Biological therapies in the spondyloarthritides—the current state

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Therapeutic options for patients suffering from the more severe spondyloarthritides (SpA) have been rather limited in the last decades. Evidence is now accumulating that anti-tumour necrosis factor (TNF) therapy is highly effective in SpA, especially in ankylosing spondylitis (AS) and psoriatic arthritis (PsA). Based on the data recently published concerning more than 1000 patients with AS and PsA, this treatment seems to be even more effective than in rheumatoid arthritis (RA). The anti-TNFα agents currently available, infliximab (Remicade), etanercept (Enbrel) and adalimumab (Humira), are approved for the treatment of RA in the USA and Europe. The situation for SpA is different from RA because there is an unmet medical need, especially in AS, since no therapies with disease-modifying anti-rheumatic drugs (DMARDs) are available for severely affected patients, especially those with spinal disease. Thus, TNF blockers may even be considered a first-line treatment in a patient with active AS and PsA whose condition is not sufficiently controlled with non-steroidal anti-inflammatory drugs (NSAIDs) in the case of axial disease, and sulphasalazine or methotrexate in the case of peripheral arthritis. For infliximab, a dose of 5 mg/kg is required, and intervals of between 6 and 12 weeks are necessary to constantly suppress disease activity—also a major aim for long-term treatment. The standard dosage of etanercept is $2 \times 25$ mg subcutaneously per week. There are almost no studies yet on adalimumab (standard dose in RA, $20–40$ mg subcutaneously every 1–2 weeks) in SpA. Infliximab and etanercept are now both approved for AS in Europe. The efficacy of etanercept was first demonstrated in PsA, and it is now approved for this indication in the USA and Europe. There is preliminary evidence that both agents also work in other SpA, such as undifferentiated SpA (uSpA). Studies should be performed to document the long-term efficacy of this treatment. There is hope that ankylosis may be preventable, but it remains to be shown whether patients benefit from long-term anti-TNF therapy and whether radiological progression and ankylosis can be stopped. Severe adverse events have remained rare. Complicated infections including tuberculosis have been reported. These can largely be prevented by appropriate screening. As it stands now, the benefits of anti-TNF therapy in AS seem to outweigh these shortcomings.

KEY WORDS: Ankylosing spondylitis, Anti-TNFα therapy, Conventional and innovative treatment, Psoriatic arthritis.

The spondyloarthritides (SpA) comprise five subtypes: ankylosing spondylitis (AS), reactive arthritis (ReA), major parts of the arthritis/spondylitis spectrum associated with psoriasis (PsO) and inflammatory bowel disease (IBD) and undifferentiated SpA (uSpA). AS is the most frequent subtype of SpA, being more prevalent than undifferentiated SpA, but psoriatic arthritis (PsA), based on the high prevalence of psoriasis, is also quite frequent, while ReA and IBD are relatively rare. The prevalence of the whole group of SpA has been recently estimated as between 0.6 and 1.9% [1–4]. AS and PsA are the SpA subsets with the most severe course of disease.

Therapeutic options for patients suffering from the more severe forms of SpA have been limited during the last decades. In contrast to RA in particular no disease-controlling anti-rheumatic therapy (DCART) has been available. Symptom-modifying anti-rheumatic drugs (SMARD) such as non-steroidal anti-inflammatory agents (NSAIDs) are widely used to ameliorate spinal pain [5, 6]. Furthermore, there is a clear role for intensive physiotherapy, as recently shown [7]. Therefore there is a clear need for more effective therapies in SpA [8]. This review concentrates on modern biological drug therapy of SpA.

Tumour necrosis factor-α blocking agents

Today there are three main biological agents targeting tumour necrosis factor-α (TNFα): the chimeric monoclonal IgG1 antibody infliximab, the recombinant 75 kDa TNF receptor IgG1 fusion protein etanercept and the fully humanized monoclonal antibody adalimumab. All three anti-TNF agents clearly work in rheumatoid arthritis (RA). Infliximab is approved in RA in combination with methotrexate (MTX) because fewer human anti-chimeric antibodies (HACA) and somewhat fewer adverse events occur with this regimen in RA [9], while etanercept is approved as monotherapy. However, in RA all agents work better when MTX is added.
The role of TNF\(\alpha\) in ankylosing spondylitis

The sacroiliac joint (SIJ) and the entheses are the most characteristic and almost pathognomonic sites involved in SpA [10, 11]. Inflammation at the interphase of cartilage and bone has been convincingly demonstrated by MRI [11–13] and by immunohistological investigations of SIJ biopsies [14–16]. In early cases of AS, dense mononuclear infiltrates invading the cartilage have been described and TNF\(\alpha\) mRNA has been detected in inflamed SIJ [14]. Thus, although RA is pathogenetically clearly different from AS, there is evidence for a pathogenetic role for TNF\(\alpha\) in both diseases. Furthermore, AS and the whole group of the SpA are associated with IBD, since such patients may develop AS and many patients with primary AS show histological gut lesions similar to Crohn’s disease (CD) [17] and TNF\(\alpha\) is expressed in the gut of patients with IBD [18].

As discussed below, anti-TNF therapy is also effective in other SpA such as psoriasis and psoriatic arthritis (PsA) [19–26].

Effect of anti-TNF therapy in the spondyloarthritides

Infliximab. In the first open pilot study on anti-TNF therapy in AS that was performed in Berlin, infliximab in a dosage of 5 mg/kg improved the disease activity of severe AS patients with a mean disease duration of 5 yr [27]. Nine out of ten patients showed an improvement of >50% in disease activity as measured by the Bath ankylosing spondylitis Disease Activity Index (BASDAI; [28]). The next infusion of infliximab was not given before a relapse occurred. A relapse was defined as 80% of the initial activity [29]. Since the first symptoms returned after a mean of 6 weeks and a relapse occurred after a mean of 12 weeks, it was decided to go for 6-week-intervals in the following randomized controlled trial [30].

Several open label studies on infliximab in AS have all revealed similar results [31–39]. In a Belgian study, 21 SpA patients including 11 with AS were treated with infliximab with a similar dose regimen but the patients had a longer disease duration (15 yr) and the time intervals between the infusions were longer, namely 14 weeks. The spinal and peripheral symptoms of all SpA patients improved significantly [31]. In the 1-yr follow-up [32], symptoms recurred in 16% at week 20, in 68% at week 34 and in 79% at week 48 before re-treatment. This was probably due to the long infusion intervals.

In Canada there were two studies, one with 24 [33] and one with 21 AS patients [34], in France there were 50 AS [35] and in Spain 42 SpA patients [36]. In the Canadian [33] and Spanish [36] studies there was a tendency that patients with long disease duration and advanced radiographic disease/ankylosis had less benefit from therapy. In the second Canadian study [34], a relatively small dose of 3 mg/kg every 8 weeks was sufficient to cause improvement. In the French study [35], the treatment effect was around 90%, probably because only patients positive for C-reactive protein (CRP) were included.

There are some longer-term data on infliximab over 1 yr [37, 38]. In a Greek study [38], 25 mainly male mostly HLA B27+ AS patients with a mean disease duration of 14 yr and active axial disease, adequate treatment were treated with infliximab 5 mg/kg given every 8 weeks for 1 yr. The unusual primary endpoint: "reduction of the patient’s global assessment of pain by >20% on a 100 mm visual analogue scale (VAS)" was reached in 23 (92%) patients. Improvement by 50% was obtained in 21 (84%) patients, and by 70% in 13 (52%).

After 6 months of infliximab therapy, the bone mineral density (BMD), as measured by dual energy x-ray absorptiometry (DXA), was found to be significantly increased in 31 patients with a mean age of 40 yr and a mean disease duration of 18 yr by about 3% at the lumbar spine and by about 2% at the femoral neck [39].

There is formal proof (evidence class I) for the efficacy of infliximab in AS in a dosage of 5 mg/kg every 6 weeks because of two randomized double-blind controlled trials [30 and van der Heijde et al., submitted]. In the first multicentre study, 70 AS patients with a BASDAI >4 and spinal pain on a VAS >4 were included [30]. The primary outcome parameter, a 50% improvement of BASDAI, was achieved in 53% of the patients treated with infliximab compared with 8% on placebo. Other parameters such as the Bath Ankylosing Spondylitis Functional Index (BASFI), the Bath Ankylosing Spondylitis Metrology Index (BASMI) and SF-36 showed a similar clear-cut improvement. There was some evidence that patients with elevated CRP levels had a greater benefit than those with low or normal levels [30]. In a similar study design, 40 patients with active SpA and more peripheral arthritis were treated with infliximab 5 mg/kg every 8 weeks [40], the same results were obtained. Taken together, both peripheral and spinal manifestations of AS clearly improve on anti-TNF therapy. This includes severe enthesitis as recently reported [41], as assessed both clinically and by a power Doppler technique [42]. Recent results from imaging follow-up studies with spinal MRI assessing both acute and chronic spinal changes have suggested a significant effect of infliximab on disease progression also on this basis [43].

After the 3-month placebo phase, the 70 patients from the German randomized controlled trial (RCT) are now being treated with infliximab at the same dose for another 4 yr. After 54 weeks, 78% of the patients were still being treated with infliximab [37], and after 2 yr this was still 70% (submitted). The intent-to-treat primary efficacy analysis at week 54 showed that almost 50% of the patients still achieved 50% improvement in BASDAI score. In the completer analysis, the mean BASDAI scores showed continuous improvement over 54 weeks down to a low disease activity level of 2.5. The dosage of NSAIDs was reduced in approximately 70% of the patients. There was no indication for a loss of efficacy to date. This on-going study will provide more information about the long-term efficacy and safety of infliximab in AS [44].

Only limited data are available regarding the optimal dosage of infliximab in SpA. In a small study we found a dose of 5 mg/kg superior to 3 mg/kg in patients with uSpA [45]. However, the lower dosage of infliximab seems to work as well. Selected patients might not need doses of infliximab higher than 3 mg/kg but most patients will need 5 mg/kg. Due to the pre-defined availability of infliximab only in 100 mg vials, most rheumatologists nowadays are using individual dosing regimens by adjusting the final dose to the body weight and the costs.

Etanercept. Treatment of AS with the soluble TNF\(\alpha\) receptor etanercept has also been studied extensively. After an initial open study from Leeds [46] three double-blind studies [47–49] have now been published which prove the efficacy of the compound in AS. In the first study [47] 40 patients were allocated to either etanercept 2 x 25 mg subcutaneously (s.c.) or placebo. In this study, as a major difference from our studies, DMARDs (taken by 40%) and steroids (taken by 25% of the patients) were allowed to be continued during the study; different outcome parameters were used. After 6 months, the main outcome parameters such as morning stiffness and nocturnal spinal pain improved significantly on etanercept but not on placebo. In the multicentre trial performed in Berlin [48], 30 AS patients with active disease (BASDAI > 4) were randomized for the initial placebo-controlled period of 6 weeks’ duration which was followed by an observational phase lasting 24 weeks. NSAID treatment could be continued but DMARDs and steroids were withdrawn. Treatment with etanercept was significantly better than placebo with an at least 50% regression of disease activity in 57% of these patients at week 6, versus only 6% in the placebo group. Disease relapses occurred a mean of 6.2 ± 3 weeks...
after cessation of etanercept. No severe adverse events, including major infections, were observed during the trial.

In the very recently published international trial [49], 277 patients were treated with either etanercept 25 mg (n = 138) or placebo (n = 139) s.c. twice weekly for 24 weeks. The primary outcome measure, the Assessments in Ankylosing Spondylitis 20% response (ASAS20) was achieved by 59% of patients in the etanercept group vs 28% of the patients in the placebo group at week 12, and by 57 vs 22% of patients, respectively, at week 24. Taken together, there is class I evidence that etanercept works in AS.

From Leeds two patients with SpA and associated CD receiving treatment with etanercept were reported whose arthritis had shown an excellent response with complete resolution of spinal pathology, whereas in parallel their CD had persisted or flared [50]. These findings suggest that the effect of TNFα blockade with etanercept in SpA differs between the joint and the bowel which is in contrast to a pathogenetic concept in which the bowel plays a major role in the SpA [17]. The efficacy of TNF blockade on the gut seems to be different from infliximab which is not infrequently used in severe CD.

The group from Leeds has also reported in a small study with 20 SpA patients that etanercept had a positive influence on the BMD of patients treated with this therapy in contrast to a placebo-treated group [51].

**Efficacy of anti-TNFα-blockade in other spondyloarthritides/other manifestations**

**Psoriatic arthritis**

Psoriasis is a chronic relapsing inflammatory skin disease affecting 1–3% of the world’s population. PsA is a chronic inflammatory rheumatic disease which affects peripheral joints and, in about a third of the patients, the spine. Most PsA patients fit into the concept of SpA. PsA affects about 20–30% of patients with psoriasis. Available therapies for psoriasis and PsA are able to suppress disease symptoms but are often poorly tolerated and virtually none are curative. Psoriasis and PsA have a substantial economic impact [24–26].

The important role of T cells and of TNFα in the pathogenesis of psoriasis and PsA—for both the dermatological and the rheumatological aspects of the disease—appears to be well established [24–26]. TNFα is found at high levels in the joint fluid and tissue of patients with PsA. TNF induces the production of other pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor. TNFα mediates multiple biological processes that may cause joint damage [24, 25, 52].

There is strong evidence that both etanercept and infliximab work in psoriasis [19, 20] and PsA [21–23]. The first controlled clinical trial of etanercept in PsA was a RCT of 60 patients with rather long-standing disease who received either placebo or etanercept 25 mg s.c. twice weekly for 12 weeks [21]. Patients achieving partial benefit from DMARD therapy with MTX were allowed to continue with this therapy. Background use of NSAIDs or prednisone 10 mg per day or less was also allowed, while all other DMARDs and topical medicines for psoriasis were discontinued. At the end of 12 weeks, 87% of patients in the etanercept group had achieved the primary end-point for arthritic activity, a Psoriatic Arthritis Response Criteria (PsARC) [53] response, compared with 26% in the placebo group. Improvement of psoriatic skin lesions was also observed: 26% of the etanercept-treated patients showed a 75% improvement in the other primary efficacy end-point, the Psoriasis Area and Severity Index (PASI) [54] at 12 weeks, while none of the placebo patients fulfilled this criterion.

The efficacy and safety of infliximab in DMARD-unresponsive PsA was recently evaluated in a 54-week, open-label compassionate-use study [22] in which 10 patients received intravenous (i.v.) infliximab at 5 mg/kg every 6 weeks. All patients achieved a 20% improvement according to the ACR20 criteria by week 2. Eight patients improved by 70% (ACR70) at week 10; six patients maintained ACR70 after week 54. At week 10 MRI revealed an 83% mean reduction in inflammation from baseline. PASI scores were reduced by 71 and 17% respectively. In a recent study from Italy [23], 16 patients with peripheral active PsA with at least 6 months of MTX therapy at a stable dosage were treated with infliximab administered at 3 mg/kg every 8 weeks while continuing to receive MTX. By week 2, significant improvements were registered in the number of swollen and tender joints, VAS for pain, patient and doctor global disease assessment scores, Health Assessment Questionnaire (HAQ), erythrocyte sedimentation rate (ESR) and CRP. At week 30, the percentages of patients satisfying ACR 20, 50 and 70% response rates were 64, 57 and 57% respectively. PASI improvement was 37% at week 2 and 86% at week 30. As described in case reports, infliximab is also effective in patients with refractory progressive psoriatic arthritis [55, 56] and SAPHO syndrome—a condition frequently associated with palmar and plantar pustulosis [57, 58]. Further investigations of the use of infliximab for PsA are under way: a placebo-controlled study of infliximab treatment of psoriatic arthritis is currently being analysed.

Taken together, both agents seem to work favourably in psoriasis and psoriatic arthritis. Criteria are needed to define the patients who are eligible for such therapy.

**Reactive arthritis**

Data about TNFα blockade in patients with chronic reactive arthritis (ReA) are scarce. Since there is evidence that triggering bacteria such as *Chlamydia, Yersinia* and *Salmonella* may persist there is a possibility that TNFα blockers could induce reactivation of persisting bacteria which may worsen the disease. Our own experience with one patient with chronic *Yersinia*-induced ReA and reports from other investigators on *Chlamydia*-induced ReA [59] suggest that treatment with infliximab may also be beneficial for patients with persistently active disease.

Two patients with acute ReA caused by *Yersinia* were successfully treated with infliximab in Finland [60]. In a patient with prior AS and subsequent ReA the peripheral joint disease responded well to three infliximab infusions; he later needed re-treatment with infliximab to control the spinal symptoms of AS.

Clearly, larger studies are needed to finally answer this question and define the patients requiring such treatment.

A 41-yr-old HIV-positive man with Reiter’s syndrome refractory to NSAID therapy who presented with severe fatigue, pain, muscle wasting, synovitis of the elbows, wrists and knees, a scaly rash in the groin area, burning during urination and severe onycholysis on all digits was treated with infliximab [61]. At baseline, the anaemic patient had a normal white blood cell count and strongly elevated inflammatory parameters. The initial HIV viral load was low (1600 copies/ml) on anti-retroviral therapy which remained unchanged over the 6 months during which the patient took infliximab. After this period, all complaints resolved, ESR and CRP normalized and the HIV titre remained low (<400 copies/ml).

**Undifferentiated spondyloarthritides**

There are many patients which have symptoms suggestive of SpA but do not fulfil the diagnostic criteria for any of the defined SpA subtypes. These patients are classified as uSpA by
use of the European Spondyloarthritis Study Group (ESSG) criteria [62]. According to these criteria, patients with uSpA have either inflammatory back pain (IBP) or asymmetrical peripheral arthritis predominantly of the lower limbs plus one additional manifestation characteristic of SpA, such as enthesitis [2]. One possible cause of IBP is sacroiliitis which may be detected early by MRI [63]. In follow-up studies 10% of these patients developed AS after 2 yr and 50% after 10 yr [64, 65].

The DMARDs sulphasalazine and MTX are often used in patients with uSpA, especially in cases with peripheral arthritis. However, there are almost no data to support this practice [44] and there is no evidence that DMARDs work for spinal inflammation. Preliminary data have suggested that infliximab is efficacious in the treatment of patients with severe active uSpA [31, 45]. Peripheral arthritis, enthesitis and spinal symptoms improved equally in six uSpA patients, better on 5 mg/kg than on 3 mg/kg infliximab [45]. In a similar study, 10 uSpA patients treated with 2 × 25 mg etanercept s.c. twice a week responded similarly well [66]. Taken together, anti-TNF therapy is a promising therapy for patients with severe uSpA.

**Inflammatory bowel diseases**

The gut is believed to play an important role in the pathogenesis of SpA. Anti-TNFα therapy with infliximab is effective for induction and maintenance therapy of CD [67, 68].

This seems less convincing in ulcerative colitis, but further study is needed [69, 70]. Etanercept, the 75 kDa TNF receptor fusion protein, seems not to be effective in CD, at least in the usual dosage [71, 50], while there are no data on adalimumab yet. In a very recent study [72], oncept, a recombinant form of the natural human soluble p55 TNF receptor, has been successfully used in 12 patients with active CD who achieved seven responses and five remissions over the first 6 weeks with sustained improvement for some months and no major side-effects. Oncept has not been used in SpA to date. The gut and joint symptoms of patients with CD treated with infliximab have been reported to improve in a small number of patients [73].

The efficacy of infliximab for CD has also been established in daily clinical practice [74].

**Uveitis**

There is some evidence from controlled trials that sulphasalazine prevents attacks of anterior uveitis (AU) associated with SpA [75, 76].

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 [77, 78]. No clear picture can be resolved: both improvement and worsening of inflammatory eye disease may occur upon anti-TNF treatment. However, most patients seem to benefit from such treatment. In one study [77] 16 patients, most of whom received etanercept for either inflammatory eye disease or associated joint disease, were studied retrospectively. Although all 12 patients with active arthritis experienced improvement in joint disease, only six (38%) improved with their eye disease. Five patients even developed inflammatory eye disease for the first time while taking a TNF inhibitor. In another study there was some improvement of ocular inflammation in patients with chronic uveitis associated with partly antinuclear antibody (ANA)-positive juvenile chronic arthritis upon treatment with etanercept [78]. 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. It needs to be stressed here that the natural course of uveitis in HLA B27-positive versus ANA-positive patients is known to be rather different.

El-Shabrawi and Hermann [79] reported beneficial effects of infliximab in a dosage of 10 mg/kg in seven patients with acute onset of HLA B27-associated AU; they were observed for a mean period of 17 months. Total resolution of AU was achieved with infliximab as the sole anti-inflammatory drug in all but one patient. A relapse was seen in four patients after a median of 5 months. The authors concluded that infliximab appears to be an efficacious therapeutic agent in active HLA B27-associated uveitis and may be a future alternative or supplement to steroid treatment. Recently other cases have been reported [80, 81]. The experience with infliximab in the RCT [30] was also positive since three vs one patient in the placebo vs the infliximab group developed AU over 3 months. However, the natural course of AU in SpA is rather benign in the vast majority of patients [82]. Thus, anti-TNF therapy should only be considered in severe refractory cases. However, controlled studies in homogeneous patient populations and a systematic comparison of local and systemic steroid therapy are needed. Sight-threatening uveitis in patients with Behçet’s disease has been successfully treated with infliximab [83].

Another possible consequence of long-standing AS is amyloidosis [84]. There is an early report on partially successful treatment of 15 rheumatological patients with histologically proven secondary AA amyloidosis and renal involvement who underwent anti-TNF therapy [85]. Amyloidosis progressed in seven patients and was stabilized in five patients, while three patients (receiving infliximab alone, infliximab plus MTX or etanercept plus MTX) experienced rapid, dramatic and sustained decreases in proteinuria and glomerular filtration rates.

Taken together, there is overwhelming evidence for the efficacy of anti-TNF therapy in AS and other SpA for many manifestations of the disease.

**Side-effects of anti-TNF therapy**

If novel very effective therapies are arising the greatest concern is of course about the undesired and potential severe side-effects. There clearly are side-effects to be considered in patients treated with anti-TNF agents [86]. After the first years of anti-TNF therapy the following types of adverse events seem to be of special concern: (1) infections including sepsis and tuberculosis [87–90]; (2) malignancies such as lymphoma [91]; (3) other haematological disorders such as anaemia and pancytopenia; (4) demyelinating disorders/neuropathy [92]; (5) congestive heart failure [93–96]; (6) elevation of liver enzymes; (7) occurrence of autoantibodies and autoimmunity [97–99]; (7) onset of lupus and vasculitis [100] and (8) infusion/injection and hypersensitivity reactions [101].

In a recent report from Spain [89], mainly on RA patients, 71 participating centres sent data on 1578 treatments with infliximab (86%) or etanercept (14%) in 1540 patients. Drug survival rates for infliximab and etanercept pooled together were 85% and 81% at 1 yr and 2 yr respectively. The estimated incidence of tuberculosis (TB) associated with infliximab in RA patients was 1893 per 100,000 in the year 2000 and 1113 per 100,000 in the year 2001. In the first 5 months of 2002, after official guidelines were established for TB prevention in patients treated with biological therapies, only one new TB case was registered.

In a recent report from Belgium [90] 107 patients with SpA were treated with infliximab for a total of 191.5 patient yr. Eight severe infections occurred, including two reactivations of tuberculosis and three retropharyngeal abscesses. No cases of demyelinating disease or lupus-like syndrome were seen. Despite reported clinical efficacy for the condition of SAPHO syndrome [58, 59], three patients with AS developed palmpoplantar pustulosis...
on infliximab therapy. All patients recovered. Infliximab had to be stopped in five patients with severe infections.

Twenty-six cases of lymphoproliferative disorders were identified [91] by the US Food and Drug Administration’s (FDA) MedWatch programme following treatment with etanercept \( (n = 18) \) or infliximab \( (n = 8) \). The majority of cases \( (81\%) \) were non-Hodgkin’s lymphomas. The interval between initiation of therapy with etanercept or infliximab and the development of lymphoma was very short \( (\text{median 8 weeks}) \). In two instances lymphoma regression was observed following discontinuation of anti-TNF treatment, in the absence of specific cytotoxic therapy directed toward the lymphoma. In general, data from a case series cannot establish a clear causal relationship between exposure to these medications and the risk of lymphoproliferative disease. However, the known predisposition of patients with RA and CD to lymphoma, the known excess of lymphoma in other immunosuppressed populations, and the known immunosuppressive effects of the anti-TNF drugs provide a biological basis for further studies on this possible association which, however, is not likely to be very strong.

Nineteen patients with neurological events during anti-TNF therapy were identified [92] by the US FDA MedWatch programme, 17 following etanercept and two following infliximab administration. All neurological events were temporally related to anti-TNF therapy, with partial or complete resolution on discontinuation. One patient exhibited a positive rechallenge phenomenon. Further surveillance and studies are required to better define risk factors for and frequency of adverse events and their relationship to anti-TNF therapies. Until more long-term safety data are available, consideration should be given to avoiding anti-TNF therapy in patients with pre-existing multiple sclerosis and to discontinuing anti-TNF therapy immediately when new neurological signs and symptoms occur.

Two trial programmes testing an anti-cytokine medication in chronic heart failure (CHF) have been halted [93]. In the RENAISSANCE and RECOVER trials (the combined analysis being termed RENEWAL), 2048 CHF patients were randomized to placebo or one of three doses of etanercept. Overall, the outcome was similar for patients on placebo or any dose of etanercept. In RENEWAL the primary end-points of death or hospitalization due to CHF were no different between etanercept and placebo. ATTACH was a phase II, multicentre, randomized, double-blind, placebo-controlled pilot trial [94] that aimed to evaluate the effects of infliximab in 150 CHF patients with stable New York Heart Association (NYHA) class III or IV disease \( (<10\% \text{ in NYHA IV}) \). In the placebo group \( (n = 49) \), none of the patients died during 28 weeks of follow-up. At 14 (28) weeks, the end-point of death or hospitalization was reached in two \( (\text{five}) \) patients on placebo, in two \( (\text{four}) \) patients on the medium dose \( (5 \text{mg/kg}) \) and in eight \( (\text{twelve}) \) patients on the high dose \( (10 \text{mg/kg}) \) of infliximab. During follow-up, compared with placebo the hazard to reach this end-point was similar in the medium-dose group, but increased in the high-dose group. At the respective lower doses there was no safety issue with regards to the use of either infliximab or etanercept. High-dose anti-TNF therapy seems not to be generally useful in patients with CHF but the situation in lower doses and in selected patients with documented inflammatory/metabolic problems or in cardiac cachexia has not yet been adequately assessed [93].

Forty-seven patients were identified by the US FDA MedWatch programme who developed new or worsening heart failure during TNF antagonist therapy [95]. There were 38 patients who developed new-onset heart failure and nine patients experienced exacerbation of heart failure. Of the 38 patients with new-onset heart failure, 19 \( (50\%) \) had no identifiable risk factors. Ten patients younger than 50 yr developed new-onset heart failure after receiving TNF antagonists. After TNF antagonist therapy was discontinued and heart failure therapy was started in these 10 patients, three had complete resolution of heart failure, six improved and one died.

From these reports it cannot be concluded that heart failure is a serious problem on anti-TNF therapy—especially since a larger post-approval report from the USA presented at ACR 2003 did not reveal any heart-related safety issues [96].

Anti-TNF therapy may lead to the formation of ANAs. In patients with RA, anti-double-stranded (ds) DNA antibodies of the IgM class may be induced by infliximab; the frequency is dependent on the assay method used [97]. Only one of the 156 patients treated with infliximab developed a self-limiting clinical lupus syndrome; that patient developed high titres of anti-dsDNA antibodies of IgG, IgM and IgA class, as detected by immunofluorescence and by two different Farr assays.

In another recent study [98], sera from 62 RA and 35 SpA patients treated with infliximab were tested at baseline and week 30 or 34. Initially, 32 of 62 RA patients \( (51.6\%) \) and six of 35 SpA \( (17.1\%) \) patients tested positive for ANAs. After infliximab treatment, these numbers shifted to 51 of 62 \( (82.3\%) \) and 31 of 35 \( (88.6\%) \) respectively. At baseline, none of the RA or SpA patients had anti-dsDNA antibodies. After infliximab treatment, seven RA and six SpA patients became positive for anti-dsDNA antibodies. All seven anti-dsDNA-positive RA patients had IgM and IgA anti-dsDNA antibodies. During the observation period, no IgG anti-dsDNA antibodies or lupus symptoms were observed. The development of antinucleosome, antihistone or anti-extractable nuclear antigen (ENA) antibodies following infliximab treatment was observed in some patients, but the numbers were not statistically significant. Taken together, development of ANA is a rather frequent event in patients on infliximab therapy, while anti-DNA antibodies occur infrequently and only rarely with lupus symptoms.

In a recent report from the UK [99] eight RA patients developed vasculitis. This is in contrast to reports suggesting that anti-TNF therapy may be useful for the treatment of vasculitis [101]. Thus, anti-TNF therapy seems to be able to both heal and cause inflammatory conditions. The reason for this is not clear.

In a large study with a total of 165 consecutive patients who received 479 infliximab infusions [100], the overall incidence of infusion reactions to infliximab was 6.1\% \( (29 \text{ of } 479) \) of infusions, affecting 9.7\% \( (16 \text{ of } 165) \) of patients. Mild, moderate or severe acute reactions occurred in 3.1\% \( (15 \text{ of } 479) \), 1.2\% \( (6 \text{ of } 479) \) and 1.0\% \( (5 \text{ of } 479) \) of infliximab infusions respectively. Use of treatment protocols resulted in rapid resolution of all acute reactions to infliximab. With the prophylaxis protocol, all patients who experienced an initial mild or moderate acute reaction were able to receive additional infusions. Four patients experienced a total of five severe acute reactions. Three patients were re-treated: two patients had no further problems, whereas one patient had a second severe acute reaction that rapidly resolved with treatment. In 11 patients who experienced 14 acute infusion reactions, serum tryptase levels were normal, suggesting that acute infusion reactions are not type I hypersensitivity reactions. Delayed infusion reactions were rare, occurring in 0.6\% \( (\text{three of } 479) \) of infusions. In patients treated with etanercept, injection site reactions occur frequently but do not generally cause severe or lasting problems.

**Immunological studies**

While immunohistological studies seem to provide rather clear-cut results, the value of measuring cytokine levels to assess or monitor disease activity remains unclear.

In an immunohistological study with eight RA patients [102] who all met the ACR 20\% \( (\text{ACR20}) \) improvement criteria at 2 weeks, TNFα synthesis was significantly reduced after treatment at two independent sites. Patients meeting the ACR 50\% \( (\text{ACR50}) \) improvement criteria were those with the highest baseline levels of TNFα synthesis. There was a significant
correlation between baseline levels of TNFα expression and change in TNFα levels in response to therapy.

In the Gent patient cohort [103], synovial biopsies were obtained from eight patients with active knee synovitis at baseline (three AS, one uSpA and four PsA). Follow-up biopsies were obtained at weeks 2 and 12 in the patients who all had clear clinical improvement after anti-TNFα therapy. Histological analysis showed that the thickness of the synovial layer tended to decrease, with a significant reduction of CD5+ + synovocytes at week 12. Vascularity in the sublining layer was reduced with decreased endothelial expression of vascular cell adhesion molecule 1 (VCAM-1). The number of neutrophils and CD68+ and CD163+ macrophages decreased, although with no significant changes in the overall degree of inflammatory infiltration since the number of CD20+ lymphocytes and plasma cells increased. The reasons for this are not entirely clear. Taken together, there are several indications that the positive clinical effects of anti-TNF therapy can also be reproduced by different immunological techniques.

Different technologies have been used for the examination of cytokines in the serum. While serum levels are usually measured by enzyme-linked immunosorbent assay (ELISA) techniques, there is also the possibility of analysing the capacity of peripheral blood (PB) or synovial fluid (SF) mononuclear cells (MNC) to secrete cytokines. The advantage of this technique, flow cytometry, is the possibility of determining the proportion of specific cells which secrete cytokines.

In an early study on cytokine serum levels in RA patients [104], TNFα levels were reported to be generally low and only half of the patients had detectable circulating TNFα at baseline. The changes that occurred following infusion of infliximab were remarkable, with a rapid and dose-dependent increase in immunoreactive, but not biologically active, TNFα, evident as early as 8–24 h and peaking by day 7. Preliminary evidence suggests that the TNFα is present in the form of a high molecular weight complex, presumably with infliximab. Similar increases in circulating immunoreactive IL-6 were noted following treatment with anti-IL-6 in other studies. Therefore, the rapid, but transiently delayed (not present at 4 h) rise in immunoreactive TNFα in patients may represent trapping of the TNFα over-produced in the disease. The highly significant falls in serum IL-6 seen at day 1 were maintained for the duration of the study; this was also found in AS patients [27].

Recently, the effect of infliximab on circulating cytokines and acute phase proteins was analysed in 36 patients with fistulizing CD of whom 22 (61%) responded to treatment [105]. Serum from patients was drawn before the infusion at baseline and every other week thereafter until week 10. Elevated TNFα, IL-1β and IL-6 were reported but no changes in circulating levels of TNFα were observed during the course of the study. Before receiving infliximab, higher levels of serum TNFα were found in patients who did not respond to infliximab compared with those who did. The significance of this finding is not clear.

In a recent study from Canada [106], serum cytokine levels of IL-1, TNFα, IFNγ, TGFβ and IL-10 were examined after 52 weeks of infliximab treatment 5 mg/kg in 22 AS patients, of whom 18 patients were responders and four non-responders according to ASAS 20 criteria. Baseline CRP and TNFα levels were higher in responders than non-responders; the other baseline cytokine levels were similar. Apart from an early rise in TGFβ and a decrease in IL-10 in responders after the first infusion, sequential cytokine analysis for the first 6 months of treatment was not related to clinical disease activity measures, suggesting that sequential cytokine analysis does not appear to be informative.

Keller et al. [107] who performed cytokine serum level determinations in 25 patients on etanercept (n = 13) or placebo (n = 12) therapy came to a similar conclusion. These authors did not find elevated serum levels in their AS patients who, however, were in part on DMARD and steroid therapy [47], as compared with healthy controls.

Nevertheless, using other techniques there is some evidence of a rather suppressed Th1 response in the SpA [108–111]. In accordance with these observations, an increased prevalence of atopic disease was found in AS patients compared with rheumatoid arthritis patients in a recent survey performed in Berlin [112].

The effect of infliximab therapy on the CD3 cytokine profile was analysed in two pilot studies by using flow cytometry technology. The study in the Gent cohort documented that treatment with three infusions of infliximab in SpA patients resulted in a rapid and sustained increase of Th1 cytokines (IFN-γ and IL-2) to levels comparable with those in healthy controls [113]. A reduction of IL-10+ T cells was observed in those patients with high baseline values. However, this effect was mainly observed in the first 4 weeks. No effect was seen on IL-4 production. In the Berlin cohort, an increase in the percentage of CD3+ TNFα or IFN-γ producers was observed at week 2 in early experiments [114]. Together, these data supported the view that TNFα blockade essentially reverses the state of anergy of Th1 cells.

However, this seems to be different when patients are being followed up for longer periods of time. After 6 and 12 weeks the TNFα secretion capacity goes down again—with some correlation to the disease activity [115, 116]. Furthermore, the antigen-specific immune response to the putative autoantigen G1 of the proteoglycan aggrecan [117–119] is suppressed [115]. In this study the cytokine secretion capacity of PB CD4+ and CD8+ T cells was investigated before and 6 and 12 weeks after the start of treatment in 10 patients [115] treated with infliximab, and before and after 6 weeks of treatment and 6 weeks after placebo was switched to infliximab [30] in 10 patients treated initially with placebo [37]. Compared with baseline, infliximab treatment induced a significant decrease at 12 weeks in the number of CD4+ and CD8+ T cells positive for IFN-γ and TNFα upon non-specific stimulation. No change in the percentage of IFN-γ+ or TNFα+ cells among CD4+ and CD8+ subpopulations was observed after 6 weeks in patients treated with placebo. However, when these patients began infliximab treatment after 6 weeks of receiving placebo, there was a similar significant decrease in IFN-γ and TNFα production by CD4+ and CD8+ T cells. Furthermore, infliximab treatment induced a significant reduction in the number of IFN-γ+ and TNFα+ CD8+ T cells after antigen-specific in vitro stimulation with G1-derived peptides. Between-group analysis showed that the change in the expression of IFN-γ and TNFα in both CD4+ and CD8+ T cells was significantly different between the infliximab and placebo groups. There was no change in the number of IL-10+ or IL-4+ T cells during treatment. No significant change in the production of TNFα and IL-10 upon in vitro stimulation of peripheral blood mononuclear cells (PBMC) with lipopolysaccharide (LPS) was detectable during infliximab treatment. Thus, in this study infliximab down-regulated both, IFN-γ and TNFα secreted by T cells but did not induce a change in cytokines produced by monocytes during 3 months of treatment. This may be a relevant mechanism for the clinical efficacy of this therapy.

In a similar study PBMC from 10 patients with AS treated with etanercept and 10 patients with AS treated with placebo [48] were investigated by flow cytometry [116]. Twelve weeks of etanercept treatment induced a significant increase in the number of non-specifically stimulated IFN-γ+ and TNFα+ CD4+ and IFN-γ+ and TNFα+ CD8+ T cells, but not in the placebo group. Furthermore, etanercept treatment induced a significant increase in the number of IFNγ + CD8+ T cells after in vitro stimulation with aggrecan derived peptides. Neutralization of peripheral TNFα did not induce a down-regulation of the ability of T cells to produce TNFα but rather an up-regulation, possibly due to a
counter-regulatory mechanism. These results might be explained by a different mode of action of infliximab and etanercept: while infliximab neutralizes soluble TNFα and binds to cell-bound TNFα, with the possible consequence of deletion of TNFα+ cells, etanercept seems to neutralize only soluble TNFα without affecting the capacity of T cells to produce TNFα and IFN-γ upon stimulation.

The value of measuring serum levels of infliximab and determining anti-infliximab antibodies is becoming clearer. MTX may reduce the clearance of infliximab from serum [120]. In a recent analysis [121] of data from the ATTRACT trial, 26% of the subjects receiving 3 mg/kg infliximab every 8 weeks had undetectable trough serum levels of infliximab at week 54. Increased ACR-N responses and more reduction of CRP levels were both associated with higher serum concentrations of infliximab, supportive of a dose–response relationship. As predicted by pharmacokinetic models, decreasing the dosing interval from 8 to 6 weeks should yield higher trough serum levels of infliximab than increasing the dose by 100 mg.

Antibodies against infliximab seem to depend on the dosage of infliximab [122]. In an early study it was mainly the group receiving 1 mg/kg of infliximab alone in which anti-chimeric antibodies were observed in approximately 50% of the patients [9].

MTX has not been not additionally given in AS studies because, as discussed above, its efficacy in AS is doubtful. The addition of MTX to infliximab to reduce the frequency of infusion reactions is, on the basis of number needed to treat (NNT) calculations, also not convincing.

In a recent study in CD patients, some of whom were treated with azathioprine in addition to infliximab, it was reported that not only did fewer infusion reactions occur but also the overall duration of the efficacy of infliximab doubled if the immunosuppressant, mostly azathioprine, was co-administered [123]. However, many patients received only one infusion of infliximab, which is more likely to induce antibodies [9]. Both mercaptopurine and its prodrug azathioprine are metabolized to active guanine phosphoribosyltransferase and to inactive metabolites which is more likely to induce antibodies [9]. Both mercaptopurine and azathioprine in addition to infliximab, it was reported that

However, many patients received only one infusion of infliximab, which is more likely to induce antibodies [9]. Both mercaptopurine and azathioprine are metabolized to active guanine phosphoribosyltransferase and to inactive metabolites which is more likely to induce antibodies [9]. Both mercaptopurine and azathioprine are metabolized to active guanine phosphoribosyltransferase and to inactive metabolites which is more likely to induce antibodies [9]. Both mercaptopurine and azathioprine are metabolized to inactive metabolites.

Infliximab bound to activated PBL and lamina propria T cells, whereas binding of etanercept was equal to that of a non-specific control antibody. Infliximab but not etanercept induced peripheral and lamina propria lymphocyte apoptosis when compared with a control antibody. Infliximab activated caspase 3 in a time-dependent manner, whereas etanercept did not. Although both infliximab and etanercept showed powerful TNFα neutralization, only infliximab was able to bind to PBL and lamina propria T cells and subsequently to induce apoptosis of activated lymphocytes. These data, together with the studies discussed above [115, 116], may provide a biological basis for the difference in efficacy of the two TNFα neutralizing drugs.

Pharmacogenomics

The relatively recent development of genetically engineered agents has the potential to alter the treatment of inflammatory diseases radically, and drugs that inhibit TNFα have been introduced as a new therapeutic class with high efficacy, rapid onset of action, prolonged effect and improved tolerance. However, these agents are expensive, and at least one-third of the eligible patients fail to show any useful response. Finding a means to predict those who will respond, and to anticipate relapse, is therefore, of obvious importance. TNFα exerts its effects through its own family of receptors (TNFR1 and TNFR2), the end results of which include apoptosis, c-Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK) activation and NF-κB activation. Activated NF-κB enters the nucleus and induces transcription of genes associated with inflammation, host defence and cell survival. The promoter region of the TNF gene lies between nucleotides −1 and −1300, and encompasses numerous polymorphic sites associated with potential binding sites for various transcription factors. Carriers of the TNF allele 2 (TNF2), which contains a single base-pair polymorphism at the −308 promoter position, produce slightly more TNFα in their intestinal mucosa than non-TNF2 carriers [126]. TNF polymorphisms may influence the nature and frequency of manifestations of SpA and IBD. After an early negative study [127] two further cohorts from clinical trials of infliximab in CD have been studied [128]. No TNF polymorphisms [TNFα promoter −238, −308, −376, −857, −1031, TNF-R-I −609, +36 (exon 1), TNF-R-II 1663, 1690 (3′-UTR)] were not associated with treatment response in either cohort. None of the polymorphisms was associated with refractory CD itself when compared with healthy controls.

The association of CARD15 (NOD2) with CD [129] but not with AS [130] is well established. No association of this gene has been identified in two independent large trials on infliximab therapy in patients with CD [131, 132]. There is a need for more pharmacogenetic studies to possibly predict response in patients who are candidates for biological therapy.
Prediction of response to anti-TNF therapy

From the first RCT with infliximab it seemed clear that CRP may be predictive of response [30]. This was substantiated in the follow-up paper [37]. Subsequently, 100 AS patients treated in two studies either with infliximab or etanercept were analysed in more detail with regard to prediction of response. A univariate analysis revealed shorter disease duration, lower BASFI (which means better function), younger age and elevated ESR or CRP as predictors of a good treatment response. Adjustment for disease duration revealed BASFI, ESR and CRP but not age to remain significantly associated [133]. The best multivariate model built by stepwise regression contained the co-variables disease duration, BASFI, BASDAI and CRP. Preliminary data from Berlin suggest that in the case of CRP being negative MRI-positivity might also turn out to be a predictor of response [134]. Thus, patients with shorter disease duration, as suggested by this parameter itself plus younger age and/or better function, and high disease activity, as indicated for example by elevated CRP or an elevated BASDAI, seem to be the best candidates for such treatment response. However, although some patients respond better than others, this is not a yes or no problem. About 70% of the CRP+ patients showed 50% improvement of BASDAI but also 30% of the low-CRP or CRP-negative patients had major responses.

Among the first 240 patients in the Belgian infliximab in CD programme [135] there were 74% responders and 27% non-responders to treatment with one to three infusions of infliximab after 4–10 weeks. Stepwise logistic regression identified age, isolated ileitis and previous surgery as inversely correlated with response, whereas isolated colitis and concomitant immunosuppressive treatment were positively correlated with response to infliximab.

The definition of patient selection and improvement criteria for AS

The questions of which patients to treat and which improvement criteria to use have been recently answered in part by international consensus conferences organized by the Assessments in AS (ASAS) Study Group [136, 137].

Because of the recent advances in the therapy of AS with biological and other agents [138–140] there is an increasing need for the definition of standards and outcome parameters for AS trials. A major effort has been initiated recently by the FDA, guided by the ASAS and organized by the Spondylitis Association of America (SAA) in Bethesda [van der Heijde et al., submitted]. A clear process for investigating the efficacy of drugs for the treatment of AS was the definition of outcome parameters for such studies by the ASAS Working Group [141] and the evaluation of 20% response criteria (‘ASAS 20’) and criteria for partial remission in AS based on the four domains of pain, disease activity, function and patient’s global assessment [142] which was recently confirmed to be optimal by a group of experts [143]. In the early anti-TNF studies a higher cut-off was used on the basis of the larger effect size of anti-TNF therapy: 50% improvement of BASDAI, in analogy to the ACR response criteria in RA [30]. This appeared to be a relevant and clinically meaningful approach to document efficacy in the trials performed so far. However, a more systematic analysis has shown that it is not the best differentiating factor. A comparison of different sets of improvement criteria for anti-TNF treatment in AS on the basis of patient data from two randomized controlled trials [30, 48] which included 99 patients (48 receiving TNFα blocking agents and 51 placebo) was recently performed [136] by testing candidate improvement criteria. There were two similarly well-performing sets of improvement criteria: (1) ≥20% improvement in five out of six domains which showed a very low percentage of responders in the placebo group (2.9%) and a high percentage in the infliximab group (67.7%) and (2) the ‘ASAS 40’ improvement criteria proposed on the same basis as ASAS 20 [136]. The BASDAI 50% improvement criteria performed less well. The improvement criteria based on a ≥20% change in five out of six domains which include the more objective domains of spinal mobility and acute phase reactants performed best. However, 20% improvement of spinal mobility and CRP or ESR might be difficult to assess. A simpler solution would be the ASAS 40% which also performed very well. No final choice between these two sets of improvement criteria inside the ASAS has been made so far. Further validation will be achieved by analysing data from the forthcoming trials with biological therapies in AS.

An international consensus on the use of anti-TNFα for treating patients with AS was obtained in Berlin in January 2003 during a meeting of the ASAS [137]. These recommendations were developed on the basis of this meeting prepared by a review of published reports in combination with expert opinion and a Delphi exercise. The final consensus comprises the following requirements:

(i) For the initiation of anti-TNF alpha therapy: (a) a diagnosis of definitive AS; (b) presence of active disease for at least 4 weeks as defined by both a sustained BASDAI of at least 4 and an expert opinion based on clinical features, acute phase reactants and imaging modalities; (c) the presence of refractory disease defined by failure of at least two non-steroidal anti-inflammatory drugs during a single 3-month period, failure of intra-articular steroids if indicated, and failure of sulphasalazine in patients with peripheral arthritis; (d) application and implementation of the usual precautions and contraindications for biological therapy.

(ii) For the monitoring of anti-TNFα therapy both the BASDAI and the ASAS core set for clinical practice should be followed regularly.

(iii) Consideration should be made after 6–12 weeks’ treatment for the discontinuation of anti-TNFα therapy: in non-responders. Response is defined as improvement of (a) at least 50% of two units (on a 0–10 scale) of the BASDAI and (b) expert opinion that treatment should be continued.

This consensus statement on anti-TNFα treatment in AS may be used for guidance in clinical decision-making and as the basis for the development of guidelines. Evaluation of the healthcare consequences of this consensus is subject to further research by the ASAS group.

There is also need for a better definition and classification of the status of AS patients. Since AS starts early and lasts for a long time and since the course and outcome of the disease differ a lot, the stage of the disease should be more clearly defined. There is a proposal for that which includes not only major clinical symptoms such as peripheral arthritis, enthesitis and uveitis, psoriasis and colitis but also the degree of radiographic damage [144] which needs to be further evaluated.

Recent studies [145] have shown that radiographic progression in AS is slow—at least if the patients examined are not pre-selected by severe disease activity. Indeed, it seems that no less than 2 yr are needed to be able to detect differences using the BASRI [146] or the Stoke Ankylosing Spondylitis Spine Score (SASSS) [147] with a reasonable number of patients. However, very recent data from the OASIS trial seem to suggest that the sensitivity to change can be improved to 10% change per yr by using the modified SASSS (148) or knowledge of the sequence of the radiographs (van der Heijde, manuscript in preparation). Furthermore, pre-selection of very active patients may increase this to 25% per yr.

There is increasing evidence that acute sacroiliitis, spondylitis and spondylodiscitis can be visualized by MRI using either...
The authors have declared no conflicts of interest.

The authors have performed and the patient, after a possibly triggering accident, needed. Hopefully it will be possible to prevent severe disease as started in the German Early SpA Cohort Study (GESPIC) is define early prognostic factors [150], such as the work just influence of such therapy on structural changes. Further data to biological therapy of the SpA, however, there are open questions NSAIDs and physical therapy remains unchanged. For research activities to find more effective treatments for AS. The novel MRI scoring system [149] performed well in assess- frequency as determined by STIR was equal in the two groups. 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 activities to find more effective treatments for AS.

Taken together, there is really a lot happening in the treat- ment of SpA. Anti-TNF therapy seems to be a powerful tool for the treatment of AS and other SpA. The important basic role for NSAIDs and physical therapy remains unchanged. For biological therapy of the SpA, however, there are open questions which need to be answered in the next years, such as the influence of such therapy on structural changes. Further data to define early prognostic factors [150], such as the work just started in the German Early SpA Cohort Study (GESPIC) is needed. Hopefully it will be possible to prevent severe disease as in a remarkable first North American case recently described [151] where the patient, after a possibly triggering accident, progressively developed very severe kyphosis with resultant major disability.

The authors have declared no conflicts of interest.

References


93 Anker SD, Coats AJ. How to RECOVER from RENAISSANCE? The significance of the results of RECOVER, RENAISSANCE, RENEWAL and ATTACH. Int J Cardiol 2002;86:123–30.


Anti-TNFα treatment for the spondyloarthritides


