Review

Therapy of ankylosing spondylitis and other spondyloarthritides: established medical treatment, anti-TNF-α therapy and other novel approaches

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Abstract

Therapeutic options for patients with more severe forms of spondyloarthritis (SpA) have been rather limited in recent decades. There is accumulating evidence that anti-tumor-necrosis-factor (anti-TNF) therapy is highly effective in SpA, especially in ankylosing spondylitis and psoriatic arthritis. The major anti-TNF-α agents currently available, infliximab (Remicade®) and etanercept (Enbrel®), are approved for the treatment of rheumatoid arthritis (RA) in many countries. In ankylosing spondylitis there is an unmet medical need, since there are almost no disease-modifying antirheumatic drugs (DMARDs) available for severely affected patients, especially those with spinal manifestations. Judging from recent data from more than 300 patients with SpA, anti-TNF therapy seems to be even more effective in SpA than in rheumatoid arthritis. However, it remains to be shown whether patients benefit from long-term treatment, whether radiological progression and ankylosis can be stopped and whether long-term biologic therapy is safe.

Keywords: ankylosing spondylitis, anti-TNF-α therapy, conventional and innovative treatment, psoriatic arthritis

Introduction

The spondyloarthritides (SpAs) comprise five subtypes: ankylosing spondylitis (AS), reactive arthritis, major parts of the arthritis/spondylitis spectrum associated with psoriasis (psoriatic arthritis; PsA) and inflammatory bowel disease associated with arthritis/spondylitis and undifferentiated SpA. AS is the most frequent subtype of SpA, being more prevalent than the undifferentiated type, but PsA, based on the high prevalence of psoriasis, is also quite frequent [1,2], while reactive arthritis and inflammatory bowel disease associated with arthritis/spondylitis are relatively rare. The prevalence of the whole group of SpAs has been recently estimated to be between 0.6 and 1.9%, with a prevalence of AS between 0.1 and 1.1% [1–4]. Thus, taken together, the SpAs have a prevalence that is not much different from that of rheumatoid arthritis (RA), which has been estimated as about 0.8%.

Of the SpAs, AS is the subset that has the most severe course. Researchers have only recently started to investigate the burden of this disease, both personal and economic, in patients who have it. It is difficult to compare RA and AS directly, not only because there are far more studies in RA, but for a number of other reasons – one being that AS usually starts considerably earlier in life, in the third decade, which means that the burden of disease lasts longer. However, some comparisons have been made using large data sets from databases. When age-

ANA = antinuclear antibody; AS = ankylosing spondylitis; ATTRACT = Anti-TNF Trial in Rheumatoid Arthritis with Comcomitant Therapy; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index; BASGI = Bath Ankylosing Spondylitis Disease Global Index; BASMI = Bath Ankylosing Spondylitis Metrology Index; DMARD = disease-modifying antirheumatic drug; FDA = [US] Food and Drug Administration; HLA = human leukocyte antigen; IFN = interferon; IL = interleukin; MRI = magnetic resonance imaging; NSAID = nonsteroidal anti-inflammatory drug; PsA = psoriatic arthritis; RA = rheumatoid arthritis; SpA = spondyloarthritis; TNF = tumor necrosis factor.

and sex-matched AS patients with severe disease were compared with RA patients with severe disease, the grades of pain and disability were similar [5]. Furthermore, absence from work and work disability is clearly greater in patients with AS than in individuals without the disease [6–8]. In a recent survey in the USA [9], the most prevalent quality-of-life concerns of patients with AS included stiffness (90.2%), pain (83.1%), fatigue (62.4%), poor sleep (54.1%), concerns about appearance (50.6%), worry about the future (50.3%) and side effects of medication (41%). Indeed, fatigue has been identified as a major problem in AS – closely associated with pain and stiffness [10]. However, many AS patients cope better with their disease than RA patients, possibly because of the earlier onset of AS and the somewhat better education in AS patients. In recent decades, patients, general practitioners and rheumatologists have arranged themselves a lot with the situation in AS, because that is what happens when there is no treatment available.

Thus, SpA in general and AS especially are more prevalent than was previously thought and have a clear socioeconomic impact on society. Against this background, it is becoming increasingly clear that more effective therapies are needed. Although there is a role for intensive physiotherapy, as was recently shown [11,12], this review concentrates on the drug therapy of AS – the most prevalent subtype of SpA, and the one with the most severe outcome.

Treatment of ankylosing spondylitis with nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) and intra-articular coriticosteroids are accepted, often-used treatments for AS [13]. NSAIDs are taken, with varying efficacy, by about 70–80% of AS patients. A good response to NSAID treatment has even been suggested as a criterion for the diagnosis of inflammatory back pain and SpA [14]. A poor response or none to NSAIDs has been identified as a poor prognostic sign in AS [15,16]. Patients' responses to NSAIDs are broadly similar but nevertheless often differ markedly from one person to another. Several NSAIDs may therefore need to be tried to identify the best one for a particular patient, and high doses are often required in severe cases [16]. Indomethacin, naproxen and diclofenac are among those most frequently used in AS, but others clearly work also [17]. Finally, an almost historical but very effective agent, phenylbutazone (not available in the USA), may be tried by experienced rheumatologists for patients with severe AS [15,18].

There is evidence that the new, more COX-2 selective drugs meloxicam and celecoxib [19,20] are no less effective in treating back pain of AS patients than conventional NSAIDs such as piroxicam and ketoprofen. The effectiveness of these newer drugs may be associated with the advantage of less serious gastrointestinal events.

However, as in other rheumatic diseases, NSAIDs are valuable only to improve the symptoms of spinal inflammtion, and there is no evidence that long-term antiphlogistic treatment affects the radiologic outcome or function. It is widely believed that relief from pain is associated with an improved ability to exercise daily – which, over time, supports the maintenance of function and helps to prevent the joints from stiffening in a handicapping position.

Other painkillers besides NSAIDs, including opioids [21] and depression-directed drug regimens [22], can be used. There seems to be only a limited potential for addiction.

Treatment of ankylosing spondylitis with disease-modifying antirheumatic drugs

There are no established disease-modifying antirheumatic drugs (DMARDs) for AS as there are for RA. The best-investigated DMARD for the treatment of AS is sulfasalazine. In the two largest placebo-controlled studies, efficacy for peripheral arthritis but no clear effects on axial symptoms was reported [23,24]. However, mostly patients with long-standing disease (of more than 14 years' duration) were treated in these studies. In an earlier placebo-controlled trial with 85 patients, 60% of whom had peripheral arthritis [25], sulfasalazine had some effect also on the spinal symptoms of AS patients who had a relatively short disease duration, of less than 6 years. The peripheral arthritis of patients with AS [23,24], as in other SpA, improved on treatment with sulfasalazine also in PsA [26]. There is also some evidence that sulfasalazine prevents attacks of AS-associated uveitis [23,27].

On the whole, sulfasalazine is effective for peripheral arthritis in SpA, but there is no clear option for the axial manifestations. However, in early and active disease there is reason to try sulfasalazine, in the absence of useful alternatives. We are performing a placebo-controlled study in which 200 patients with early AS (duration of symptoms less than 5 years) are treated with sulfasalazine or placebo for 6 months. We hope the findings will allow further, evidence-based conclusions about the efficacy of sulfasalazine in early AS and undifferentiated SpA.

Much less information is available about the efficacy of other DMARDs in AS. Since very early occasional reports [28], there have been a few small, open studies using methotrexate, which reported a potential effect in AS [29–31]. In a retrospective study, no effect was seen [32]. Only one placebo-controlled study, with a total of 30 active AS patients who were treated with an oral dose of 10 mg methotrexate weekly, has been published in abstract form [33]. The authors of that investigator-driven study did not see significant benefits of this treatment, either for AS or for peripheral arthritis. Pharmaceutical companies have little interest in carrying out clinical trials

to test the efficacy of methotrexate in AS, since this drug is already used by many rheumatologists [34] – in the absence of proven efficacy.

There are no studies beyond case reports on the treatment of AS patients with other DMARDs that are effective in the treatment of RA, such as gold, azathioprine, cyclosporin A or leflunomide. An intensive regimen with intravenously administered azathioprine was recently used with some success in single cases [35]. Similarly anecdotal are the data on antimalarial agents, gold or cyclosporin A in AS, while there is some very recent evidence that the latter compound works in psoriatic arthritis [36].

Treatment of ankylosing spondylitis with corticosteroids

AS has been generally neglected in past studies to identify effective agents. As an example, there has not been even one controlled study to test the efficacy of systemic corticosteroids in AS or other SpAs.

Although there is little doubt that both AS and RA are inflammatory rheumatic diseases, there is a lot of evidence that the pathogenesis differs, in the same way as the genetic background clearly does [37]. Another fascinating difference is that patients with AS are generally less responsive to corticosteroid therapy. This may be explained in the future by differences in the membrane expression of glucocorticoid receptors in the two diseases [38,39].

Surprisingly, aside from single observations and open studies with high doses in a few patients [40–42], only very limited data on steroid treatment for AS and SpA are available. Personal, uncontrolled clinical experience suggests that, in contrast to what happens with RA and other inflammatory rheumatic diseases, systemic glucocorticoids in general do not work very well in AS, at least when given in low and moderate dosages. However, there are probably subgroups of patients who respond better than others: those with peripheral arthritis, those with anterior uveitis, those with concurrent inflammatory bowel disease, those with elevated concentrations of C-reactive protein, those who are negative for human leukocyte antigen (HLA) B27 [43,44] and females (Braun J, unpublished). Clearly, these proposals are interesting enough to justify further study. There is little doubt that intra-articular corticosteroids work quite well for short-term improvement in peripheral arthritis, including disease of the hips [45] and sacroiliitis [46,47]. In the sacroiliac joints, the effect of computed-tomography-guided injections seems to last longer than that of the blind injection technique, which is also feasible [48].

Radiation and immunosuppressive therapy

Radiation therapy for AS has successfully relieved spinal pain in the past, but the associated risk of malignancy turned out to be too great [49,50]. Refractory heel pain in SpA can still be treated by radiation [51].

A rather pure application of radium chloride Ra 224 with a cumulative dose of 10 MBq given intravenously in 10 portions over 10 weeks has recently been approved for the treatment of severe AS in Germany, mainly on the basis of older, successful open studies [52]. With the higher doses of ^{224}Ra used formerly, the risk of chronic myeloid leukemia was slightly increased [53]. There is a need for controlled trials [54]. Radium chloride is not available in other countries.

More therapies targeting the immune system, including lymphocyte-oriented apheresis [55], have been tried in AS, with some positive effect. Stem cell transplantation because of lymphoma in a patient who also happened to have AS has been reported [56]; in another patient, SpA-like symptoms developed [57].

Use of bisphosphonates for the treatment of ankylosing spondylitis

The efficacy of bisphosphonates in metastatic bone disease is well established [58]. There have been two positive reports from small, open studies in the treatment of AS with pamidronate. Both spinal and peripheral disease, including enthesitis, were successfully treated by this intravenously applied bisphosphonate [59,60], which is active against osteoclasts and is occasionally used for the treatment of osteoporosis. A gain in bone mass could be a desirabe side effect in AS, in which osteoporosis is associated with an increased risk of fractures [61]. Recent results from a Canadian controlled study, in which a 60-mg dose of pamidronate was compared with a 10-mg dose, suggest that the larger dose is significantly more effective [62]. In this study, in 84 patients with AS (67 male and 17 females; mean age 40 years; mean disease duration 14 years), significantly greater reductions at 6 months were noted in the 60-mg than in the 10-mg group, according to scores on the BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) (-2.2 ± 2 vs -0.9 ± 1.7; $P = 0.002$), the BASFI (Bath AS Functional Index) (1.7 ± 2.1 vs -0.2 ± 1.6; $P < 0.001$), the BASGI (Bath AS Global Index) and the BASMI (Bath AS Metrology Index). Significantly more patients in the 60-mg group than in the 10-mg group achieved a $>25\%$ reduction in their BASDAI score (63.4% vs 30.2%, respectively; $P = 0.004$), while the reductions in the erythrocyte sedimentation rate and in C-reactive protein were not significantly different in the two groups. Adverse events were frequent, consisting mainly of transient arthralgias or myalgias after the first intravenous infusion (in 68.3% and 46.5% of patients in the 60- and 10-mg groups, respectively). Of clinical significance is the sometimes rather acute reaction, with pain, fever and leukopenia, in relatively young AS patients, which is rarely observed in older

women with osteoporosis. This impressive reaction may be very suggestive to patients, who feel that there is really something going on. Our own experience with 12 patients suggests that the overall efficacy is not enormous, but there are individual patients who seem to benefit in terms of reduced pain and disease activity. A positive effect on reduced bone mineral density can also be expected.

Thalidomide for severe ankylosing spondylitis

Thalidomide (α-*N*-phthalimidoglutarimide) is a synthetic derivative of glutamic acid, which was put on the market as a sedative in 1956. After removal from the market because it caused congenital malformations, it has now undergone a revival, and it was approved for the treatment of erythema nodosum leprosum by the Food and Drug Administration in the USA in 1998. Thalidomide is increasingly used for the treatment of malignancies [63], on the basis of its potential for blocking tumor necrosis factor (TNF) [see below; 64]. Thalidomide has now been tried in AS; in an open study with 12 patients in France [65], 5 of 12 patients stopped taking thalidomide before 6 months because of side effects. The most consistent efficacy was on the erythrocyte sedimentation rate and/or C-reative protein. In a Chinese open study with 30 male patients affected with severe, active, refractory AS [66], 80% of the 26 patients who completed the study had a positive clinical response. Decreased expression of several proinflammatory genes, including TNF-α and IL-1, in peripheral blood mononuclear cells from AS patients after thalidomide treatment was reported [67]. Thalidomide has also been effective in refractory Crohn's disease [68], whereas in RA, the response to similar doses was rather poor [69]. The toxicity and the side effect of fatigue might prevent extensive use of thalidomide.

TNF-α blockade in the treatment of ankylosing spondylitis

Today there are two main biologic agents targeting TNF-α: the chimeric monoclonal IgG_1 antibody infliximab (Remicade) with human constant and murine variable regions and the recombinant 75-kD TNF receptor IgG_1 fusion protein etanercept (Enbrel). Both capture soluble TNF-α in the plasma; etanercept also captures TNF-β. Infliximab also binds to cell-membrane-bound TNF-α, possibly leading to cell lysis. These differences may account for the somewhat different clinical efficacies of the two compounds. The elimination half-life is 210 hours for infliximab and 115 hours for etanercept. The manufacturers estimate that the numbers of patients treated with these compounds worldwide are, respectively 200,000 and 150,000.

Both agents clearly work in RA [70–75]. Infliximab is approved for use in RA in combination with methotrexate, because fewer antibodies against infliximab and somewhat fewer adverse events were found with this regimen [71], while etanercept is approved as a monotherapy for the disease. Methotrexate has not been given additionally in AS studies because, as discussed above, its efficacy in this disease is doubtful and many patients need to be treated to prevent rather mild side effects of infliximab therapy.

The sacroiliac joint and the entheses are the most characteristic, and almost pathognomonic, sites involved in SpA [76]. Inflammation at the interface of cartilage and bone has been convincingly shown by magnetic resonance imaging (MRI) [77,78] and immunohistological investigations on biopsies [79,80]. Especially in early cases of AS, dense mononuclear infiltrates that invade the cartilage can be seen [81,82]. These infiltrates contain T cells and macrophages, which secrete TNF-α [83]. In the light of the early, successful trials of infliximab in RA [70–72], the decision to investigate the efficacy of the TNF-α-blocking monoclonal antibody infliximab in patients with AS was the logical next step, although it must be stressed that RA is pathogenetically clearly different from AS. Further support for a possible efficacy of infliximab in AS came from two other sets of data. Firstly, AS and the whole group of SpAs are associated with chronic inflammatory bowel diseases [84]: patients with inflammatory bowel disease may develop AS and more than 50% of patients with primary AS have histological gut lesions similar to Crohn's disease [85]. Furthermore, TNF-α is strongly expressed in the inflamed gut of patients with inflammatory bowel disease, and anti-TNF-α therapy with infliximab is effective and approved for Crohn's disease [86]. It might be similarly effective in ulcerative colitis, but further study is needed [87,88]. Etanercept seems not to be effective in Crohn's disease, at least in the usual dosage [89] – a finding that may offer clues to the pathogenesis of the disease. Importantly, in patients with Crohn's disease treated with infliximab, joint symptoms improved [90]. Another body of data supporting the hypothesis that infliximab's efficacy might extend to AS is the observation that anti-TNF-α therapy is effective in other SpA-related inflammatory rheumatic diseases such as psoriatic arthritis [91,92] and severe psoriatic skin lesions [93,94]. As already mentioned, other inflammatory rheumatic diseases such as RA respond favorably to anti-TNF strategies [70–75]. In the case of infliximab, it was even found that the radiographic progression of the disease could be stopped [75].

Effect of anti-TNF therapy in spondyloarthritides

In the open pilot study performed in Berlin, infliximab ameliorated the disease activity in patients with severe AS with a mean disease duration of 5 years [95], as measured by the BASDAI [96]. Eleven patients received three infusions of infliximab (5 mg/kg body weight at weeks 0, 2 and 6). Significant efficacy was already noted on the first day of therapy. Spinal pain, fatigue and morning stiffness in particular were ameliorated, and so was peripheral arthritis.

Nine of ten patients showed an improvement of >50% on the BASDAI; the median improvement of the BASDAI after 4 weeks was 70%. Importantly, quality of life, as measured by the 'short form' 36-item instrument (including only 12 questions instead of 36), significantly improved after 4 weeks. In comparison with an age- and sex-matched normal, healthy German population, the AS patients studied had clearly impaired initial assessments; in particular, their level of physical functioning was very low. This level was significantly increased by anti-TNF-α therapy within 4 weeks. One patient has remained in remission for at least 18 months after only the initial three infusions of infliximab. As major side effects, three patients developed allergic reactions and could not receive further treatment.

The patients in this study were followed up for another 9 months. The next infusion of infliximab was not given until after a relapse, which was defined as at least 80% of the initial activity [97]. The first symptoms came back after a mean of 6 weeks and a relapse occurred after a mean of 12 weeks. These patients were treated three more times. Although all responded again, they did less well than at the start of the study, probably because there was no initial saturation phase in the repeat treatments.

In the meantime, there have now been several open-label studies on infliximab in AS [98–102]. In a Belgian study, 21 SpA patients, including 11 with AS, were treated with infliximab with a dose regimen similar to that in the study just discussed, but the patients had a longer disease duration (15 years) and the intervals between the infusions were longer (14 weeks). The spinal and peripheral symptoms of all these patients with SpA improved significantly [98]. There have been other studies – two in Canada, one with 24 [99] and one with 21 AS patients [100]; one in France, with 50 AS patients [101]; and one in Spain, with 42 SpA patients [102] – in which treatment with infliximab was successful, all with a similarly good response in about 80% of the patients. In one Canadian study [99] and the Spanish study [102], patients with disease of long duration and with advanced radiographic disease/ankylosis apparently benefited less from the therapy. In the other Canadian study [100], a relatively small dose, 3 mg/kg every 8 weeks, was sufficient to cause significant improvement.

In a French study, the bone mineral density of 31 patients (26 men and 5 women, mean age 40 years, mean disease duration 18 years) increased by 3.3 ± 5.5% at the lumbar spine ($P < 0.002$), and 1.9 ± 3.1% at the femoral neck ($P < 0.008$) after 6 months of infliximab therapy [103].

A recent randomized, double-blind, controlled trial in Germany has provided class-B evidence (according to 'evidence based medicine' criteria) that infliximab is effective against AS [104]. This placebo-controlled, multicenter study conducted over 12 weeks included 70 AS patients with a BASDAI >4 and spinal pain on a visual analogue scale >4. A highly significant effect of infliximab treatment (5 mg/kg body weight given at weeks 0, 2 and 6), with the primary outcome parameter of a 50% improvement of disease activity (BASDAI), was achieved in the treated group in comparison with the placebo group. Again, other parameters such as BASFI, BASMI and the short-form 36-item instrument showed a similar clear-cut improvement. There is some evidence that patients with elevated concentrations of C-reactive protein benefited more than those with low or normal levels [104]. Preliminary results from imaging follow-ups with spinal MRI assessing both acute and chronic spinal changes suggest a significant effect of infliximab on disease progression assessed on this basis. Taken together, these data strongly suggest a major breakthrough in the short-term therapy of severe AS.

After the placebo phase of the study, these 70 patients are now being treated with infliximab at 5 mg/kg body weight every 6 weeks for 2 years. After 48 weeks (when this article was written), about 75% of the patients are still being treated. So far, there is no indication of loss of efficacy. When complete, the study should provide more information about the long-term efficacy and safety of infliximab treatment in AS.

Another controlled study, from Belgium, has been recently published [105]. Both primary end points of this study, improvement in the patient's and the physician's global assessment of disease activity on a visual analogue scale, improved significantly in the infliximab group in comparison with baseline values, while there was no improvement in the placebo group. Significant efficacy was noted as early as week 2 and was sustained up to week 12, until the end of this study.

Regarding the optimal dosage of infliximab in SpA, only limited data are available. In a small study, we and our colleagues found that a dose of 5 mg/kg body weight was better than 3 mg/kg in patients with undifferentiated SpA [106]. However, the lower dosage of infliximab seemed to work also. Some patients may not need doses of infliximab higher than 3 mg/kg.

Treatment of AS with the soluble TNF-α-receptor etanercept has not been studied as extensively in SpA, but preliminary data from single cases [107], an open study [108] and now a double-blind study [109] also indicate a clearly favorable effect. This is in accord with our own preliminary experience with this therapy in 30 patients. In a study by Davis and coworkers in California [109], 40 patients were given either etanercept (25 mg given subcutaneously twice daily) or a placebo. A major difference from our own studies was that patients taking DMARDs (40%) or steroids (25%) were allowed to continue taking them during the study. Furthermore, different outcome parame-

ters were used. After 6 months, main outcome parameters such as morning stiffness and nocturnal spinal pain had improved significantly in patients given etanercept but not in those given the placebo. The disease activity combination score used in that study had also improved significantly by 6 months but not by 6 weeks. Further studies with this drug are in progress or being planned.

There are various targets of SpA therapy (Table 1). In AS, the main targets are spondylitis, spondylodiscitis and peripheral arthritis. Other targets that are sometimes difficult to treat are enthesitis [76] and uveitis [110]. As has already been mentioned, there are targets in the skin (psoriasis) and the gut (colitis associated with inflammatory bowel disease), which have been shown to respond well to anti-TNF therapy.

There is evidence from the Berlin randomized, controlled trial and from case reports that anti-TNF therapy is beneficial in patients who are refractory to standard local and systemic treatment of enthesitis with NSAIDs, DMARDs and steroids, even in longstanding cases [104,111,112].

Table 1

Spondyloarthritides – main targets for treatment

Back pain due to:	
	sacroiliitis
	spondylitis or spondylodiskitis
	enthesitis
	ankylosis
Joint pain due to:	
	enthesitis
	peripheral arthritis
Organ involvement due to:	
	anterior uveitis
	psoriasis
	colitis
	involvement of internal organs (heart, lung, amyloidosis)

Concerning anterior uveitis associated with SpA, there is some recent evidence from controlled trials that sulfasalazine does prevent attacks [23,27], while the data for methotrexate are less clear. In a recent retrospective study [113], 160 patients with chronic uveitis of noninfectious origin were treated with methotrexate. Control of inflammation was achieved in 76% of patients and steroids were spared in 56%. Visual acuity was maintained or improved in 90% of patients.

The response of patients with all kinds of inflammatory eye disease to anti-TNF has been recently looked at in a limited number of patients [114]. The picture is not clear: both improvement and worsening of inflammatory eye disease upon treatment with infliximab have been found. In one study [115], 16 patients (4 males and 12 females, aged 7 to 78 years) who received etanercept ($n = 14$) or infliximab ($n = 2$) for either inflammatory eye disease or associated joint disease were studied retrospectively. Uveitis ($n = 9$) and scleritis ($n = 7$) occurred in patients with RA ($n = 11$), AS ($n = 1$), and psoriatic SpA ($n = 1$), and 3 patients had uveitis without systemic signs of disease. Although all 12 patients with active articular inflammation experienced improvement in joint disease, only 6 of 16 with ocular inflammation (38%) experienced improvement in their eye disease. Five patients even developed inflammatory eye disease for the first time while taking a TNF inhibitor.

In a prospective study [116] with 10 children suffering chronic active uveitis, 7 had uveitis associated with pauciarticular juvenile RA and 5 were positive for antinuclear antibodies (ANAs). All patients for whom previous therapy with topical steroids and methotrexate and/or cyclosporine had failed were treated with etanercept at 0.4 mg/kg body weight twice weekly for the first 3 months, and then, if their eyes did not improve, with 25 mg twice weekly (mean 1.1 mg/kg body weight) for at least 3 additional months. Within 3 months, 10 of 16 affected eyes (63%) showed a rapid decrease in cell density in the anterior chamber ($P = 0.017$), including remission in 4 eyes. Uveitis exacerbated during etanercept therapy in only 1 child (7%). After a dosage increase to an average of 1.1 mg/kg after 3 months in seven children, no further improvement was noted. It is well known that the natural course of uveitis in HLA $B27^+$ versus ANA^+ patients is rather different. The authors concluded that treatment of uveitis with etanercept in systemic and/or topical form (which has not been studied so far) needs further study.

In a recent report from Austria, El-Shabrawi and Hermann [117] reported a beneficial effect of infliximab with HLA-B27-associated uveitis in three patients. The same authors have recently published in abstract form their experience with this treatment over one year [118]. Seven consecutive patients with an acute onset of an HLA-B27-associated acute anterior uveitis were treated with a single dose of infliximab (10 mg/kg given intravenously). One patient received a second infusion 3 weeks after the first dosage, because of a relapse. The median duration ($\pm$SD) of uveitis was 8 ± 12 days. All the patients responded to infliximab with a rapid improvement of clinical symptoms and a decrease of cells in the anterior chamber of the eye. Only one patient did not develop total resolution of the uveitis. On follow-up, three of the seven patients were found to have experienced a relapse after a

median of 120 days. These authors concluded that infliximab was very effective for treating acute anterior uveitis.

Most recently, treatment with infliximab has also been reported beneficial in patients with uveitis associated with Crohn's disease [119].Thus, the results from these uncontrolled observations are basically positive. In addition, our own experience with infliximab in a randomized trial with AS patients [104] is also suggestive of a beneficial effect, since three patients out of 35 in the placebo group, versus one out of 35 in the infliximab group, developed uveitis over 3 months.

However, the natural course of anterior uveitis in SpA is rather benign in the vast majority of patients. Thus, anti-TNF therapy should only be considered in severe, refractory cases. Controlled studies in homogeneous patient populations and a systematic comparison with local and systemic steroid therapy is clearly needed.

Side effects of anti-TNF therapy

Although new, very effective therapies are arising, the greatest concern is of course about undesired and potentially severe side effects. There clearly are side effects to be considered in patients treated with anti-TNF agents. Information about side effects can come from various sources: directly from the clinical studies performed, from publication of the cases reported to the US Food and Drug Administration (FDA) or other agencies, from the data released by the drug companies, from case or group reports of cases and from personal experience. Every source has advantages but also shortcomings: clinical studies are controlled and randomized but special 'ideal' patients are selected for a limited amount of time; reports to the FDA are relevant because they reflect how the product is used in clinical practice but they are uncontrolled and they may lead to both underestimation and overestimation of the real risk due to the Weber effect and reporting bias; data from the drug companies should be most complete but the reports are also difficult to control and the reports are potentially influenced by the financial interest of the companies; case reports and single experiences may not be truly indicative, but they may, nevertheless, induce strong feelings because of personal experience. Thus, we have to select an optimal mixture from these different sources to arrive at valid statements; this is difficult. At the moment, final statements are still difficult because of the paucity of data available.

After the first years of anti-TNF therapy, the following seven types of adverse events seem to be of special concern for patients so treated:

1. infections, including sepsis and tuberculosis
2. malignancies, such as lymphoma
3. other hematologic disorders, such as anemia and pancytopenia
4. demyelinating disorders/neuropathy
5. worsening of congestive heart failure
6. occurrence of autoantibodies and autoimmunity
7. infusion/injection and hypersensitivity reactions.

From the postmarketing data collected by the FDA on the basis of spontaneous reporting – which are, according to agency officials, known to be of limited reliability – about 18,400 adverse events are known for etanercept and 2300 for infliximab, including 290 and 201 deaths, respectively. These figures do not indicate that the mortality is increased and there is also no reason to think that there is a difference in mortality between the two compounds. These data are taken from the FDA website (www.fda.gov), where they are regularly updated. The estimated overall frequency of treatments worldwide is about 200,000 for infliximab and 150,000 for etanercept. The main reason for the different numbers of adverse events reported is that there was a telephone system installed for etanercept, which facilitates reporting, including by the patients themselves. Therefore, it is likely that the total number of adverse events for etanercept is an overestimate.

Although, on the basis of their different pharmacologic profiles (see above), it is generally conceivable that infliximab and etanercept have a distinct potential to cause adverse events, most statements made in this article rather relate to a class effect of these biologic agents, because this best reflects current knowledge. There may be a few exceptions, one of which may be with regard to tuberculosis (see below).

Infections

The outstanding and most frequent problem with both biologic agents are infections, accounting for 28% of all reports regarding etanercept and 39% for infliximab. The numbers of infections and deaths on treatment with the two agents were 5143 and 291, respectively, with etanercept and 901 and 228 with infliximab (double reporting possible; see above).

As recently reported, infection with mycobacteria seems to be associated with anti-TNF therapy, as it now stands, and mainly for infliximab [120]. By the end of November 2001, 117 cases had been reported to the agency [121]. The risk of developing tuberculosis in the first year of infliximab therapy has been estimated at 0.03% in the USA and 0.2% outside the USA. However, there have also been 18 cases of tuberculosis, including 5 deaths (up to 30 June 2001) associated with etanercept therapy, and one case of osteoarticular tuberculosis in a child has been published [122]. It is not clear at present whether the patients treated with etanercept are demographically comparable with those who received infliximab. Demographic factors could explain differences – especially if it becomes

clear that patients treated with etanercept have lived in a safer environment. In the Berlin [104] and the Belgian randomized AS/SpA trials [105] with infliximab, disseminated tuberculosis occurred in one case at each site.

What is the reason for this increased frequency of tuberculosis? Since most of the infections of patients treated with inflixmab occurred during months 2–5 after the initiation of therapy, reactivation of latent tuberculosis seems to be the most likely explanation. However, both activation of latent tuberculosis and also new infections in the case of challenge with virulent microbes may occur [121]. Reactivation of tuberculosis has also been described in vaccinated patients [123].

TNF-deficient mice had similar survival rates in a conventional environment but were clearly more susceptible to a challenge with mycobacteria than normal controls [124]. Indeed, TNF seems to affect several aspects of the immune response to mycobacteria, including IFN-γ-independent but TNF-dependent nonspecific mycobactericidal effects of macrophages [121]. However, the immunologic mechanisms that explain the link between TNF blockade and the failure of granuloma to contain bacilli are poorly understood. The T cells in TNF-deficient mice infected with tuberculosis seem to function normally [125]. All things considered, TNF-α has important, clinically relevant immune functions that need to be effective for clearance of certain microbes including mycobacteria. Whether a reactivated infection is due more to a heavy bacterial load or to a genetically determined functional variant or to alteration of the immune system needs to be determined. For example, there are at least partially genetically determined differences in the capacity to secrete cytokines such as TNF-α between individuals and between patients and controls [126; see below].

Other types of infection have been reported in patients treated with both anti-TNF agents. These include rare but fatal cases of severe pneumonia [127,128], meningitis [129], sepsis [130], histoplasmosis [121,131] and aspergillosis [132]. Furthermore, infections with listeria, *Pneumocystis carinii,* coccidioides, and candida [131] were listed in the FDA database.

In the ATTRACT trial (Anti-TNF Trial in Rheumatoid Arthritis with Comcomitant Therapy), there were seven deaths of patients treated with infliximab, versus four of control RA patients treated with methotrexate only [75]. The deaths were mostly related to the cardiovascular system or were due to advanced age. However, several patients died from severe infections, including sepsis and tuberculosis (see below).

According to the Centocor (manufacturer of infliximab) database containing data from all studies performed ($n = 1372$), there were 22% serious adverse events (SAE) on infliximab, versus 16% on placebo. In the totality of studies with infliximab, 63% of the patients had at least one infection, versus 51% of controls ($n = 192$). Treated infections were identified in 36% of the patients, versus 26% of the controls. Serious infections, however, occurred in 6.3% of infliximab-treated patients, versus 6.8% of patients on the placebo. The most frequent localization was the respiratory tract. Serious pneumonia was reported in 1% of the infliximab-treated patients, versus 0.5% among controls.

In recent, open-label, multicenter trials with infliximab, 8.5% of 553 RA patients in the USA had serious adverse events [133], and in a German trial, 25 of 263 RA patients (9.5%) withdrew because of side effects and 6 had a serious infection [134].

In a recent retrospective review of the medical records of 180 patients [135], most with RA ($n = 144$) started on etanercept, 81% of these patients remained on therapy for >6 months and 43% for >12 months. Corticosteroid dose reduction was possible in 56%, and tapering of the methotraxate dose was possible in 51%. Forty-three patients (23.9%) discontinued etanercept. Serious adverse events occurred in 5 patients (2.9%), mostly infections including psoas abscess secondary to infection with *Mycobacterium avium intracellulare,* septic wrist, bacteremia, and septic total hip replacement. There were two deaths associated with infection.

The FDA database also contained many reports of infections without an identified organism, with 28 deaths during or after etanercept administration and 11 with infliximab.

Fatal infections may occur with both agents. Tuberculosis has been more frequently reported with infliximab. However, as things stand now, the overall quality and quantity of the data are not good enough to make consistent risk/benefit calculations. Before treatment, patients should be informed about their immunocompromised status, especially in the first months of therapy, and educated to take signs of infection seriously and present to the responsible physician as soon as possible. Thus, all patients who are treated with anti-TNF therapy should be carefully screened for infections and treated with antibiotics if there is a suspicion of bacterial infection. Caution is needed before starting anti-TNF therapy, since latent infections such as subclinical pulmonary tuberculosis, or of abdominal tuberculosis in patients with Crohn's disease, may be overlooked [136]. If there is a suspicion or a high risk of exposure, patients should not be treated with anti-TNF agents. Pre-emptive treatment with isoniaziol for the first 6–9 months of therapy should be given in patients who need and have agreed to start infliximab treatment and who are at risk of latent tuberculosis, being

positive for purified protein derivative or who have x-ray evidence of exposure to mycobacteria or a recent history of confirmed tuberculosis contact.

Malignancy/hematologic disorders

The FDA database showed 26 cases of lymphoma reported with etanercept and 10 with infliximab. In a long-term follow-up of patients treated with etanercept, no increased incidence of malignancies was observed [137]. A similar finding has been reported for infliximab [138]. Rapid development of squamous cell carcinoma has been reported in a few patients treated with etanercept [139].

Looking at all studies with infliximab, 17 (1.2%) of the patients who had received at least one dose of infliximab had a reported malignancy (including lymphomas), whereas in the control group only 1 case was noted (0.5%). Since both patients with RA and with Crohn's disease have an increased risk of malignancy, particularly lymphoma, no final conclusions can be drawn but, also due to the limited time frame of follow-up so far, the issue has not been completely clarified yet.

There have been seven cases of aplastic anemia in patients taking etanercept, five of whom died. Two cases of pancytopenia during treatment with infliximab have been reported.

A very small increase in the incidence of malignancies in patients treated with anti-TNF agents cannot be definitely excluded at present, but no increased frequencies have been observed to date. Etanercept may be associated with the onset of aplastic anemia, which, however, is a rare event.

Blood counts should be taken regularly in patients who are receiving anti-TNF therapy.

Neurologic disorders

The FDA database contained 16 reports of demyelinating disease in patients receiving TNF antagonists, in 15 cases associated with etanercept. This has been recently reported [140]. Earlier, two patients with multiple sclerosis were reported to have developed multiple sclerosis lesions while being treated with infliximab [141]. The basis for the discrepancy between the earlier and the more recent report is unclear [142]. Furthermore, two cases of optic neuritis and one of Guillain-Barré syndrome in a patient with RA have been reported. At present, it is unclear whether there is an increased risk of such disorders associated with anti-TNF therapy.

Etanercept may be associated with the onset of demyelinating disease, which, however, is a rare event. Patients should be regularly asked for neurologic symptoms.

Heart failure

Patients with congestive heart failure (a score >II on the New York Heart Association scale) should not be treated with either etanercept or infliximab, because, after early encouraging results, clinical studies with both agents indicated that more patients died or were hospitalized on anti-TNF therapy than on a placebo; this difference appeared to be pronounced in patients who received a high dose of infliximab (10 mg/kg). Not all these studies have been published yet.

Patients with heart failure, especially severe heart failure, may be at risk of worsening of their disease upon anti-TNF therapy. This needs to be carefully considered when therapeutic decisions are made.

Miscellaneous disorders

Development of diabetes mellitus has been reported in a young patient on etanercept [143]. Single cases of vasculitis have been described in patients treated with either agent [144,145].

Autoantibodies

Anti-TNF therapy is associated with the formation of certain autoantibodies. Looking at all those patients treated with infliximab from whom samples from before and after therapy were available ($n = 1058$), 55% became ANA^+ at some time point, while 19% became positive on placebo. Of the patients positive for ANA at baseline, 36% became ANA-negative during the study. Autoimmune diseases such as drug-induced systemic lupus erythematosus or lupus-like syndrome (a term that is not very sharply defined) occurred very rarely – in 0.4% of all patients studied. Development of ANA or DNA antibodies was not predictive of the development of such symptoms. In an overview of data from all studies concluded with infliximab up to June 2001, 4.3% out of 1897 patients and 2% out of 192 controls discontinued treatment; 30 (16%) developed anti-dsDNA and 4 (0.2%) out of the patient group developed clinical signs of lupus-like syndrome (Centocor, data on file).

Treatment with etanercept was associated with the development of drug-induced lupus in one patient [146]. The induction of autoantibodies in patients treated with etanercept has been described: ANA developed in 11% (versus 5% on placebo) and anti-DNA antibodies occurred in 15% (versus 4% on placebo). Furthermore, the development of non-neutralizing antibodies to etanercept has been described in 5% of patients.

Patients have been tested for the development of antibodies to infliximab (anti-chimeric antibodies = HACA). In the ATTRACT trial, the overall incidence of these antibodies was 8.5%. Although there is a small trend towards a higher incidence of infusion reactions in patients who are

positive for these antibodies, there is no indication to add methotrexate to infliximab to prevent infusion reactions.

Infusion/injection site reactions

The most frequent adverse event with etanercept is a local reaction at the injection site; such reactions are generally not a serious problem.

Infusion reactions due to infliximab were defined as any reaction during or 1 hour after the end of the infusion. During the studies with infliximab, infusion reactions occurred in 20% of all patients treated and in about 5% of all infusions given. The most common symptoms were headache (3.8%), dizziness (2.8%) and nausea (3.1%). Serious infusion reactions were rare (0.9%). Discontinuation of treatment due to infusion reactions occurred in 2.6% of the patients (Centocor, data on file).

Delayed adverse reactions 3–12 days after the infusion were reported in one study of patients with Crohn's disease. On the whole, delayed hypersensitivity reactions were infrequent.

It is not clear whether immunosuppressants such as methotrexate or azathioprine should or can be succesfully added to infliximab to prevent antibody formation and allergic side effects.

Influence of anti-TNF therapy on biologic parameters

As already mentioned, the pathogenesis of RA differs from that of AS. In contrast to patients with RA [147,148], those with SpA seem to have an impaired Th1/Th2 balance [149]), with decreased T-cell production of IFN-γ and IL-2 and increased IL-10 synthesis [150–158], in both the peripheral blood compartment and synovial membrane. Elevated IL-10 in the synovium of patients with psoriasis [150] and in synovial fluid mononuclear cells of patients with reactive arthritis [149] has also been reported. Also, IL-10 plasma levels in SpA have been reported to correlate with disease activity [151]. In patients with severe reactive arthritis [152], in HLA B27$^+$ AS patients and in HLA B27$^+$ healthy persons, a lower fraction of TNF-α-producing peripheral blood T cells than in HLA B27$^-$ healthy individuals was found [153]. Taken all together, these data suggest that an impaired Th1 capacity contributes to the pathogenesis of SpA and also that gut mucosal lymphocytes are actively involved in the disease.

The effect of infliximab therapy on the CD3 cytokine profile was analysed in two pilot studies using FACS (fluorescence-activated cell sorting) technology. One study, in a Ghent cohort, documented that treatment with three infusions of infliximab in patients with SpA resulted in a rapid and sustained increase of Th1 cytokines (IFN-γ and IL-2), to levels comparable with those in healthy controls [154]. A reduction of IL-10$^+$ T cells was observed in those patients with high baseline values. However, this effect was only observed in the first 4 weeks. No effect was seen on IL-4 production. In a Berlin cohort, an increase in the percentage of CD3$^+$ TNF-α or IFN-γ producers increased significantly at week 2 [155]. Together, these data support the view that TNF-α blockade essentially reverses the state of anergy of Th1 cells. However, this seems to be different when the patients are being followed up for longer periods. After 6–12 weeks, the TNF-α secretion capacity goes down again – with some correlation to the disease activity [156]. The specific immune response to the putative autoantigen G1 of the proteoglycan aggrecan is suppressed [157].

In the Ghent patient cohort [158], synovial biopsies were obtained from eight patients with active knee synovitis at baseline (three with AS, one with undifferentiated SpA and four with PsA). Follow-up biopsies were obtained at weeks 2 and 12. In all eight patients, there was a clear clinical improvement after anti-TNF-α therapy. Histological analysis showed that the thickness of the synovial layer tended to decrease, with a significant reduction of CD55$^+$ synoviocytes at week 12. Vascularity in the sublining layer was reduced, with decreased endothelial expression of VCAM-1 (vascular cell adhesion molecule 1). The numbers of neutrophils and of CD68$^+$ and CD163$^+$ macrophages decreased, although with no significant changes in the overall degree of inflammatory infiltration, since the numbers of CD20$^+$ lymphocytes and plasma cells increased. There is no explanation for the latter finding to date. Taken together, there are several indications that the positive clinical effects of anti-TNF therapy can also be reproduced by different immunological techniques.

The definition of new outcome parameters for ankylosing spondylitis studies

A major step forward in the investigation of effective drugs for the treatment of AS was the definition of outcome parameters for such studies by the Assessments in Ankylosing Spondylitis (ASAS) Working Group [159]. Furthermore, the group's definition of the 20% response criteria and criteria for partial remission in AS are based on the four domains of pain, disease activity, function and patient's global assessment [160]. In our recent study, we have extended the response criteria by setting it at 50%, by analogy to the response level used for RA [104]. This seems to be a relevant and clinically highly meaningful approach to document efficacy for expensive treatment strategies.

Clearly, the different clinical features of AS and for the whole group of SpA need to be differentially assessed. An overview is given in Table 1.

Table 2

Possible criteria for the definition of refractory ankylosing spondylitis

Diagnosis of AS according to 1984 modified New York criteria
Persistent disease activity for at least 4 months (BASDAI?)
Stage of disease (degree of ankylosis)
Insufficient conventional therapy (definition needed)
Failure of at least three NSAIDs (including phenylbutazone?) at maximal dose to constantly suppress disease activity
Failure of NSAIDs treatment is not necessary if NSAIDs are not tolerated or renal insufficiency is present
Failure of DMARD therapy (3 g sulfasalazine daily for 4 months)
Failure of intra-articular corticosteroid therapy (at least 2 injections?)
Failure of low-dose prednisolone (<10 mg daily for 1 week?)

AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; DMARD, disease-modifying antirheumatic drug; NSAID, nonsteroidal anti-inflammatory drug.

Another important cut-off that needs to be set is the definition of 'refractory' or 'persistently active' AS. Possible criteria are listed in Table 2.

There is also a need for a better definition and classification of the status of AS patients. Because AS starts early and lasts long, and because the course and outcome of the disease differ greatly from patient to patient, the stage of the disease should be more clearly defined. There is a proposal for that in progress, which includes not only major clinical symptoms such as peripheral arthritis, enthesitis, uveitis, psoriasis and colitis, but also the degree of radiographic damage.

Recent studies [161] have shown that radiographic progression in AS is slow – at least, if the patients examined are not preselected for severe disease activity. Indeed, it seems that no less than 2 years is needed to be able to detect differences using the BASRI [162] or the SASSS (Stoke Ankylosing Spondylitis Spine Score) [163] with a reasonable number of patients. However, there is increasing evidence that acute sacroiliitis, spondylitis and spondylodiscitis can be visualized by MRI using either contrast or STIR (short tau inversion recovery) techniques [78]. In contrast to conventional imaging by x-rays, in which mainly the result of inflammation, bony changes and ankylosis but also erosions can be seen, acute spinal inflammation can be visualized by MRI. In Berlin, an improvement in detection of spinal inflammation MRI has already been shown in our open study [95]. Similar results were obtained in Leeds [107]. The MRIs of the multicenter study [104] are just being evaluated. Preliminary results suggest that regression of spinal inflammation occurs after 3 months in patients treated with infliximab (about 40% improvement) but also with placebo.

Table 3

Anti-TNF therapy in ankylosing spondylitis – open questions

Long-term efficacy?
Arrest of progression of ankylosis?
Differing responses in different targets?
Dosage?
Intervals?
Continous or intermittent therapy?
Individualization of treatment?
Long-term safety?
Repeated screening for autoantibodies?
Adding of DMARDs to suppress antibody formation?
Duration of tuberculosis prophylaxis?

Thus, the availability of tools (both clinical and imaging) for the conduction of studies and the finding that active AS can be effectively treated, as shown for infliximab, will hopefully trigger research to find more effective treatments for AS.

There is really something going on in the field of spondyloarthritides. Anti-TNF therapy seems to be a powerful tool for the treatment of AS and other SpAs. As discussed above, however, there are open questions that need to be answered in the coming years (see Table 3). The important basic role for NSAIDs and physical therapy remains unchanged.

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