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Review

Treatment of ankylosing spondylitis and extra-articular manifestations in everyday rheumatology practice

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The SpAs are a group of overlapping, chronic, inflammatory rheumatic diseases including AS, a chronic inflammatory disease primarily affecting the SI joints. In addition to inflammatory back pain, AS patients are also more likely to experience extra-articular manifestations belonging to the SpA concept which can affect the eyes, the gastrointestinal tract and the skin and other related inflammatory conditions. This review focuses on current progress in treatment options in SpA with special emphasis on extra-articular features. 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 treatment of extra-articular manifestations and comorbidities. Analyses of trials of anti-TNF agents in patients with AS have revealed significant reductions in the incidence of flares of uveitis and IBD with infliximab and adalimumab (uveitis only) treatment but not with etanercept. All three anti-TNF agents (infliximab, adalimumab, etanercept) have demonstrated efficacy in psoriasis (not associated with AS). When evaluating as to which agent to use in the treatment of AS, an important consideration is the overall well-being of the patient. This should include any additional inflammatory burden that manifests in other parts of the body, which may currently be subclinical. Based on current evidence, among TNF inhibitors, the monoclonal antibodies (infliximab and adalimumab) are more appropriate than etanercept if extra-articular manifestations or comorbid conditions are present or suspected. To date, infliximab appears to be the best studied agent with a wide spectrum of proven efficacy.

Key words: Ankylosing spondylitis, Extra-articular manifestation, Biologic therapy, Tumour necrosis factor-α, Quality of life.

Introduction

SpAs [1] are overlapping, chronic, inflammatory rheumatic diseases that primarily include AS, ReA, arthritis with associated IBD and PsA [2]. SpAs are the most common rheumatic diseases, affecting ~0.5–1.9% of the population [3–6]. Evidence supports a role of HLA-B27 allele as genetically linking to the pathophysiology of AS and other SpAs [2]. The main links between these diseases include association with HLA-B27, similar patterns of peripheral joint involvement with asymmetrical arthritis and the possible occurrence of sacroiliitis, spondylitis, enthesitis and uveitis. The leading clinical symptoms for all SpA subsets are inflammatory back pain and/or asymmetrical arthritis predominantly of the lower limbs [1].

AS, the most common and severe subtype of the SpAs is a chronic inflammatory disease primarily affecting the SI joints [1, 7] with an estimated prevalence of 0.2 and 1.2% [3, 5, 6, 8]. Typically manifesting in the third decade of life [2, 9, 10], AS is 2.5-times more common in men than women [11].

It is now clear that inflammation in AS is strongly dependent upon TNF-α. Dense mononuclear infiltrates containing T cells and macrophages, secreting TNF, have been observed in joints of AS patients [12–14]. Additionally, trials of TNF-α inhibitors in AS have yielded impressive results [15–18], supporting the pathogenic role of TNF-α in AS.

Inflammatory back pain is the key clinical symptom in AS [19]. Additionally, radiographic evidence of sacroiliitis is required for the diagnosis of AS [20]. In early and acute stages of sacroiliitis, findings on conventional radiography can be normal, making diagnosis difficult, although other imaging techniques may show SI inflammation [21]. However, in more advanced disease, sclerosis and erosions are evident in radiographic images of the SI joint; as disease progresses, ankylosis, the most characteristic feature of AS, can cause these entities to vanish from the radiograph [21].

Although AS is primarily a disease of the axial skeleton, peripheral joint involvement occurs in up to 70% of the patients [22]. Involvement of the axial joints, including shoulders and hips, is more common in AS than the involvement of more distal joints [23]. Unfortunately, axial disease has proven very difficult to treat and the conventional DMARDs used to treat RA have proven ineffective [24–26].

In addition to AS, HLA-B27 is strongly associated with ReA, PsA, acute anterior uveitis, IBD and aortic incompetence with heart block [2]. Other parts of the body besides the joints that are affected by SpAs are known as extra-articular manifestations, which can affect the eye, urogenital tract, gastrointestinal (GI) tract and skin. An epidemiological study of 847 patients in Belgium who fulfilled the modified New York criteria for AS found that 42% had one or more extra-articular manifestations, including acute anterior uveitis (27%), IBD (10%) and psoriasis (11%) [7]. This illustrates the relatively high frequency of extra-articular manifestations in AS patients. Additionally, 83% of this population was found to carry the HLA-B27 allele [7]. Other epidemiological studies have found even higher incidences of extra-articular manifestations [27, 28], thought to be a consequence of uncontrolled systemic inflammation (Table 1). Extra-articular manifestations can also affect the kidneys, lungs, heart and bones.

Most clinicians understand that the presence of comorbid conditions reduces the quality of life (QoL) of patients. Two patients with the same degree of back pain and radiographic findings will not share the same QoL if one of them also has psoriasis, for example. The presence of comorbidities is a significant determinant of the mental health-related impact of AS on QoL [42]; therefore, it is important to screen for extra-articular manifestations and comorbid conditions in patients diagnosed with AS to ensure appropriate management. Clinical signs such as diarrhoea, skin/nail problems, eye discomfort, redness or pain

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and unexplained weight loss or fever should be considered 'red flags' for further investigation. The presence of extra-articular manifestations or comorbid conditions can guide treatment decisions and address the underlying cause of inflammation.

Extra-articular manifestations related to the SpA concept

Eye. Acute anterior uveitis (iritis) is a common extra-articular manifestation in AS patients [28]. Uveitis is usually monolateral and characterized by painful red eye with photophobia, increased tear production and blurred vision [43]. 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 mild eye discomfort followed by the development of marked redness and pain—and is unilateral [44]. There is a strong tendency for recurrence, which frequently occurs in the contralateral eye [44]. Uveitis usually resolves within 2–3 months without residual visual impairment [45]. If inadequately treated, it can progress to hypopion, synechia, cataract, glaucoma or vision loss [43]. In PsA and IBD, uveitis may be unilateral or simultaneously bilateral, insidious in onset, chronic in duration and may involve the posterior eye [46–48].

Patients with AS have a 20–30% chance of developing uveitis during the course of their disease [44]. Conversely, patients with an acute onset anterior uveitis that are HLA-B27 positive are highly likely to have an associated sacroiliitis and/or peripheral arthritis [44]. Indeed, incidence rates have been reported of up to 90% of patients with HLA-B27-associated acute anterior uveitis that have definite or possible AS [44].

Corticosteroids are a mainstay of uveitis treatment. 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. NSAIDs and cytotoxic drugs, such as SSZ and MTX, have a limited role in treatment [44].

High levels of TNF-α have been shown in the aqueous humor of patients with clinical uveitis [49]; therefore, TNF-α inhibitor treatment seems to be a logical approach. A small 46-week trial of the TNF-α inhibitor infliximab in patients with intermediate and/or posterior uveitis, intolerant or unresponsive to standard therapy, demonstrated effectiveness with significant improvements in visual acuity [50]. A meta-analysis of studies using the TNF-α 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-α inhibitors *vs* placebo) in patients with AS. When either agent was analysed separately, the difference between infliximab and placebo was highly significant ($P = 0.005$) compared with the difference between etanercept and placebo ($P = 0.05$). While a trend towards a greater reduction in uveitis incidence with infliximab therapy over etanercept was evident, this, however, did not reach significance ($P = 0.08$) [29].

A retrospective study of patients with SpA further confirms the efficacy of TNF-α inhibitors in reducing acute uveitis flares (Fig. 1) [51]. Patients receiving TNF-α inhibitors were selected from a hospital database, and those who experienced a uveitis flare at any time point were identified. Fifty patients with SpA and uveitis were selected, and 46 received sufficient follow-up for analysis following initiation of TNF-α inhibitor treatment: 33 patients received anti-TNF antibodies [infliximab ($n = 25$) or adalimumab ($n = 8$)] and 13 patients received the soluble TNF receptor (etanercept). TNF-α inhibitors reduced the incidence of uveitis flares from 51.8/100 patient-years prior to anti-TNF

TABLE 1. Extra-articular manifestations related to the SpA concept and their prevalence in AS

Extra-articular manifestation	Prevalence in patients with AS, %
Anterior uveitis	30–50 [28, 29]
IBD	5–10 [28, 30]
Subclinical inflammation of the gut	25–49 [31–33]
Cardiac abnormalities	
Conduction disturbances	1–33 [34]
Aortic insufficiency	1–10 [34]
Psoriasis	10–20 [21, 28]
Renal abnormalities	10–35 [35, 36]
Lung abnormalities	40–88 [37–39]
Airway disease	82 [39]
Interstitial abnormalities	47–65 [38, 39]
Emphysema	9–35 [37, 39]
Bone abnormalities [40, 41]	
Osteoporosis	11–18 [41]
Osteopenia	39–59 [41]

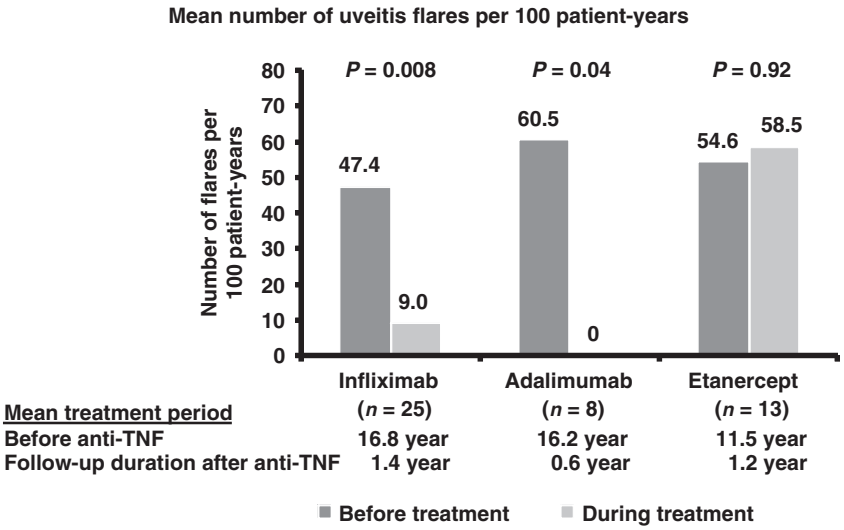


FIG. 1. Incidence of uveitis flares prior to and during treatment with TNF-α inhibitors [51].

treatment to 21.4/100 patient-years while receiving anti-TNF treatment ($P = 0.03$). 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; $P = 0.04$). Two patients who never had uveitis before anti-TNF treatment developed uveitis while taking etanercept. However, patients receiving etanercept were less likely to be receiving additional DMARDs, which may have influenced the incidence of flares, although this was not statistically significant [51]. An open-label study with adalimumab demonstrated reduced rates of uveitis flares in patients with AS ($n = 1250$). Patients received adalimumab 40 mg every other week for 12 weeks. There was a significant reduction in uveitis flare rates per 100 patient-years when comparing the flare rates before adalimumab therapy to flare rate during adalimumab therapy (15 *vs* 7.4/100 patient-years; $P < 0.001$) Overall, adalimumab reduced the flare rates by ~50% [52].

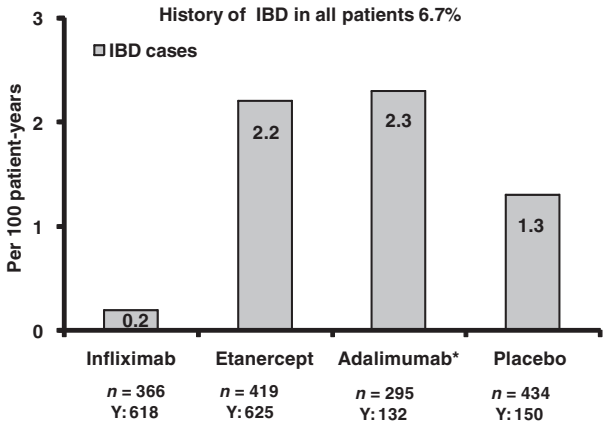
GI tract. A strong relationship exists between gut and joint inflammation in SpA [53]. Ileocolonoscopic evidence of microscopical signs of gut inflammation is present in up to 60% of the AS patients, unrelated to GI complaints [53]. Over time, a fraction of these patients evolved into full-blown IBD [54]. Furthermore, when investigated, remission of joint inflammation was always connected with a disappearance of gut inflammation [53]. Evidence for TNF involvement in the pathogenesis of IBD associated with AS has been provided by studies in mice [55]. Deletion of TNF sequence elements rich in A and U nucleotides [AU-rich elements (AREs)] from the mouse genome resulted in the development of chronic inflammatory arthritis and Crohn's-like disease in mutant mice, and features of SpA [56]. The absence of AREs affects the mechanisms for TNF mRNA destabilization and translational repression, resulting in overexpression of TNF [55]. The origin of the so-called gut–joint axis is not formally known yet but several hypotheses exist including a role for stromal cells [56, 57].

IBD has been identified in up to 10% of the patients with AS [28]. Conversely, AS is diagnosed in 3–10% of the patients with IBD, although radiological evidence of sacroiliitis is reported to be present in 14–46% [58]. Indeed, SpA-related musculoskeletal symptoms are the most common extra-intestinal manifestations of IBD [59].

Treatment of IBD has traditionally relied on corticosteroids to reduce flares and immune modulators, such as 5-aminosalicylic acid, AZA, mercaptopurine and MTX, to maintain remission [60]. However, surgical treatment would often be warranted. The advent of biologic treatments has provided an alternative option to surgery in patients who are refractory or intolerant of other medical treatment [60].

Infliximab and adalimumab are licensed for the treatment of Crohn's disease (CD) in Europe and the USA [61–64], whereas infliximab is additionally licensed for the treatment of ulcerative colitis (UC) and paediatric CD in Europe and the USA [61]. However, etanercept has not proven effective in IBD [65]. Whereas etanercept is efficacious in treating the spinal pathology and arthritis associated with AS, case reports reveal that associated CD remains persistent or flares during etanercept therapy [66]. Certolizumab pegol is another licensed treatment option for patients with CD in the USA [67].

A meta-analysis of trials of TNF-α inhibitors in AS patients investigated the incidence of flares or new onset of IBD (Fig. 2) [59]. 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 IBD 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-α 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 IBD 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 [59]. An open-label study with adalimumab ($n = 1250$) demonstrated some improvement in IBD in patients with AS. Symptomatic IBD was reported in 4.7% of the patients at baseline. Of those patients, 20% at baseline reported no IBD interference in the past 7 days, and at 12 weeks 48% of the patients reported this response [68].



*Calculations are based on a relatively small number of patients. Y: patient-years.

FIG. 2. Incidence of IBD flares or new-onset disease according to TNF-α inhibitor treatment received [59].

Additionally, it is recommended that adalimumab be administered in much higher initial 'induction' doses when given for the treatment of CD (80 mg) than would be used in the treatment of AS (40 mg) [63]. The efficacy of adalimumab in UC is also currently unclear. These factors may help explain the difference in flare incidence between adalimumab and infliximab.

Skin. Cutaneous manifestations can be associated with SpAs. Psoriatic skin lesions manifest before arthritis symptoms in three-quarters of patients with PsA [69]. Psoriasis has been observed in up to 20% of the patients as a secondary disorder in AS, regardless of age of onset [28]. Patients with concomitant psoriasis tend to exhibit more peripheral joint involvement [70]. Involvement of the SI joint and the spine occur in ~5% of the patients with psoriasis [21]. Furthermore, the presence of extra-articular manifestations can have implications on the degree of disease involvement and progression. In a large AS patient sample, association with psoriasis was found to produce a worse disease course than either primary AS or AS associated with IBD [71].

Bone. Although osteoporosis and osteopenia are well-established complications of AS, the exact mechanisms remain unclear [72]. A large proportion of AS patients (63%) are either osteopenic or osteoporotic [40] affecting up to 59 and 18% of the patients with AS, respectively [41]. Importantly, a correlation has been shown between low femoral BMD and risk of vertebral fractures in AS patients [73]. Gratacós *et al*. [74] have shown in a follow-up of 19 months that active AS patients without bony ankylosis had

a bone mass reduction superior to inactive AS patients. Bone loss in active AS patients, in particular at the femoral neck, has also been confirmed [75].

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 [38]. Recent studies, however, have shown promising results in terms of bone density improvements using TNF-α inhibitors. In a subanalysis of the 24-week ASSERT trial, significant increases in mean spinal BMD were observed in AS patients treated with infliximab compared with placebo where BMD remained unchanged (2.5 *vs* 0.5, $P < 0.001$) [76]. The impact on vertebral fracture frequency is still unclear.

Heart. Cardiac abnormalities including conduction disturbances and aortic insufficiency are not uncommon in patients with AS. Both cardiac and aortic tissue have shown intimal proliferation of small arteries and fibrosis, similar to that seen adjacent to affected joints. [77] Prevalence estimates vary widely from 1 to 33% for conduction disturbances and from 1 to 10% for aortic insufficiency [34, 78]. AS is associated with an excess mortality from cardiovascular disease of around 20–40% [27]. Inflammation is well known for its role in the initiation and progression of atherosclerosis, and the chronic inflammation and immune dysregulation associated with AS is thought to be involved in accelerated atherosclerosis [79]. A higher prevalence of atherosclerosis has been demonstrated in patients with AS compared with controls, which may help explain the increased cardiovascular risk in the AS population [80]. Anti-TNF-α treatment is thought to have a favourable effect in reducing cardiovascular risk in patients with chronic inflammatory disorders. In a study of 60 patients with RA, AS and PsA (24, 26 and 10 patients, respectively), infliximab treatment modified the unfavourable lipid profile in patients, inducing a modest, but sustained increase in serum high-density lipoprotein cholesterol (HDL-C) levels [81]. Additionally, anti-TNF-α treatment with etanercept was shown to significantly improve microvascular function for both endothelium-dependent vasodilation ($P = 0.03$) and capillary recruitment ($P = 0.006$) in patients with AS [82].

Lungs. Pulmonary abnormalities are also documented in patients with AS [39]. It has been proposed that a potential mechanism could be a direct result of the same mechanism affecting the joints [83]. Prevalence estimates vary widely, with pulmonary abnormalities being reported in 40–88% of the AS patients using high-resolution CT [37–39]. The abnormalities include evidence of airway disease (82%) and interstitial abnormalities (47–65%), and emphysema (9–35%) [37–39], thickening of the interlobular septa (33%), mild bronchial wall thickening (29%) and pleural thickening (29%) may be detected [84]. If alveolitis is found, it is mainly characterized by lymphocytosis at bronchoalveolar lavage [85].

Kidneys. The incidence of renal abnormalities increases in patients with AS. Likely causes include an increased incidence of glomerulonephritis, particularly associated with deposition of immunoglobulin A (IgA)–containing immune complexes, and renal amyloid deposition (amyloidosis) [35, 36]. Usually amyloidosis is secondary (amyloid A, reactive) and may be characterized by proteinuria and renal insufficiency and accompanied by malabsorption and bleeding. Amyloidosis is more prevalent in aggressive and active AS and in older patients with long-standing disease. At the moment of abdominal subcutaneous fat aspiration, most patients (80%) had subclinical amyloid deposits [86, 87].

The incidence of renal abnormalities (including IgA glomerulonephritis, microscopic haematuria, microalbuminuria and decreased renal function and creatinine clearance) has been shown to range from 10 to 35% in patients with AS [86, 87]. Some case reports suggest the potential role of TNF-α inhibitors in improving AA amyloidosis. In this report, patients were treated with etanercept over 1 year [88].

Are there differential effects with anti-TNF therapies?

The use of TNF-α inhibitors (infliximab, adalimumab, etanercept) results in substantial improvements in both signs and symptoms of AS also contributing to an improved functional status and QoL [15–18, 89]. The efficacy of TNF-α inhibitors in extra-articular manifestations and comorbid conditions appears to vary from agent to agent. Etanercept appears to have very little effect on uveitis and IBD, while the incidence of flares of both conditions appears to be reduced with infliximab treatment for AS; there are comparatively relatively little data available for adalimumab at present [29, 51, 59]. Infliximab has been shown to be very effective in treating the underlying inflammation present in extra-articular manifestations [28, 29, 90–93]. Additionally, infliximab has been proven efficacious in the treatment of psoriasis and in patients with PsA (both independent of AS).

Modes of action differences of these agents may, at least in part, explain the differences in their efficacy profiles. Each molecule of infliximab is believed to bind two TNF-α molecules. Alternatively, three molecules of infliximab are believed to bind to one TNF-α trimer, allowing few or no receptor-binding sites free on a TNF-α molecule (Fig. 3) [94]. Relatively stable complexes of infliximab have also been shown to form with both soluble and transmembrane TNF-α [94]. Infliximab did not dissociate from soluble TNF-α in radiolabelled TNF-α-binding assays in the presence of unlabelled competitor after >3 h of incubation [94]. Additionally, after 2 h of incubation in the presence of excess unlabelled infliximab, etanercept or soluble TNF, radiolabelled infliximab did not dissociate from transmembrane TNF. These results indicated that infliximab/TNF complexes are less bioactive than soluble TNF dissociated from etanercept [94]. Adalimumab binds both soluble and membrane-bound TNF-α [95] and forms a relatively stable complex. Extensive

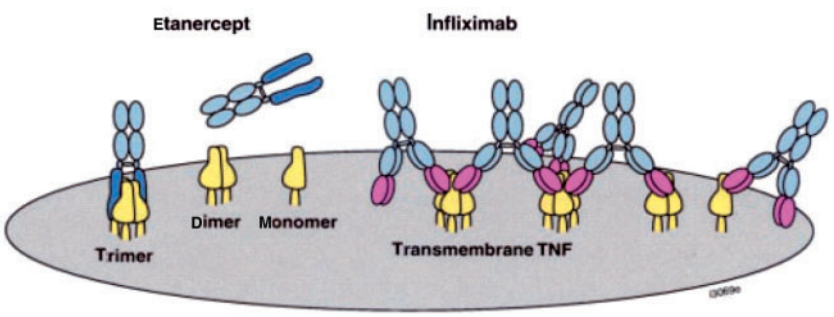


FIG. 3. Binding of infliximab and etanercept to cell surface transmembrane TNF. Reproduced with permission from the American Society for Pharmacology and Experimental Therapeutics [94].

characterization studies of the TNF-α-binding characteristics of adalimumab have not been conducted; therefore, more data are needed.

Etanercept is a bivalent molecule that binds to the interface of two TNF subunits in a 1:1 ratio, occupying two of the three receptor sites on TNF-α but leaving the third receptor site open (Fig. 3) [94, 96]. Etanercept shows little affinity for monomeric TNF-α subunits compared with trimeric TNF-α because the receptor-binding site on the TNF-α is in the cleft formed in the TNF-α complex [96].

Etanercept has a high affinity for soluble TNF-α; however, the resultant complex is relatively unstable [96]. Radiolabelled binding assays found that transmembrane TNF/etanercept complexes are also relatively unstable. The relative instability of etanercept/TNF complexes could, in part, explain the observed relative reduction/absence of efficacy for etanercept in some TNF-α-related conditions [94].

These data suggest that of the TNF-α inhibitors, the monoclonal antibodies (infliximab and adalimumab) may be more favourable in the treatment of extra-articular manifestations associated with AS compared with the receptor fusion protein, etanercept. Although differences among the TNF-α inhibitors have been observed in *in vitro* or animal models, head-to-head studies are needed to establish the difference in efficacy of these agents in treating AS-associated extra-articular manifestations.

Treatment approach

The evidence that extra-articular manifestations and comorbid conditions are common and may be serious when associated with AS suggests that physicians should consider their potential presence in the patient when selecting a therapy. Emerging knowledge that these manifestations may be consequences of the same inflammatory pathology should direct the physician to identify a therapy that will treat the patient as a whole. Achieving suppression of uncontrolled inflammation throughout all body systems has the potential to improve patient QoL and outcomes.

Prior to the advent of biologic agents, treatments for AS were limited to symptomatic relief; no established treatment had been found to arrest the demineralization of bone or ossification of ligaments and tendons that are characteristic of advancing AS [97]. NSAIDs have been the cornerstone of pharmacological intervention in AS, rapidly reducing inflammatory back pain [98–104]. However, the use of NSAIDs is often limited by GI side effects and, after the withdrawal of NSAID treatment, rebound symptoms of inflammation generally appear within a few days [105]. A reduction in radiographic progression of AS with continuous NSAID use, rather than 'as-required' use, has recently been demonstrated in a 2-year randomized controlled trial [106]. Therefore, NSAIDs should be considered prior to the initiation of TNF-α inhibitors [107].

SSZ, a DMARD used in the treatment of RA, has demonstrated some efficacy in peripheral arthritis; however, axial symptoms do not appear to improve [97, 108, 109]. More recently, TNF-α inhibitors have been established as safe and effective for the treatment of signs and symptoms of active AS [16, 18, 110]. The return of symptoms following cessation of a TNF inhibitor suggests that TNF inhibitors should be maintained in the long term to ensure maximum patient benefit [111]. Furthermore, 4-year follow-up data suggest that infliximab may decelerate the progression of structural changes compared with previously documented controls. Larger studies are required to confirm this [112].

Although the goal of treatment is to suppress underlying inflammation, there is some controversy in the field on the impact of new bone formation, a hallmark feature in AS. It is possible that even though there is continued suppression of inflammation bone formation, ankylosis may occur once the pathological cascade has been triggered [113]. Data from research by Lories *et al*. suggest that BMP signalling plays a key role in the pathological cascade of bone formation. Controlling inflammation alone may not be sufficient to inhibit structural progression; therefore, complementary therapy targeting BMP signalling may be beneficial [114].

Factors predicting a major clinical response to TNF-α inhibitor therapy in active AS include younger age, shorter disease duration, better functional status, raised acute-phase reactants, higher disease activity and widespread inflammation in the spine as detected by MRI [115, 116]. Regarding the achievement of a $\geqslant$50% improvement in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), there does not appear to be any patient feature that predicts a response to one TNF-α inhibitor over another, and thus there appears to be little to distinguish TNF-α inhibitors in terms of BASDAI response alone [115].

The lack of efficacy of etanercept in CD is widely known and acknowledged in the international Assessment in Ankylosing Spondylitis (ASAS) consensus statement for the use of anti-TNF agents. It is recommended that infliximab is used when there is underlying CD [107]. This line of thinking can be extrapolated to consider other extra-articular manifestations and comorbid conditions, such that the most appropriate treatment for the entire patient is chosen. Both infliximab and adalimumab may be suitable options in treating an AS patient with associated extra-articular manifestations; however, infliximab is the best studied agent to date.

Conclusions

AS is a disease characterized by sacroiliitis with associated inflammatory back pain, leading to ankylosis of the spine. Chronic inflammation associated with AS can also underlie pathological processes in other parts of the body leading to extra-articular manifestations and comorbid disease. The extra burden that additional inflammatory disease manifestations can place on a patient can result in a reduction in QoL and indicate worse outcomes. Treating the inflammatory disease process underlying both the AS and extra-articular symptoms significantly benefits the patient. While there appears to be no difference in efficacy for the currently available TNF-α inhibitors with regard to treatment of AS symptoms, there are considerable differences regarding extra-articular symptoms. Etanercept does not appear to be effective in reducing the incidence of either IBD or uveitis flares, while infliximab and adalimumab do appear to have some effect, although more data are required for adalimumab. All three agents have demonstrated some level of efficacy in psoriasis (not associated with AS). There appear to be important pharmacodynamic and pharmacokinetic differences between the TNF-α inhibitors that may potentially contribute to their efficacy in different disease states.

Whereas not every patient with AS will exhibit inflammatory disease also in other organ systems, the incidence of extra-articular manifestations, including the GI tract, eye, skin, bone, lung and kidney, is much greater than in the general population and thus should always be considered. Many patients may have asymptomatic or low-grade inflammation that has yet to manifest as full-blown disease, and enquiry about bowel habits, skin problems, nail changes and ocular problems may help to identify these patients. Once inflammation is identified in more than one organ system, it would seem sensible to treat the inflammation throughout the whole body rather than focusing on one area. If treatment with a TNF-α inhibitor is warranted, the monoclonal antibodies (adalimumab and infliximab) would appear to be preferred above etanercept for the management of AS with current or likely future, extra-articular manifestations and comorbid conditions. However, currently, infliximab is the best studied monoclonal antibody with a wide spectrum of proven efficacy.

Rheumatology key messages

- Chronic inflammation associated with AS can lead to extra-articular manifestations.
- Consider the overall patient well-being when selecting treatment in patients with AS.

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