints, the spine, and often the hips or peripheral joints, which predominantly affects young men. In the latest years, special attention has been paid to the enthesitis involvement in AS – some authors propose that enthesitis is a key structure in the

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pathogenesis of the disease and so, in this context, synovitis is considered secondary to enthesitis [3,4]. Peripheral arthritis could be detected frequently in large joints such as shoulders, hips or knees, but probably the most important of them is hip impairment, as it can indicate a poor prognosis for the disease course [5,6].

Extra-articular involvement is a frequent feature of the SpA, gathering all the signs and symptoms that share the same etiopathogeny with the disease itself (SpA concept-related manifestation), and can be present at any moment in the disease evolution, even at the first manifestation, before the axial or articular manifestations. These extra-articular manifestations include eye, skin and bowel involvement, and classical SpA treatment and anti-tumor necrosis factor (TNF) therapy influences the course of these symptoms.

On the other hand, there are other extra-articular manifestations that are seldom related to joint or axial manifestations (non-concept-related manifestation of SpA), and classical SpA drugs have no effect on them. They include cardiac, pulmonary, renal and neurologic manifestations, as well as osteoporosis and amyloidosis (TABLE 1).

Concept-related extra-articular manifestations

Eye manifestations

The most frequent extra-articular involvement in AS is inflammation of the uvea (uveitis), the prevalence reported for anterior acute uveitis (AAU) ranging from 16 to 40% [7,8].

In a large series of patients, the mean frequency of active episodes of uveitis was 0.8 ± 0.6 per year [9]. Uveitis usually occurs after the onset of rheumatologic symptoms, but AAU may be the first symptom of the systemic disease, preceding other clinical manifestations. Several studies have shown that the diagnosis of previously unknown systemic inflammatory disease was made as a result of the ophthalmological consultation after an episode of uveitis in more than 50% of the patients with SpA and uveitis, and up to 91% in UndSpA [10].

The association between the human major histocompatibility complex (MHC), *HLA-B27*, and AAU was originally described in 1973 and remains one of the strongest HLA-disease associations [11].

AAU in AS *HLA-B27*-positive patients is characterized by a clear male preponderance, males being affected 1.5- to 2.5-times more often than females [12], in contrast to *HLA-B27*-negative AAU, which does not show any gender difference [13].

The first episode of anterior uveitis in *HLA-B27*-positive patients most commonly occurs between the ages of 20 and 40 years [14], whereas the age at onset of uveitis in *HLA-B27*-negative patients tends to occur a decade later [15].

Intraocular inflammation is generally an acute unilateral episode, with sudden onset and limited duration accompanied by photophobia and hyper eye discharge. Bilateral involvement is infrequently seen during the course of the disease. In rare cases, prolonged, uncontrolled, anterior uveitis can cause extended inflammation of the posterior segment of the eye and subsequent cystoid macular edema, which is the main cause of irreversible visual impairment in patients with prolonged, uncontrolled uveitis.

The first line of treatment usually prescribed is topical corticosteroids and cycloplegic agents, in order to prevent iris-lens synechia. When additional treatment is needed, periocular injections of corticosteroids is used more often than systemic corticosteroids.

Tumor necrosis factor inhibitors have been successfully used in the treatment of refractory uveitis, particularly in patients with Behçet's disease [16].

Moreover, high levels of TNF have been detected in ocular fluids of patients with SpA [17], and there is evidence that showed the participation of this cytokine in its pathogenesis [18]. The study of Sugita *et al.* first provided evidence for the presence of an increased level of the soluble TNF- α receptors in the ocular fluids of patients with active uveitis, which stimulates T cells that infiltrate from ocular fluids to increase TNF- α production during the inflammatory condition [19]. Thus, the authors conclude that the soluble forms of the TNF receptors are among the inflammatory cytokines that play a major role in ocular inflammation. Therefore, it has been suggested that TNF inhibitors can prevent recurrences of uveitis. The results of the study of Gritz *et al.* included a large series of patients with AS under treatment with TNF inhibitor, demonstrating the reduction in the incidence of anterior uveitis [20], as was also shown in the study of Braun *et al.* [7], which revealed that anti-TNF therapy (infliximab and etanercept) prevented flares of anterior uveitis in patients with severe AS. Another study performed by Guignard *et al.* evaluated the efficacy of anti-TNF agents (infliximab, etanercept and adalimumab) in reducing the occurrence of uveitis flares in patients with SpA, suggesting a difference in the efficacies of the soluble TNF receptor and anti-TNF antibody treatments [21]. The study demonstrated that the

overall incidence of uveitis flares in SpA patients, decreased with anti-TNF treatment, with a relative risk of 2.4. However, when analyzing each agent, it was concluded that soluble TNF receptor treatment did not reduce flares, whereas anti-TNF antibodies greatly reduced flares. The authors also observed that there were patients receiving etanercept treatment in whom uveitis flares appeared for the first time during the treatment (which did not occur with anti-TNF antibody treatment), as was previously seen by Reddy *et al.* [22].

These episodes were often severe and occurred not only in patients with AS, but also in patients with rheumatoid arthritis, which is usually associated with scleritis but not with isolated uveitis. In addition, exacerbation of intraocular inflammation by TNF inhibitors has occasionally been observed in experimental models of autoimmune uveitis [23].

An important question that arises is: why is etanercept associated with cases of uveitis as compared with infliximab and adalimumab? One explanation could be that this is due to the additional inhibitory effect of etanercept on TNF- β , in contrast with infliximab and adalimumab that are only effective against TNF- α . However, TNF- β has been associated with uveitis in animal models [23] and, therefore, it would be expected that etanercept could produce a greater inhibitory effect on uveitis than infliximab and adalimumab, rather than *vice versa*. Another theory suggests that etanercept and infliximab have different effects on cell apoptosis. As etanercept does not induce apoptosis, this may represent the cause of its ineffectiveness in Crohn's disease (CD), where, in the case of uveitis, the explanation could be that, as a soluble receptor, etanercept prolongs the half-life of TNF within the eye, and thus potentially leads to uveitis if the receptor ligand complex is not cleared. Thus, etanercept is different from the anti-TNF- α monoclonal antibodies in terms of treating the uveitis flares, and it has been suggested that anti-TNF- α antibody treatment is preferable to treatment with the soluble TNF- α receptor agent in patients with SpA experiencing recurrent uveitis flares [24,25].

Other options in reducing uveitis flares, usually used as a steroid-sparing medication are: sulfasalazine [26], methotrexate [27], and mycophenolate mofetil, which has been proven to be safe and effective as a second- or third-line adjunct/alternative immunosuppressant in the difficult or refractory cases of uveitis, and also when used in combination with ciclosporin A, tacrolimus and anti-TNF agents [28]. In a

Table 1. Extra-articular manifestation of spondylarthropathies.

Clinical features	Frequency
Concept related extra-articular manifestations	
Eye	
Anterior acute uveitis	30–40% symptomatic HLA-B27 strongly associated
Intestinal	
Intestinal inflammation	5–10% symptomatic 60% asymptomatic HLA-B27 associated
Skin	
Psoriasis	90% psoriasis vulgaris
Pyoderma gangrenosum	In 5% of UC and 2% of CD
Erythema nodosum	Up to 15% of patients with IBD
Circinate balanitis	12–14% of patients with ReA
Keratoderma blennorrhagica	Typical for ReA
Non-concept related extra-articular manifestations	
Pulmonary	
Restrictive pulmonary pattern	Subclinical
Apical fibrosis	1–2%, subclinical
Pleuro-pulmonary lesions	60–80%, subclinical
Cardiac	
Valvular pathology	2–10% symptomatic
Conduction disturbances	Frequently asymptomatic
Myocardopathy	Increased with disease duration of more than 15 years and patient age of more than 45 years
Renal	
IgA nephropathy	Rare
Amyloid nephropathy	Symptomatic (>90% proteinuria)
NSAID nephropathy	Rare, symptomatic
Osteoporosis & vertebral fractures: 10–20% vertebral fractures	
Neurological	
Atlanto-axial subluxation	Frequently subclinical
Cauda equina syndrome	Rare, symptomatic
Radiculopathies	Variable symptomatology

CD: Crohn's disease; HLA: Human leukocyte antigen; IBD: Inflammatory bowel disease; ReA: Reactive arthritis; UC: Ulcerative colitis.

recent study comparing antimetabolite drugs in patients with noninfectious uveitis, Galor *et al.* suggested that the time to control ocular inflammation was faster with mycophenolate than with methotrexate, and for azathioprine therapy, a higher rate of treatment-related side effects compared with the former two agents has been noted [29].

Intestinal manifestations

Spondylarthropathies are associated with inflammatory gut lesions that can evolve to IBD. Between 5 and 10% of AS patients have IBD, particularly CD, but also ulcerative colitis (UC) [30]. Ileocolonoscopy and further histological analysis revealed subclinical gut

inflammation in approximately 60% of patients with AS [31], frequently of the terminal ileum. The intestinal lesions are histologically divided into acute (neutrophil dominant) and chronic (lymphocyte dominant). This classification refers to the morphological characteristics and not to the onset or duration of the disease. The acute type resembles an acute and self-limiting bacterial enterocolitis, with a well-preserved mucosal architecture (FIGURE 1). By contrast, intestinal architecture is profoundly altered in the chronic type of inflammation, with blunted and fused villi and distorted crypts (FIGURE 2). The infiltrate consists of a mixed cell population, with lymphoid infiltrates in the chronic subtype, and primarily neutrophilic predominance in acute inflammation. The chronic form closely resembles ileal CD, being characterized by the formation of granulomas. It has been suggested that ileitis in SpA represents subclinical CD that does not evolve to CD in most of the patients due to a lack of genetic or environmental factors. The acute type was more frequently observed in ReA, whereas chronic inflammation is more linked with UndSpA and AS, especially in AS patients with peripheral arthritis [32]. Furthermore, ileocolonoscopy studies confirmed the strong relationship between gut lesions and the synovial

lesions in the swollen joints [32], which revealed that gut and joint inflammation are related in SpA [33–35].

This theory is also sustained by the fact that chronic lesions on gut histology were associated with more advanced radiological signs of sacroiliitis and spondylitis, and with more erosive and destructive peripheral articular disease. In addition, on follow-up in patients with SpA in whom a second ileocolonoscopy was performed, remission of joint inflammation was associated with the disappearance of the gut inflammation, whereas persistence of arthritis was mainly associated with the persistence of gut inflammation [35]. Most patients with normal histology or acute intestinal lesions had exhibited transient arthritis, whereas the majority of those with chronic intestinal lesions had persistent inflammatory joint symptoms. It has also been shown that the presence of chronic ileal lesions predict an aggressive evolution of the arthritis in patients with AS [34], but systematic screening of AS patients by ileocolonoscopy is not routinely recommended in the absence of gut symptoms, as only a small group of AS patients with subclinical gut inflammation will develop IBD over time. Of 123 patients with SpA, eight (6.5%) patients developed CD 2–9 years after the appearance of rheumatic symptoms in the study by Mielants *et al.* [33].

These clinical findings demonstrate that gut inflammation is linked to peripheral joint disease in SpA, raising the question of a common immunological and inflammatory pathway in these two distinct organs. In this regard, there were initial hypotheses that had tried to demonstrate an intestinal–spondylitic association in *HLA-B27*-positive patients with AS in relation to a shared amino acid sequence between B27 and *Klebsiella*'s nitrogenase enzyme [36], or between certain subtypes of collagen and some other bacteria such as *Yersinia enterocolitica* and *Saccharomyces cerevisiae* [37]. Maki-Ikola *et al.* studied the relationship between levels of IgA anti-*Klebsiella pneumoniae* and the inflammatory changes of the intestinal mucosa in AS patients with the axial and peripheral form of disease [38]. They observed a high level of IgA anti-*Klebsiella pneumoniae* in the plasma of patients with the axial form of the disease and associated intestinal inflammation, but not in patients with the peripheral form of AS or the axial form without inflammatory intestinal involvement, which may support the idea of the involvement of *K. pneumoniae* in different forms of AS. However, these studies do not provide any explanation as to why the disease should develop,

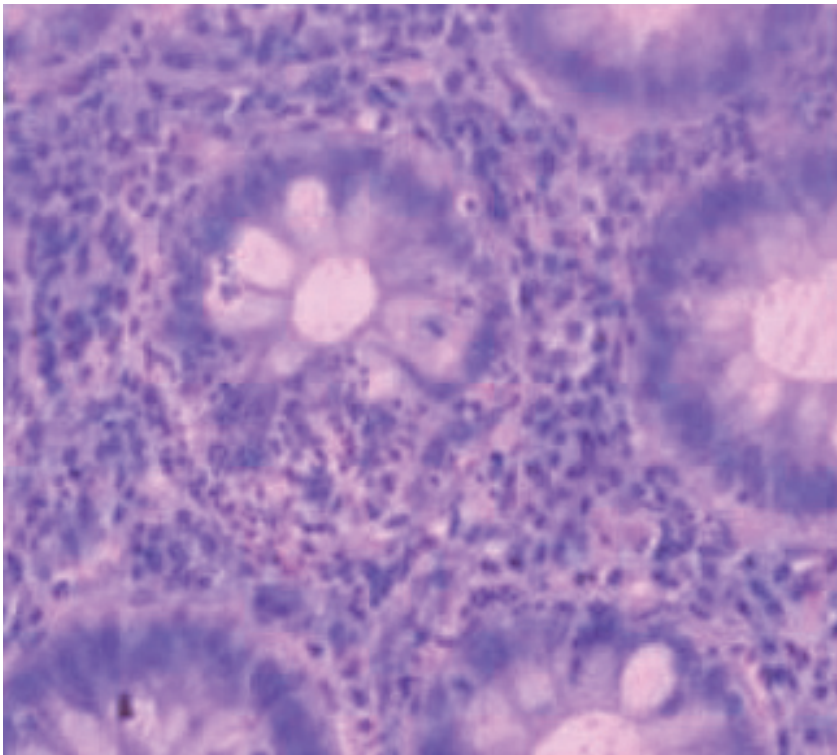


Figure 1. Acute ileitis. The neutrophilic infiltrate resembles bacterial enterocolitis. Reproduced from [153].

since the above findings relate to disease activity rather than to the diagnosis. More recent studies that evaluated both humoral and cellular response in AS patients compared with healthy relatives, and could not support the above hypothesis [39]. Despite sharing a common sequence of amino acids [36], the tertiary structure is rarely affected (the basis of antigenicity), a fact that cast doubt on this *Klebsiella* hypothesis.

The association with *HLA-B27* is less strong in IBD-associated AS, with only 25–33% [40–42] of the patients being *HLA-B27*-positive, in contrast with idiopathic AS in which 75–95% of the patients are *HLA-B27*-positive. The observation that *HLA-B27*-negative patients with SpA seemed more susceptible to develop ileitis (in particular, CD), suggested that other genes are also implicated [42,43].

There is evidence for an association between intestinal inflammation in AS with the CD-related *CARD15* mutations [44]. Laukens *et al.* demonstrated that *CARD15* polymorphisms in patients with SpA are associated with a higher risk of evolution to chronic gut inflammation. Of all patients with SpA carrying the *CARD15* polymorphisms tested, 71% displayed chronic gut inflammation, none had acute inflammation and 29% had normal histology, suggesting that these polymorphisms are associated with a higher risk for development of chronic gut inflammation.

The association between *CARD15* and radiographic sacroiliitis was independent of *HLA-B27* [45], which is consistent with the nonassociation or weak association of radiographic sacroiliitis with *HLA-B27* in IBD patients [43,45,46].

Although carrying *CARD15* mutations puts AS patients at risk for subclinical intestinal inflammation [44], this remains asymptomatic in the majority of patients with SpA, and it can be considered a unique model for detection of early genetic markers for CD [47]. It is thus questionable if an ileocolonoscopy should be performed in SpA. Therefore, if the patient has *HLA-B27*-negative AS, an ileocolonoscopy may be indicated, since this subgroup may be at particular risk for developing symptomatic CD. It is also important that an ileoscopic distinction is made between ileitis of SpA and NSAID enteropathy (which affect the small intestine), as metronidazole, sulfasalazine and misoprostol all reduce the inflammation, bleeding and protein loss in NSAID enteropathy, while only sulfasalazine is known to affect the spondylarthropathic ileitis. Ileocolonoscopy can differentiate between the two conditions, since the ‘diaphragmatic’

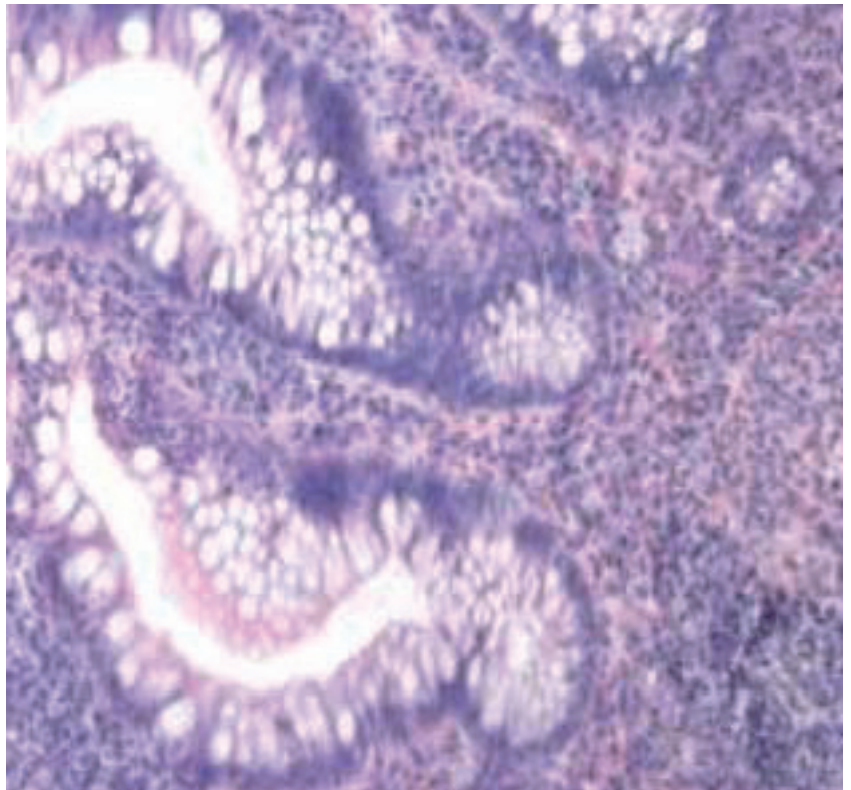


Figure 2. Chronic ileitis: the villus architecture is disturbed. Villi are irregular and surrounded by oedematous lamina propria containing mainly mononuclear cells. Reproduced from [153].

NSAID-induced strictures are very characteristic; however, in certain cases, surgery is necessary for the differential diagnostic [48].

The treatment options for patients with active AS associated with IBD include physiotherapy, local corticosteroid injections, NSAIDs and anti-TNF agents. Unfortunately, conventional DMARDs, such as methotrexate, azathioprine or sulfasalazine, which are all effective for treating IBD, are considered to be ineffective or poorly effective in the axial form of AS [49,50]. Likewise, anakinra, an IL-1 receptor antagonist, and leflunomide are not effective in treating axial symptoms in AS, and have not yet been tested in IBD [51,52]. The co-occurrence of IBD in patients with AS has important therapeutical implications in the light of the use of NSAIDs, because the underlying bowel disease can be re-activated. NSAIDs are the first-line therapy in all AS patients [49]. There are numerous reports on patients without AS, suggesting that NSAIDs exacerbate IBD or re-activate pre-existing IBD [53,54]. Both NSAIDs and Cox-2 inhibitors appear to be capable of triggering a flare-up of IBD by inhibiting the intestinal production of prostaglandins involved in the tissue reparative process, and therefore they should be avoided, when possible, in patients with

IBD [55]. On the other hand, a retrospective evaluation of the effects of NSAID therapy in patients with IBD failed to reveal any correlation between NSAID use and the likelihood of active IBD [56]. Given the aforementioned data, in daily practice AS patients should be assessed with regards to the symptoms suggestive of IBD. If IBD is suspected on clinical grounds, endoscopic examinations should be performed. If a diagnosis of IBD is then made, NSAIDs should be used intermittently in low to moderate doses [47].

TNF- α antagonists are effective for both articular and intestinal inflammation, and are currently used for the induction of remission and for maintenance of IBD associated with active AS. Although all three anti-TNF- α compounds, infliximab, etanercept and adalimumab, had shown short-term and long-term efficacy in controlling signs and symptoms in patients with active AS [57], for both spinal disease and peripheral arthritis, their action upon intestinal inflammation is not equally effective. Infliximab [58,59], and more recently adalimumab [60,61], were proven effective in CD and UC [62,63], whereas etanercept treatment failed to provide clinical efficacy [64,65]. Thus, it seems that although etanercept is clearly effective in treating signs and symptoms of sacroiliitis and spondylitis, with clear regression of active inflammatory lesions of the spine as detected by magnetic resonance imaging [66], gut inflammation does not respond to etanercept therapy [64,65,67]. The differences in incidence of new flares of IBD in patients with AS treated with anti-TNF therapies were recently reviewed [57], with data from seven placebo-controlled trials and two open trials. The authors performed a combined analysis of all mentioned studies on IBD flares in patients with AS during anti-TNF therapy, and concluded that, unlike etanercept, infliximab efficiently prevents flares and newly developed IBD. In this review, the incidence of IBD in AS patients treated with infliximab was 0.2/100 patient-years, while for etanercept-treated groups it was 2.2/100 patient-years, compared with 1.3/100 patient-years in the placebo groups. On average, the risk for a patient with AS developing a flare or new-onset IBD appears to be ten-times higher for etanercept than for infliximab. The few data available on adalimumab also suggest a decreased incidence of IBD flares in AS patients [68,69], but cases of clinical activity of CD and UC in AS patients treated with adalimumab were reported [69]. One possible explanation for this difference in activity is provided by the signaling characteristics of these biologicals. Both anti-TNF antibodies, but not etanercept, bind transmembrane-bound TNF

on lamina propria T lymphocytes and, by reverse signaling (dimerization of transmembrane TNF by infliximab) and activation-induced cell death, induce apoptosis of activated lymphocytes, thereby covering a fundamental defect in CD [70,71].

Thus, both infliximab and adalimumab are capable of improving IBD and reducing IBD flares, while etanercept is not, which is why a positive history of IBD should be considered as a contraindication for etanercept therapy in AS patients. However, there is still no evidence regarding the screening for silent gut inflammation in patients evaluated for anti-TNF therapy.

Skin manifestations

A variety of skin manifestations may often be seen in patients with AS and other SpA, yet there is no clear data about the relationship between skin lesions and the *HLA-B27* antigen. Four types of skin lesions are usually found in spondylitic patients.

Circinate balanitis & keratoderma blennorrhagica

Circinate balanitis and keratoderma blennorrhagica are both very typical lesions seen in ReA and frequently precede the onset of arthritis. Circinate balanitis is defined by circinate or gyrate white ulcerative plaques that grow centrifugally and eventually cover the entire surface of the gland penis. The penile shaft and scrotum can be involved. The lesions become keratotic and painful in circumcised patients. Keratoderma blennorrhagica develops 1–2 months after the onset of arthritis – it begins as clear vesicles on erythematous bases and progresses to pustular keratotic lesions that coalesce to form plaques that are painful under pressure and affect 12–14% of the patients with ReA (palmoplantar pustulosis). The palms and soles are most commonly involved with these keratotic papules, plaques and pustules that resemble pustular psoriasis, from which it cannot be clinically or histologically differentiated [72]. Other possible locations of keratodermic lesions are the finger tips, trunk and skull. These lesions are not associated with the disease evolution.

Erithema nodosum

Erithema nodosum is the cutaneous disorder most frequently seen in patients with associated IBD, occurring in up to 15% of patients [73]. It typically appears as raised, tender, red or violet subcutaneous nodules that often do not exceed 5 cm in diameter. The nodules are most often located on the extensor surfaces of the

extremities, particularly over the anterior tibial area. Biopsy of these lesions shows focal panniculitis. Commonly, it appears at the same time as intestinal disease activity, and the treatment of the underlying bowel disease usually determines healing of the lesions.

Pyoderma gangrenosum

Pyoderma gangrenosum (PG) is an ulcerative disease of the skin of unknown origin, with approximately 50% of cases being associated with an underlying systemic disease, most commonly IBD, arthritis or a lymphoproliferative disorder [74]. It occurs in up to 5% of patients with UC and 2% of patients with CD, and it often has more severe consequences than erythema nodosum [75].

The lesions may initially appear as single or multiple erythematous papules or pustules frequently preceded by skin trauma, with chronic and relapsing appearance. It most commonly occurs on the legs, but any area of the body can be involved, including the abdominal wall adjacent to stomas after colectomy. Subsequent necrosis of the dermis leads to the development of deep ulcerations that contain purulent material (FIGURE 3) that is usually sterile on culture, with biopsy revealing nonspecific findings consistent with sterile abscess. PG accompanies the activity of intestinal disease in up to 50% of patients, and the therapy towards underlying IBD does not usually produce the healing of the skin lesions [76,77]. In this case, the treatment needs to include high doses of prednisone for several weeks, or methylprednisolone pulses. Other potential therapies include ciclosporin A after initial steroids or in combination with steroids [78]. The drug induces an early response, but has little impact on the incidence of recurrences [79]. Therefore, combination with other drugs can become necessary, even after initial response to ciclosporin A monotherapy. The combination of steroids with diaminodiphenylsulfone (dapsone), only for patients with a normal glucose-6-phosphate dehydrogenase level, is the most popular therapy. Azathioprine and sulfasalazine are a good choice when the underlying disease is UC or CD. Cyclophosphamide pulse therapy followed by either azathioprine or methotrexate is an effective treatment in steroid-refractory CD. In cases of CD-associated PG, long-term remissions, lasting for up to 30 months, may be achieved in this regimen [80]. The TNF- α inhibitor infliximab was reported to be effective in PG associated with IBD combined with low-dose methotrexate [81]. A number of placebo-controlled trials additionally confirmed the good response of PG to treatment with infliximab [82,83]. The



Figure 3. Pyoderma gangrenosum.

positive effect on PG was also seen with etanercept [84]. A topical or systemic antibiotic should be added in case bacterial superinfection is either suspected or documented.

Psoriasis

Psoriasis is present, by definition, in more than 70% of patients with PsA. Psoriatic lesions are present before arthritis but, in 15% of the patients, arthritis precedes skin lesions [85]. Axial manifestations occur in only approximately 5% of cases, whereas 20–50% of patients have involvement of both the spine and the peripheral joints [86], and only those patients with axial manifestations and/or predominately symmetrical peripheral arthritis of the lower limbs fit the pattern suggested by the European Spondyloarthropathy Study Group (ESSG) classification of SpA [87]. Any type of psoriasis may be present in SpA, but, in 90% of cases, vulgar psoriasis is present. There is no relationship between extension, localization and the intensity of the skin involvement by psoriatic lesions and the severity of articular involvement. Only 35% of the patients describe concomitant skin lesions and articular activity. Sudden and intense onset of psoriasis associated with articular involvement or rapid deterioration of previous skin lesions in a patient with PsA should raise the suspicion of HIV infection.

Axial involvement in most patients with PsA may present either as sacroiliitis, often asymmetric and asymptomatic, or spondylitis affecting any level of the spine in a 'skip' fashion. When compared with patients with AS, patients with PsA seldom have impaired mobility or progress to ankylosis [88].

Since only half of patients with PsA have progressive disease, mild PsA is quite common and often successfully treated with NSAIDs [89]. Methotrexate is frequently used as the primary DMARD in PsA, because of its efficacy in

treating both skin and joint involvement and its low cost [90,91]. Sulfasalazine showed modest benefit in patients with PsA [92], while leflunomide showed a 59% probability of achieving Psoriatic Arthritis Response Criteria (PsARC) in patients in a randomized, double-blind, placebo-controlled study [93]. Other DMARDs, including anti-malarials, ciclosporin and gold, are less frequently used because evidence for their efficacy is less convincing than for methotrexate, sulfasalazine and leflunomide [89].

Most dermatologists avoid systemic corticosteroids in the treatment of patients with psoriasis because of the potential risk of pustular and erythrodermic flares when discontinued. However, rheumatologists often use systemic corticosteroids in the short- and long-term treatment of PsA, in small dosages (5–10 mg/day). Short-term data indicated that both etanercept [94] and infliximab can delay radiographic progression in patients with PsA [95]. For adalimumab it was also shown to reduce signs, symptoms and disability in patients with active PsA, as well as improving psoriasis lesions in patients [96]. In a recent study, the biologic treatment (infliximab, etanercept and adalimumab) for PsA lead to a sustained response in long-term therapy with a low rate of nonresponse; the majority of non-responder patients had responded to second- and third-line therapy [97]. There are published cases describing psoriasis or psoriasiform lesions after TNF- α antagonist therapy in some patients. The development of psoriasis was seen in all types of inflammatory diseases treated with TNF- α antagonists [98], and it is considered a class effect that has been reported with all the currently available TNF- α antagonists [99]. The prevalence of this adverse effect has been estimated at 1.5–5% of patients taking TNF- α antagonists [100]. The skin lesions develop within the first few months of therapy, palmoplantar pustulosis being the most common feature [99]. Out of the three anti-TNF agents, a previous history of psoriasis seemed more common in patients who experience psoriasis onset or exacerbation during etanercept therapy (55%). Thus, previous psoriasis may be a risk factor for psoriasis exacerbation during etanercept therapy [100].

Non-concept extra-articular manifestations

Cardiac manifestations

In daily clinical practice symptoms of heart involvement in AS patients are rarely seen. Based on published findings, clinically significant cardiac disease occurs only in 2–10% of patients [101].

Recent studies have shown that cardiovascular complications in SpA also include impaired endothelial function and coronary microvascular function, suggesting that vascular pathologies such as atherosclerosis could also be involved in the increased cardiovascular mortality rates. Potential mechanisms for cardiovascular complications include a chronic inflammatory condition with increased levels of circulating cytokines and acute phase reactants and a more atherogenic lipid profile. The beneficial effects of statin treatment on circulating inflammatory mediators and atherogenic lipid profiles could reveal new therapeutic options for patients with SpA [102].

Three types of cardiac lesions can be found in AS patients: valvular pathology, conduction disturbances of the atrioventricular node and myocardial involvement.

Valvular pathology

Valvular pathology consists of aortitis and aortic insufficiency (isolated aortic regurgitation, aortic root and ascendant aorta dilatation), sometimes with the need for cardiac surgery. In addition, the affection of the anterior mitral valve leaflet fibrosis and mitral regurgitation may be seen. These abnormalities are the result of the sclerosing inflammatory process, involving aortic root, aortic valve cusps that may extend into the ventricular septum and the atrioventricular node, leading to conduction disorders. The prevalence of sub-clinical aortic root and valve disease may be as high as 82% in AS patients when transesophageal echocardiography is performed [103].

Conduction disturbances of the atrioventricular node

Conduction disturbances of the atrioventricular node are in most cases silent incomplete blocks, revealed through routine electrocardiograms, and are only in a few cases complete blocks that require a pacemaker. Screening for a prolonged QT time has been recommended since it might be associated with arrhythmias in asymptomatic patients [104].

Myocardial involvement

Several studies have reported cardiac abnormalities of left ventricular diastolic function [105–107]; nevertheless, cardiological evaluation with echocardiography should not be recommended routinely in patients with long-standing AS [105].

Although the prevalence of cardiac abnormalities does not seem to be related to therapy or the severity of the skeletal disease, cardiac

manifestations have been associated with age over 45 years and disease duration of longer than 15 years [108].

Pleuropulmonary manifestations

Lung involvement in AS was initially described in 1941, but it has only been since 1965 that it was considered as an extra-articular manifestation of the disease. Respiratory abnormalities have been reported in from 0% to over 30% of AS patients [109].

Pleuropulmonary lesions are believed to be an uncommon and delayed manifestation of AS. Histological studies of transbronchial biopsies found nonspecific interstitial fibrosis with degeneration of collagen and elastic fibers and, in some cases, focal lymphocytic infiltrates were seen. In patients with advanced disease, cystic cavities were visible within the fibrous areas. No granulomas or signs of vasculitis were found [110–112].

The high-resolution computed tomography (HRCT) changes included apical fibrosis, interstitial lung disease, emphysema, bronchiectasis and pleural thickening. In general, the HRCT changes were of a mild degree, and no correlation was observed between HRCT abnormalities, pulmonary function test parameters and the indices of AS. Spontaneous pneumothorax was reported to be a rare complication, but tended to occur in those patients with fibrobullous disease [113].

Respiratory function impairment

Costovertebral joint involvement, which leads to chest wall rigidity, is responsible for the restrictive ventilation pattern of the disease. Although expiratory muscle performance is maintained, the chest wall rigidity causes muscle exhaustion, so that complete expiration cannot be achieved. Vital capacity (VC) is proportionately decreased with disease severity, but patients with advanced disease rarely have a VC of less than 60% of that predicted. Residual volume (RV) and functional residual capacity (FRC) are increased or normal, in contrast to findings in other restrictive diseases. Thus, the decrease in total lung capacity ($TLC = VC + RV$) is less important than the decrease in VC [114].

Pulmonary fibrosis

Apical fibrosis is the most recognized pulmonary manifestation of AS, and it develops in the upper lung lobes and follows a progressive course. The frequency of upper lobe fibrosis is variable in different published series. A retrospective review of 1028 AS patients found 22 patients (2.1%) with apical lung fibrosis detected on chest

radiographs [115]. Pulmonary fibrosis associated with AS by its location in the upper part of the lungs is, in contrast with the basal involvement, frequently seen in pulmonary fibrosis associated to other systemic diseases [111,116,117]. The main complications associated with apical fibrosis are infections (*Aspergillus* and atypical mycobacteria) and pneumothorax. Smoking is widely believed to promote apical fibrosis and interstitial inflammation. Exposure to tobacco smoke is associated with increased macrophages and neutrophil counts in the deep lung parenchyma [118].

Pleural & parenchyma involvement

Thickening of the apical pleura is commonly concomitant with apical fibrosis, although it may precede the fibrosis, indicating that the two abnormalities are related to each other. Apical bronchiectasis is usually an asymptomatic lesion, due to the airways traction by the fibrotic lung parenchyma, which in its early stages is not visible on chest x-rays [119].

Chest x-ray should be routinely obtained in AS patients, and HRCT should be considered in patients with normal radiographic findings, but abnormal physical findings [120]. In addition, with the increasing use of anti-TNF- α agents in patients with AS, both HRCT and bronchiolo-alveolar lavage are useful for ruling out TB before treatment initiation in patients with chest radiographic abnormalities. Physicians should be aware of the abnormalities associated with AS, so that they can distinguish them from changes caused by TB or other infections. Prophylactic measures, including smoking cessation and physiotherapy to improve overall and respiratory function, are useful. It is not known if early appropriate treatment of AS decreases the risk of pleuropulmonary involvement [116,118]. Life-threatening pulmonary complications include massive hemoptysis secondary to *Aspergillus* [121], and cardiorespiratory failure due to bacterial infection.

Renal manifestations

The most frequent etiology of renal impairment in patients with AS is secondary amyloidosis, affecting approximately 5–13% of the studied populations with AS [122,123], followed by IgA nephropathy, mesangioproliferative glomerulonephritis, membranous nephropathy, focal segmental glomerulosclerosis and focal proliferative glomerulonephritis [124].

Treatment-associated nephrotoxicity may result in NSAID nephropathy or disease-modifying agent toxicity, which are used in SpA on a long-term basis. The nephrotoxic potential of

NSAIDs is well known – renal deterioration may result in tubulointerstitial nephritis or as decrease in medullary blood flow in patients with pre-existing renal damage [125].

Amyloid nephropathy is the most frequent renal manifestation seen in AS. Clinically, it appears as a late complication of AS, associated with a long-term inflammatory status, and it is frequently seen in patients who also present peripheral arthritis. Histologically, it is characterized by important glomerular amyloid deposits. Proteinuria is present in 90% of the cases and may be accompanied by microhematuria. The prognosis is related to the extent of renal failure (creatinine >2 mg/dl) and not to the severity of proteinuria. The factors implicated in producing renal failure are not well known, but it has been suggested that vascular deposits of amyloid in the renal vessels could be involved in the progression of renal failure [126].

TNF- α has a central role in the pathogenesis of amyloidosis. TNF- α , like other pro-inflammatory cytokines including IL-6 and IL-1, stimulates hepatocytes to produce serum amyloid A (SAA), which is the precursor of type amyloid A amyloid fibrils [127]. TNF- α also plays a role in the proteolysis of SAA to AA amyloid in macrophages. Furthermore, TNF- α enables the expression of receptor for advanced glycation end products (RAGE) by macrophages in amyloid deposits. RAGE and amyloid fibrils interaction is responsible for cytotoxicity and tissue damage by signaling the cascade that causes sustained activation of NF- κ B [128].

Although renal disease is the most significant organ manifestation of secondary amyloidosis, digestive manifestations may also be present, and they together account for 90% of the symptoms associated with secondary amyloidosis. This is why colestasis, diarrheic or pseudo-occlusive syndrome due to big amyloid masses in intestinal submucosa may occur. In rare cases, vascular amyloid deposits can lead to intestinal perforation.

The diagnosis of secondary amyloidosis needs to be demonstrated by either subcutaneous fat biopsy or biopsies taken from rectal submucosa that will confirm the diagnosis.

Diminishing the overproduction of SSA may be achieved by reducing the inflammatory status of the disease. It was shown that the adequate treatment of AS also diminishes proteinuria and slows down renal failure, but disease flares were associated with the reactivation of proteinuria [129]. There is literature data that have shown the efficacy of azathioprine or methotrexate [130,131] in patients. Chlorambucil

and cyclophosphamide have also shown some efficacy in renal amyloidosis, as compared with historical controls [132]. However, the risk of myelotoxicity, leukemia, and sterility [133] is to be considered. Colchicine has also been used for proteinuria; some studies even described histological regression of amyloid deposits [134].

Although there are few published reports about the efficacy of anti-TNF agents in secondary AA, they are a promising treatment as they reduce amyloid load and disrupt RAGE-induced propagation of amyloidogenesis and tissue damage. It is known that patients with amyloidosis can have renal, hepatic and/or cardiac failure that might alter the pharmacokinetics of anti-TNF and/or the tolerance to treatment. These patients can also be at high risk for infections and thrombosis. Etanercept had been used as a choice treatment for amyloidotic renal involvement complicating AS and it was well tolerated, rapid and highly effective in suppressing proteinuria and stabilizing renal function [127,135].

IgA nephropathy

IgA nephropathy represents a rare cause of glomerulonephritis associated with AS. Histologically, there are mesangial deposits indistinguishable from primary IgA glomerulonephritis (Berger's disease). High levels of IgA in the serum of patients with AS have shown association with disease activity in some studies [136]. There is no specific treatment for the condition – in advanced cases dialysis and renal transplant are the only possible therapeutic choice.

Osteoporosis & vertebral fractures

The association of AS and osteoporosis (OP) has been described by several studies since the 1990s. It was usually the AS that was diagnosed first, although occasionally OP may be the presenting feature [137].

An increased prevalence of axial OP occurs even in early, mild forms of AS, and the demineralization process continues for many years until the advanced stages of the disease. In AS patients, OP is largely confined to the axial skeleton, in contrast to the pattern of OP seen in rheumatoid arthritis. OP is also more common in patients with syndesmophytes, cervical fusion and peripheral joint involvement. These variables are not all independent, as they may be indicators of disease duration.

Cytokines such as TNF- α and IL-6 may play an important part in the pathogenesis of OP in early AS, and IL-6 levels have been correlated with markers of disease activity and severity. In

late AS, mechanical factors such as decreased mobility and the support provided by extraspinal bone may play a role in vertebral OP [138]. The rigid spine of spondylitic patients is at risk of fracture, deformities and kyphosis. Increased hyperkyphosis can, therefore, be regarded not only as a clinical consequence of the disease, but also as an indicator of vertebral fractures [139].

Measurements of bone formation and bone degradation markers may provide insight into the pathogenesis of OP in AS. Currently, the data are scarce for determining what role they should play in routine clinical management. Both decreased bone formation and increased bone catabolism have been reported in patients with AS, although there is no clear consensus of findings between different groups. For this reason it is difficult to justify the use of such markers in clinical practice.

Measurements of 25-OHD₃, 1,25-OHD₃ and PTH were normal, while osetocalcin level was low in AS patients studied by Franck and Keck [139], but abnormal for Lange *et al.* [140], who observed decreased levels of 1,25-OHD₃ and PTH in patients with AS. These studies emphasize the necessity of simultaneous measurement of many indicators of bone formation and resorption [138]. Bone formation and resorption biochemical markers do not correlate with bone mineral density (BMD) of the lumbar spine or femoral neck [141,142]. No significant differences were seen in any marker of bone turnover in AS patients with vertebral fractures compared with AS patients without vertebral fractures [143].

Bone mineral density measurement early in the disease should include dual x-ray absorptiometry of both spine and hip, as BMD may be severely reduced at these sights. The development of syndesmophytes in late AS can lead to difficulties in lumbar dual energy x-ray absorptiometry (DEXA) interpretation, as they may hide osteoporotic vertebrae. In this regard, more accurate assessment of lumbar BMD, and one that correlates better with femoral neck BMD, may be obtained by quantitative CT scanning or DEXA scanning of the lateral aspect of L3 vertebra [138].

The main clinical manifestations of OP are due to vertebral fracture. In daily practice, vertebral fractures can be overlooked, even when they are symptomatic, as acute and chronic back pain is common in AS patients. Vertebral pain is frequently attributed to disease activity, as long as the vertebral fracture is not considered in the differential diagnosis of back pain. The delay in diagnosis of the vertebral fractures in patients

with pre-existing back pain is responsible of increased morbidity in AS patients [144]. The prevalence and incidence of vertebral fractures is therefore influenced by the definition of the degree of deformation of the vertebral body. In cross-sectional studies, there are controversies regarding which deformities of vertebral bodies should be considered fractures. In addition, there are no available data about the prevalence of vertebral deformities/fractures in the young adult population, which make it difficult to interpret them in AS patients younger than 50 years of age. In 2006, seven new case reports were published in addition to the already long list on distinctive characteristics of some aspects of vertebral fractures in AS [145–147].

These fractures are characterized by their unusual location (e.g., at the cervical spine, involvement of the posterior arch of the vertebrae), their anatomic location (transvertebral with variable degrees of dislocation, transdiscal through the syndesmophytes) and their complications with variable degrees of neurological deficits [148].

In strong contrast with postmenopausal OP, there are reports that suggest the presence of neurological complications after fractures of the vertebral body or its dorsal components in patients with AS. These complications include spinal cord or nerve root lesions, and the occurrence of paravertebral hematomas resulting in variable degrees of sensory or motor deficits. Due to defective fracture healing, pseudoarthrosis with instability in the posterior arch structures of the vertebrae can occur [148]. The resulting neurological deficit ranges from mild sensory loss to complete paraplegia, with a higher incidence of spinal cord injury among patients with AS. Vertebral compression fractures are more frequent in AS males (13.7%) than females (8.3%), and increase with age, disease duration and spinal restriction, the presence of peripheral joint involvement and more extensive syndesmophyte formation [148].

If there is suspicion of vertebral fractures, radiographs of the spine should be performed. Additional imaging techniques are indicated in cases of persistent post-traumatic pain, in order to avoid delays in diagnosis and therapy.

The treatment of OP in AS is at present similar to that used for OP, although in this population, most being male and young, there is a limited role for hormone-replacement therapy, exercise regimens and bisphosphonates being widely used. Drug treatment for OP should be considered in patients with vertebral fractures or a BMD with a T score of less than -2.5. From

a pathophysiological perspective, the target for avoiding vertebral fractures is not only to prevent bone loss within the vertebrae, but also to prevent excessive bone formation around the vertebrae. Recently, Demis *et al.* observed that the anti-TNF- α therapies are effective in this type of OP, probably due to their capacity to inhibit the inflammatory response, as well as balancing the bone remodeling [149].

Neurological manifestations

Atlantoaxial subluxation is a late-phase complication, affecting 2% of patients, less than in rheumatoid arthritis and, in contrast with rheumatoid arthritis, it is not accompanied by neurological symptomatology [150]. Isolated noncompressive thoracic and lumbar lesions are associated with disease activity and are typically transitory. Cauda equina syndrome affects patients with advanced AS, and is due to increased pressure of the cerebrospinal fluid, which determines arachnoidal dilatation and cyst formation, finally affecting nerve roots down to D12. Other authors consider this is secondary to arachnoiditis, which would be responsible for initiating the symptomatology. Clinical features consist of sensitive disturbances of the inferior limbs and of the perineal region. Motor and sphincter alterations (rectal and urinary) are less frequent at initial phases, and become evident with late disease. The diagnosis is clinical and it is sustained by CT and MRI findings. Electromyography is not necessary for diagnosis, although it is useful in evaluating the extent of neurological lesions and their progression in time.

There is no effective treatment, either medical or surgical, for this condition, but rehabilitation for the neurological deficit may be helpful [151].

Expert commentary & future perspective

Since the introduction of TNF blockers, important changes have been obtained in the therapeutic response previously not known with molecules such as NSAIDs, methotrexate or sulfasalazine. Nevertheless, there is literature data that shows a lack of a suitable therapeutic response in at least 30% of the patients treated with these new anti-TNF therapies.

New molecules have been developed for the control and treatment of patients with AS (golimumab, abatacept and rituximab). These agents were also initially used in patients with rheumatoid arthritis in which they have demonstrated good therapeutic effect in controlling disease activity.

Golimumab, a next-generation human anti-TNF- α monoclonal antibody (CNTO 148), has demonstrated good results in rheumatoid arthritis patients, and also in a Phase III study in AS patients. Golimumab is being studied as a monthly subcutaneous injection, and as an every-12-week intravenous infusion (approximately 30-min) therapy. According to the findings from the Golimumab – A Randomized Study in Ankylosing Spondylitis Subjects of a Novel Anti-TNF mAB Injection (sc.) Given Every Four Weeks (GO-RAISE) trial, more than half of the patients receiving monthly subcutaneous injections of golimumab 50 mg and 100 mg experienced significant and sustained improvement in the signs

Executive summary

- Uveitis is the most frequent extra-articular manifestation of ankylosing spondylitis (AS), with the strongest human leukocyte antigen (HLA)-B27 disease association.
- Anti-tumor necrosis factor (TNF)- α therapy has proved to be efficient in controlling uveitis attacks, although there is evidence of uveitis induced by anti-TNF- α therapy in patients.
- Gut inflammation is linked to peripheral joint disease in spondylarthropathies (SpA), and there is a strong relationship between gut lesions and synovial modifications of the inflamed joints.
- Both infliximab and adalimumab are capable of improving inflammatory bowel disease (IBD) associated with AS and reduce IBD flares when compared with etanercept, which is why a positive history of IBD should be considered as contraindication for etanercept therapy in AS.
- Psoriasis or psoriasiform exanthema may be induced by all anti-TNF agents – skin lesions develop within the first few months of therapy, with palmoplantar pustulosis being the most common feature.
- Screening for prolonged QT time has been recommended, since it might be associated with asymptomatic arrhythmias in AS patients.
- Pulmonary fibrosis in AS is typically located in the upper lungs, in contrast with the pulmonary fibrosis due to other systemic diseases.
- Secondary amyloidosis is a late complication of AS, being associated with a long inflammatory status in patients in which renal and digestive symptoms are the most frequent, but peripheral arthritis is also seen in patients. There are studies that have demonstrated the efficiency of biological therapy in treating this complication, particularly etanercept.
- Axial osteoporosis is an early manifestation of AS. Bone mineral density measurements should be made early in the disease course and should include dual x-ray absorptiometry measurement of both the spine and hip.
- Vertebral fractures of osteoporotic spine occur in unusual locations and, in contrast with postmenopausal osteoporosis, present a higher degree of neurological complications.

and symptoms of active AS. Clinical benefit was demonstrated as early as week 4 after one dose, and was maintained through week 24 [152].

Compounds such as abatacept (CTLA4 Ig recombinant protein that blocks the process of costimulation with the CD 80/86 and CD28) and rituximab (anti CD-20) have shown excellent results in rheumatoid arthritis patients, which have motivated new clinical trials in AS. An open-label pilot clinical trial with abatacept in AS (AbAS-01 [201]) investigates the efficacy and safety of abatacept in 30 AS patients from baseline up to week 30. Abatacept will be administered intravenously according to the prescription used in rheumatoid arthritis.

The rituximab trial is a Phase II open-label clinical trial in AS [202] for evaluating the efficacy and safety of rituximab when added to NSAIDs and/or methotrexate both for TNF- α inhibitor-naïve patients or patients who have experienced TNF- α inhibitor failure, in patients with moderate to severe AS.

These are Phase II trials, in the recruitment stage, with good expectations regarding the results of management of the approach for AS patients.

Added to the development of ambulatory consults focused on an early diagnosis of AS, these new therapies could open an encouraging horizon for the patients with early diagnosis, by providing a more effective new therapeutic approach and also by avoiding the possible late complications of the disease.

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