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Review article

Extra-articular manifestations of ankylosing spondylitis: Prevalence, characteristics and therapeutic implications

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ABSTRACT

Ankylosing spondylitis (AS) is the most frequent and most severe subtype of spondyloarthritis and can be an outcome of any of the other spondyloarthritis subtypes. It primarily affects the axial joints, most notably the sacroiliac joints. Other sites of involvement include the spine, peripheral joints, and entheses (capsules, ligaments, and tendons). Inflammatory enthesopathy progressing to ossification and ankylosis is the pathologic basis for the disease. Extra-articular manifestations vary widely in terms of both frequency and severity. The most common extra-articular manifestations are represented by uveitis, bowel disease, heart, lung, skin, bone and kidney involvement. This review focuses on prevalence and clinical characteristics of the most common extra-articular manifestations in AS, and discuss the diagnosis and therapeutic difficulties that rheumatologists faces when dealing with such manifestations. The advantages of treatment with non-steroidal anti-inflammatory drugs (NSAIDs), especially if continuous use is envisaged, should be weighted against possible gastrointestinal and cardiovascular disadvantages. In the presence of history of gastrointestinal complaints or a high cardiovascular risk, NSAIDs should be used with caution. TNF inhibition has demonstrated effectiveness in the treatment of AS symptoms and all currently available anti-TNF agents appear to have similar efficacy. However, the efficacy of anti-TNF agents varies in the presence of extra-articular manifestations. Etanercept appears to have very little effect on inflammatory bowel disease and limited efficacy on the course of uveitis probably inferior to the monoclonal antibodies infliximab and adalimumab.

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Ankylosing spondylitis (AS) is the most frequent and most severe subtype of spondyloarthropathies and can be an outcome of any of the other spondyloarthropathies subtypes [1]. It primarily affects the axial joints, most notably the sacroiliac joints (which can be regarded as the hallmark of AS; it is present in nearly all patients and occurs early in the course of the disease). Other sites of involvement include the spine, peripheral joints, and entheses (capsules, ligaments, and tendons) [1,2]. Typically manifesting in the third decade of life with an estimated prevalence of 0.2–1.2%, AS is 2.5-times more common in men than women. Inflammatory enthesopathy progressing to ossification and ankylosis is the pathologic basis for the disease. Extra-articular manifestations vary widely in terms of both frequency and severity. The most common extra-articular manifestations are represented by uveitis, bowel disease, lung, heart, skin, bone and kidney involvement (Table 1). Many epidemiological studies have found higher incidences of extra-articular manifestations to be a consequence of uncontrolled systemic inflammation [3]. Screening for extra-articular manifestations in patients diagnosed with AS is important to ensure appropriate management as the presence of extra-articular manifestations may

influence treatment decisions. Clinical signs such as a painful red eye; diarrhea; skin/nail problems; and unexplained weight loss or fever are considered classical 'red flags' for further investigation.

This review focuses on prevalence and clinical characteristics of the most common extra-articular manifestations in AS, and discuss the diagnostic and therapeutic difficulties that rheumatologists faces when dealing with such manifestations.

1. Eye involvement

Uveitis is a general term used to describe inflammation of the uveal tract, which is the middle layer of the eye, between the sclera, conjunctiva and the anterior chamber on the outside and the retina on the inside [4]. Uveitis is the most common extra-articular manifestation in AS patients. Patients with AS have a 20–30% chance of developing uveitis during the course of their disease. Moreover, prevalence increases with disease duration. It is in about 90% of the cases anterior, acute and monolateral [5]. Clinically, it is characterized by painful red eye with photophobia, increased tear production and blurred vision. Inflammation occurs within the anterior chamber and may involve the uveal tract in either the iris or the ciliary body, with spillover of vitreous inflammatory cells into the space behind the lens. The initial episode usually has an acute onset (1 to 2 day prodrome of

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Table 1
Prevalence of extra-articular manifestations in ankylosing spondylitis.

Extra-articular manifestations	Prevalence in % [reference]
Anterior uveitis	20–30 [5]
Inflammatory bowel disease	5–10 [15]
Histological inflammation of the gut	50–60 [14]
Lung abnormalities on high resolution CT	52 [60]
Heart conduction disturbances	3–33 [44]
Aortic insufficiency	6–10 [45]
Psoriasis	10–25 [22]
Renal abnormalities	10–35 [65]
Osteoporosis	11–18 [31]
Vertebral fractures	10–18 [39]

mild eye discomfort followed by the development of marked redness and pain—and is unilateral. There is a strong tendency for recurrence, which frequently occurs in the contralateral eye. Uveitis usually resolves within 2–3 months without residual visual impairment. If inadequately treated, it can progress to hypopion, synechia, cataract, and glaucoma. Reduction of visual acuity is not exceptional.

The pathogenesis of uveitis in spondyloarthropathies is still not well understood. Acute anterior uveitis, the most frequent pattern associated with AS, usually has a good prognosis and responds to appropriate treatment with topical mydriatics, cyclopegics and corticosteroids. However, it should be managed as an emergency to avoid complications. Topically applied prednisolone acetate is well absorbed across the cornea and can be effective but is less so for posterior inflammation. Dilating drops, such as scopolamine, may be used to prevent posterior synechiae and to relieve pain resulting from ciliary muscle spasms that control pupil size. Periocular corticosteroid injections can also be used, as well as brief courses of oral corticosteroids, for persistent inflammation despite topical therapy. When flares of acute anterior uveitis are frequent (more than three flares per year), several studies showed that sulphasalazine could diminish the number of recurrences [6–8]. Furthermore, in those patients on sulphasalazine, new episodes were less severe. Recently, some recent articles have reported the efficacy of anti-TNF α in the treatment of uveitis in AS; in particular, it appears that anti-TNF antibodies (infliximab and adalimumab) decrease the rate of recurrences [9]. A meta-analysis [10] of studies using the TNF-inhibitors etanercept and infliximab revealed that both agents significantly reduced the incidence of uveitis flares compared with placebo (placebo: 15.6/100 patient-years; infliximab: 3.4/100 patient-years; etanercept: 7.9/100 patient-years; $P=0.01$; TNF-inhibitors vs placebo) in patients with AS. A retrospective study of patients with SpA further confirms the efficacy of TNF-inhibitors in reducing acute uveitis flares [11]. However, this analysis demonstrated a clear difference between etanercept and the anti-TNF antibodies (infliximab and adalimumab); the incidence of uveitis remained unchanged with etanercept treatment (54.6 vs 58.5/100 patient-years; $P=0.92$), whereas it was dramatically reduced following anti-TNF antibody treatment (infliximab: 47.4 vs 9.0/100 patient-years; $P=0.008$, adalimumab: 60.5 vs 0/100 patient-years; $P=0.04$). Recently, a systematic review focused on reports of uveitis in clinical trials of etanercept in AS (4 placebo-controlled; one active-controlled; and three open-label). In placebo-controlled trials, the uveitis rate per 100 subject years for etanercept (8.6 [4.5, 14.2]) was lower than that for placebo (19.3 [11.0, 29.8] $p=0.03$). In the active comparator trial, rates for etanercept and sulphasalazine were similar (10.7 [5.5, 11.6] and 14.7 [6.4, 26.5], respectively; $p=0.49$) [12]. An open-label study with adalimumab demonstrated reduced rates of uveitis flares in patients with AS ($n=1250$) [13]. Overall, adalimumab reduced the flare rates by 50%.

2. Gastro-intestinal tract involvement

A close relationship exists between joint disease and gut inflammation. For example, in predisposed individuals, bacterial infection of the

gut with *Shigella*, *Salmonella*, *Yersinia* or *Campylobacter* may be followed by a peripheral arthritis referred to as reactive arthritis within a few days to weeks after the onset of diarrhoea. For a long time, reactive arthritis has been considered to be a benign condition as it is a self-limiting condition in most cases. However, up to 20% of patients with reactive arthritis develop AS within 10–20 years. Crohn's disease or ulcerative colitis has been reported to be present in 5–10% of patients with AS. Subclinical gut inflammation revealed by ileocolonoscopy was found in 25–49% of AS patients and microscopic lesions as detected by histological analysis of gut biopsies are found even more frequently than macroscopic signs of gut inflammation, with a prevalence of up to 50–60% [14]. Furthermore, when investigated, remission of joint inflammation was always connected with a disappearance of gut inflammation. Conversely, AS is diagnosed in 3–10% of the patients with inflammatory bowel disease, although radiological evidence of sacroiliitis is reported to be present in 14–46% [15].

Non-steroidal anti-inflammatory drugs (NSAIDs) are the mainstay of medical therapy in AS and are recommended as first-line therapy in all AS patients. However, NSAID therapy in AS patients with concomitant inflammatory bowel disease may have deleterious effects on intestinal symptoms. Thus, given the available evidence, AS patients in daily practice should be assessed thoroughly by taking a detailed history for symptoms suggestive of inflammatory bowel disease. If inflammatory bowel disease is suspected on clinical grounds, endoscopic examinations should be performed. If a diagnosis of inflammatory bowel disease is then made, NSAIDs should probably be used intermittently in low to moderate doses and patients be monitored closely together with a gastroenterologist.

The treatment options offered to patients with active AS associated with inflammatory bowel disease include conventional disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate, azathioprine or sulphasalazine and anti-TNF agents. Unfortunately, conventional DMARDs, which are all effective for treating inflammatory bowel disease, are considered to be ineffective or only marginally effective in AS if axial symptoms, i.e. back pain, predominate. Anti-TNF agents are highly effective in treating active AS, as shown by several large placebo-controlled studies. All of the three anti-TNF agents (infliximab, etanercept and adalimumab) have been approved for use in AS in many countries worldwide. According to the recommendations of the Assessment in Ankylosing Spondylitis International Working Group, anti-TNF agents may be initiated in patients with active AS who are refractory to or cannot tolerate NSAIDs [16,17]. However, in contrast to the excellent efficacy of anti-TNF agents on musculoskeletal symptoms of AS, infliximab, adalimumab and etanercept exert quite different effects on the gut. Infliximab and adalimumab are licensed for the treatment of Crohn's disease in Europe and the USA, whereas infliximab is additionally licensed for the treatment of ulcerative colitis and paediatric Crohn's disease in Europe and the USA. However, etanercept has not proven effective in inflammatory bowel disease. Whereas etanercept is efficacious in treating the spinal pathology and arthritis associated with AS, case reports reveal that associated Crohn's disease remains persistent or flares during etanercept therapy [18].

A meta-analysis [19] of trials of TNF-inhibitors in AS patients investigated the incidence of flares or new onset of inflammatory bowel disease. Nine trials were evaluated: seven placebo-controlled and two open labels, with a total of 1130 patients included. The incidence rates for flares or new onset of inflammatory bowel disease were 0.2, 2.2, 2.3 and 1.3 per 100 patient-years during treatment with infliximab, etanercept, adalimumab and placebo, respectively. While there was no significant difference in the incidence rates between placebo and the TNF-inhibitors, there was a significant difference in favour of infliximab over etanercept ($P=0.001$) and adalimumab ($P=0.02$). Furthermore, in patients with a history of inflammatory bowel disease flares, flares were 18 times more likely to occur in etanercept-treated AS patients and 4.2 times more likely in adalimumab-treated AS patients than in

infliximab-treated AS patients. Data with adalimumab were quite limited due to the total period of exposure of 132.3 patient-years compared with 618 patient-years for infliximab and 625.4 patient-years for etanercept. An open-label study with adalimumab ($n=1250$) demonstrated some improvement in inflammatory bowel disease in patients with AS. Symptomatic inflammatory bowel disease was reported in 4.7% of the patients at baseline. Of those patients, 20% at baseline reported no inflammatory bowel disease interference in the past 7 days, and at 12 weeks 48% of the patients reported this response. Additionally, it is recommended that adalimumab be administered in much higher initial 'induction' doses when given for the treatment of Crohn's disease (80 mg) than would be used in the treatment of AS (40 mg) [15]. The efficacy of adalimumab in ulcerative colitis is also currently unclear. This difference in clinical efficacy profiles has attracted great interest, but its scientific basis remains uncertain [20]. The possible explanations for the difference may be conceived as relating either to differences in the abilities of TNF antagonists to achieve adequate serum concentrations (i.e., pharmacokinetic differences); differences in their respective abilities to achieve therapeutic concentrations in inflammatory microenvironments (i.e., differences in tissue penetration); or differences in their abilities to bind to TNF and induce therapeutic effects (i.e., mechanistic differences) [21].

3. Skin involvement

In various series, between 10% and 25% of the patients with typical AS have concomitant psoriasis lesions. Involvement of the SI joint and the spine occur in 5% of the patients with psoriasis. Patients with concomitant psoriasis tend to exhibit more peripheral joint involvement [22]. Furthermore, association with psoriasis was clearly found to produce a worse disease course than either primary AS or AS associated with inflammatory bowel disease [23]. Today, the three TNF α antagonists are registered for treating psoriasis and psoriatic arthritis (etanercept, infliximab, adalimumab) with similar reported efficacy [24–27]. However, paradoxically between 1.5 and 5% of the patients may present an onset or exacerbation of psoriasis during treatment with the TNF-inhibitors [28].

4. Bone involvement

Diffuse osteoporosis responsible for loss of bone strength is a well known feature of AS. The bone loss may be present early in the course of the disease and predominates at the spine [29]. Late in the disease, vertebral fractures constitute a rare but non negligible source of morbidity and mortality related mainly to neurological compromise [30].

Densitometric studies showed that a large proportion of AS patients (63%) are either osteopenic or osteoporotic affecting up to 59 and 18% of the patients with AS, respectively [31]. We found osteopenia and/or osteoporosis in about one-third of patients with very early disease and demonstrated worsening bone loss with advancing age and longer disease duration [32]. In another study, we used quantitative CT rather than dual X-ray absorptiometry to evaluate lumbar spine bone mineral density in patients with AS [33]. The results showed low bone mineral density in two thirds of cases. Although dual X-ray absorptiometry remains the standard of reference for studying osteoporosis, physicians must be aware that this technique overestimates spinal bone mineral density in patients with advanced AS, the reason being the presence of ossification at various spinal sites (syndesmophytes, vertebral ligament ossification, and facet joint fusion). Thus, dual X-ray absorptiometry is reliable at the femoral neck but not at the lumbar spine in patients with late-stage AS where quantitative CT may be a good alternative [34]. Another important issue that must be kept in mind is that persistent inflammation uncontrolled by medications is the main predictor of bone loss as we [35] and others [36] showed in longitudinal studies.

The reported prevalence of vertebral fractures in AS varies between 10 and 17%. Cooper et al. [37] reported an increased odds ratio (OR) of 7.6 (95% confidence interval (CI): 4.3–12.6) for clinical vertebral fractures on the basis of the radiologist's report, as found in the medical records of each of all 158 patients suffering from AS in the Rochester area between 1935 and 1989. A study reported by Ralston et al. [38] in 1990 evaluated the vertebral fracture rate in 111 AS patients with a mean age of 41 years and a mean disease duration of 17 years. Vertebral fractures were detected using a standardized vertebral height index determined on lateral radiographs of the spine. Abnormalities were found in 20 (18%) patients (vertebral fractures in 15 and biconcave deformities in five). We showed recently in a series of eighty patients with AS (mean disease duration 10.8 years) which were evaluated systematically with fracture vertebral assessment using dual X-ray absorptiometry (Fig. 1) that 18.8% of patients had a vertebral fracture (Genant grades 2 and 3). Osteoporosis was mainly related to disease activity while vertebral fractures appeared to be related to the duration and structural severity of the disease rather than bone mineral density [39]. In a primary care-based nested case-control study conducted from the GPRD database (231,778 fracture cases and 231,778 age- and sex-matched controls) [40] a history of AS was assessed from the medical records and AS was diagnosed in a total of 758 people. This study showed that patients with AS have an increased risk of clinical vertebral fractures (OR: 3.26; CI: 1.51–7.02) without an increased risk of non-vertebral fractures while in patients with concomitant inflammatory bowel disease the risk of any clinical fracture is increased.

Other studies indicate that wedged vertebral fractures measured on lateral spine radiographs contribute to hyperkyphosis [41]. Furthermore, several studies reported a high prevalence (between 29 and 91%) of major neurological complications after clinical vertebral fractures [42].



Fig. 1. Example of vertebral fracture assessment using dual X-ray absorptiometry in a patient with ankylosing spondylitis.

The cause of osteoporosis associated with AS remains debated. The most likely scenario at present is that several mechanisms act in conjunction to cause bone loss: genetic factors, chronic inflammation, adverse effects of medications, silent bowel disease, and a gradual decrease in spinal mobility caused by worsening ankylosis.

In AS, preventive treatment for bone loss and vertebral fracture prevention are rarely used: analgesia with NSAIDs and regular physiotherapy tend to be the norm. Recent studies, however, have shown promising results in terms of bone density improvements using TNF- inhibitors [43]. The impact on vertebral fractures frequency is still unclear. Even the use of bisphosphonates seems logical in patients with AS and osteoporosis with or without vertebral fractures, this class of drugs have never been studied in this indication.

5. Heart involvement

The prevalence of heart pathologies in patients with AS has been reported to be 10% to 30% [44]. Various studies indicate a higher rate of conduction disturbances, valvular heart diseases and cardiomyopathies in patients with AS when compared with the normal population [45]. It is related to a sclerosing inflammatory process that primarily involves the aortic root and the aortic valve cusps and may lead to cusp retraction and aortic regurgitation. In addition to the aortic root, the chronic inflammation may extend into the ventricular septum and cause conduction disturbances, or involve the elastic and muscle fibres of the aortic wall and decrease its distensibility. Less frequently, it may also involve the endocardium and myocardium. Thus, conduction disturbances of the heart, such as atrioventricular blocks, bundle-branch blocks and intraventricular blocks have been observed regularly (3–33%). Screening for a prolonged QT time has been recommended since it might be associated with HLA-B27. Various pathologies may affect the heart valves, mainly the aortic valve (reported prevalence of aortic regurgitation varies from 6 to 10%) [45]. The spectrum of these structural changes is wide and can range from only minor thickening of the valves or nodules on the valves to severe regurgitation requiring surgical replacement of the affected valve. Clinical signs of cardiomyopathy were often associated with diastolic and/or systolic dysfunction of the ventricles [46]. As a consequence of these pathologies, heart insufficiency and stroke were found to be increased in patients with AS. This is associated with a decreased life expectancy in this population.

Patients with AS have an approximately twofold increased death rate compared to the general population, which is predominately caused by increased cardiovascular risk [47,48]. A recent study showed that the prevalence rate for myocardial infarction is approximately 2–3 fold increased as compared with the general population [49]. However, although a non-significant trend was observed which may indicate that AS patients with a history of myocardial infarction have a more severe disease, the authors observed no significant associations between disease activity or severity markers and a history of myocardial infarction. This might be due to the small number of cases limiting statistical power or the cross-sectional nature of the study.

The inflammatory process appears to have an important role in causing this excess cardiovascular risk, since it resembles similar processes that contribute to all stages of atherosclerosis, from early atheroma formation to plaque instability and thrombus development responsible for cardiovascular events. A recent study has shown impaired endothelial function, which is a key early event in atherogenesis, in patients with AS compared with healthy controls [50]. Current evidence indicates that also treatment may contribute to the cardiovascular risk.

Increased TNF α levels may have an important role in the pathogenesis of endothelial dysfunction in AS. Impaired coronary microvascular function was recently found in patients with AS, and correlated well with serum C-reactive protein and TNF α levels [51]. A

recent study demonstrated that patients with active AS have impaired microvascular endothelium-dependent vasodilatation and capillary recruitment in skin, which improves after TNF α -blocking therapy with etanercept [52].

It is important to remember, however, that NSAIDs remain the cornerstone in the treatment of AS and that with most NSAIDs, an increase in the thrombotic risk must be expected [53]. Moreover, NSAIDs and coxibs may cause or exacerbate hypertension and thereby contribute to cardiovascular events, irrespective of any intrinsic prothrombotic effects of these agents. For example, 9% of AS patients who used celecoxib or any NSAID daily had hypertension compared with 3% of patients who used these drugs on an on-demand basis [54]. Given the gastrointestinal and cardiovascular risks of continuously or intermittently taking NSAIDs or coxibs, for each individual AS patient, one needs to deal with the questions regarding when and how we should prescribe these agents and whether the treatment should be on a daily or on an 'on-demand' basis. Recently, a 2-year randomized, prospective, controlled trial in AS patients compared the efficacy of continuous celecoxib therapy to that of intermittent 'on-demand' use [55]. The results suggest that continuous therapy retards radiographic disease progression. Another important information we have to deal with is that the risk of a primary myocardial infarction appears to be increased for several weeks after the withdrawal of NSAID treatment, especially if the treatment was long term and another systemic inflammatory disease is present at the same time. The cause is assumed to be a vascular rebound effect [56].

The conclusion of all these controversial data may be that, if AS symptoms permit, patients do not have to be exposed continuously to selective or non-selective NSAIDs and that further gastrointestinal and cardiovascular risk can be avoided [57].

6. Lungs involvement

Pulmonary abnormalities are also well documented in patients with AS [58]. However, more than 50 years after the seminal description, pathophysiology of pleuropulmonary involvement in AS remains an enigma. The most likely explanation is a disease-specific inflammatory process whose course is parallel to that of the joint manifestations.

The advent of high resolution computed tomography (CT) in the mid 1980s has permit to examine the entire lung parenchyma and pleura in many conditions with diffuse lung disease using a non-invasive method [59]. We looked in a series of 55 patients to determine the prevalence of lung involvement and the spectrum of abnormalities revealed on high resolution CT in patients with AS [60]. High resolution CT revealed abnormalities in 29 patients (52.7%), whereas plain chest radiography was abnormal in only 2. Abnormalities consisted of interstitial lung disease (n=4), apical fibrosis (n=5), emphysema (n=5), bronchiectasis (n=4), ground glass attenuation (n=2), and non-specific interstitial abnormalities (n=26). Only apical fibrosis and bronchiectasis were statistically more frequent with increasing disease duration (Table 2).

The effect of anti-TNF blockers on interstitial lung fibrosis and other abnormalities has never been evaluated. However, this issue may become even more important as these agents are now widely prescribed for AS. Moreover, many recent case reports described contrasting effects on pulmonary fibrosis in patients with RA. Ostor et al. [61] reported fatal exacerbation of RA-associated fibrosing alveolitis in three patients receiving infliximab. We also observed a case of rapid exacerbation of fibrosing alveolitis in a patient with RA receiving infliximab [62]. On the other hand, Bargagli et al. [63] described a beneficial effect of infliximab in the treatment of RA associated with interstitial lung disease.

The administration of anti-TNF agents is associated with an increased risk of reactivation of latent tuberculosis even the measures recommended to screen and to prevent this reactivation have been

Table 2

Results of chest high resolution CT in 55 patients with ankylosing spondylitis and distribution of the lung abnormalities with disease duration. Results are expressed as number (percentage) [60].

	Total n (%)	Disease duration <5 years n = 30	Disease duration ≥ 5 and <10 years n = 14	Disease duration ≥ 10 years n = 11	p
Normal	26 (47.2)	11 (36.7)	6 (42.9)	2 (18.2)	NS
Emphysema	5 (9.0)	1 (3.3)	1 (7.1)	2 (18.2)	NS
Upper lobe fibrosis	5 (9.2)	1 (3.3)	1 (7.1)	3 (27.3)	0.029
Brochiectasis	4 (7.2)	1 (3.3)	–	3 (27.3)	0.028
Interstitial lung disease	4 (7.2)	2 (6.7)	1 (7.1)	1 (9.1)	NS
Ground glass attenuation	2 (3.6)	2 (6.7)	–	–	NS
Non-specific interstitial change	26 (47.2)	14 (46.7)	5 (35.7)	7 (63.6)	NS
Pleural thickening	13 (23.6)	8 (26.7)	3 (21.4)	3 (27.3)	NS
Parenchymal bands	13 (23.6)	6 (20.0)	3 (21.4)	4 (36.4)	NS
Blebs	7 (12.7)	3 (10.0)	2 (14.3)	2 (18.2)	NS
Parenchymal micronodules	7 (12.9)	4 (13.3)	2 (14.3)	1 (9.1)	NS
Subpleural bands	6 (10.9)	1 (3.3)	4 (28.6)	1 (9.1)	NS
Irregular interfaces	4 (7.2)	4 (13.3)	–	–	NS

shown to be effective [64]. Thus, in clinical practice, thoracic high resolution CT may be useful to identify a suspicious abnormality in chest X-rays, especially when anti-TNF therapy is planned. Clinicians must be aware of the thoracic CT abnormalities observed in AS, which must not be confounded with tuberculosis lesions.

When studying lung function testing, AS is associated with a pure restrictive pattern due to rigidity of the chest wall. In our study [60], 16 of the studied patients (n = 55) had a restrictive pattern, and 11 of these 16 had abnormalities by thoracic CT. Nevertheless, we found no correlation between high resolution CT changes and lung function testing results. In contrast, lung function testing results were correlated with variables reflecting the severity of symptoms and structural damage related to AS, in keeping with earlier evidence that severity of axial disease but not presence of CT lesions governed the severity of the restrictive pattern.

7. Kidney involvement

The incidence of renal abnormalities (including glomerulonephritis, particularly associated with deposition of immunoglobulin A (IgA)-containing immune complexes, renal amyloid deposition, microscopic haematuria, microalbuminuria and decreased renal function and creatinine clearance) has been shown to range from 10 to 35% in patients with AS. Amyloidosis is more prevalent in aggressive and active AS and in older patients with long-standing disease [65]. There are, however, scant data on the prognostic significance of positive fat tissue aspiration in patients with AS without overt clinical signs of AA amyloidosis. Gratacos et al. [66] reported that results of a fat tissue aspiration test were positive in 7% of 137 patients in an unselected AS series, and showed that, during a mean follow-up period of 5 years, the finding was associated with clinical amyloidosis in only half of the patients, the latter indicating a poor prognosis. A Finnish hospital-based study of patients with AS with a mean follow-up time of 25 years demonstrated an overall mortality rate 1.5 times higher than expected, which was explained by a high incidence of deaths from AS, mainly due to AA amyloidosis [47]. Some case reports suggest the potential role of TNF-inhibitors in improving AA amyloidosis. In this report, patients were treated with etanercept over 1 year [67].

8. Extra-articular manifestations and therapeutic consequences

Screening for extra-articular manifestations in patients diagnosed with AS is important for appropriate management. Some explorations should be systematically done to screen for the most common extra-articular manifestations even in asymptomatic patients. It is the case for pulmonary x-rays, lung function testing, EKG, bone density measurement, ophthalmic exam, biological exams including protein-

uria, urea and creatinine. Clinical signs such as history and/or presence of gastrointestinal complaints or diarrhea; skin and/or nail problems; eye discomfort, redness or pain; heart murmur and/or dyspnea and unexplained weight loss or fever should stimulate physicians to refer patients immediately for further investigation in collaboration with other specialists (ileocolonoscopy, echocardiography, Holter EKG, thoracic high resolution CT...etc). The recent evidence that patients with AS are at high cardiovascular risk suggest that classical risk factors for atherosclerosis should also be screened and treated correctly in parallel to inflammation control to avoid cardiovascular complications.

NSAIDs are still the first-line treatment in the management of AS, and they are effective in controlling symptoms such as pain and stiffness and maintaining mobility in many patients. A recent randomized trial suggested that the progression of radiological damage occurs less on continuous use of celecoxib compared with on-demand use [55]. If such findings were confirmed by other studies, the therapeutic value of NSAIDs in AS may extend beyond symptom control. However, for each individual patient, the expected advantages of treatment with NSAIDs should be weighted against any possible gastrointestinal and cardiovascular disadvantages. In patients with inflammatory bowel disease, history of gastroduodenal pain or high cardiovascular risk, NSAIDs should be used with caution, and patients be monitored closely together with a gastroenterologist and/or a cardiologist.

Disease-modifying antirheumatic drugs (DMARDs) are widely used for second-line therapy in AS, but the evidence for their efficacy is poor. The term 'DMARD' has been borrowed from rheumatoid arthritis, and none of the DMARDs have been shown to prevent or significantly decrease the rate of progression of structural damage which is required to be qualified as a disease-controlling antirheumatic drug for AS. Sulphasalazine is the most extensively studied DMARD and studies suggest some degree of clinical benefit confined to peripheral joint involvement, but no evidence of benefit in axial disease. However, there is some evidence that sulphasalazine can reduce the number of uveitis flares in patients receiving this drug for AS manifestations.

The use of TNF-inhibitors (infliximab, adalimumab, etanercept) results in substantial improvements in symptoms of AS also contributing to an improved functional status. However, the efficacy of TNF-inhibitors in extra-articular manifestations appears to vary from agent to agent. Etanercept appears to have very little effect on inflammatory bowel disease and limited efficacy on uveitis (at best comparable to sulphasalazine and probably inferior to the monoclonal antibodies infliximab and adalimumab), while the incidence of flares of both conditions appears to be reduced with infliximab and adalimumab treatment for AS. The lack of efficacy of etanercept in Crohn's disease is widely known and acknowledged in the international Assessment in

Ankylosing Spondylitis International Working Group consensus statement for the use of anti-TNF agents [68]. Clinical differences between the TNF antagonists are more likely a result of differences in their modes of administration, pharmacokinetic profiles, tissue penetration, and/or abilities to induce therapeutic effects by other means.

9. Learning Points

- The most common extra-articular manifestations are represented by uveitis, bowel disease, heart, lung, skin, bone and kidney involvement.
- Osteoporosis is common in patients with AS and is mainly related to disease activity while vertebral fractures are related to the duration and structural severity of the disease rather than BMD.
- Patients with AS have an approximately twofold increased death rate compared to the general population, which is predominately caused by increased cardiovascular risk and the prevalence rate for myocardial infarction is approximately 2–3 fold increased as compared with the general population.
- In the presence of history of gastrointestinal complaints or a high cardiovascular risk, NSAIDs should be used with caution.
- The efficacy of anti-TNF agents varies in the presence of extra-articular manifestations. All are effective on musculoskeletal symptoms, osteoporosis, psoriasis and cardiovascular risk. Etanercept appears to have very little effect on inflammatory bowel disease and limited efficacy on the course of uveitis probably inferior to the monoclonal antibodies infliximab and adalimumab.

Conflict of Interests

Prof. A. El Maghraoui received fees from Pfizer, Abbott, Roche and MSD for CME activities.

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