Infliximab: a chimeric anti-TNF-α monoclonal antibody for the treatment of ankylosing spondylitis and other spondyloarthritides

Dominique Baeten
Division of Clinical Immunology & Rheumatology, Academic Medical Center/ University of Amsterdam, F4—18, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands
Tel.: +31 20 566 2171.
Fax: +31 20 691 9658.
d.l.baeten@amc.uva.nl

Infliximab is a chimeric, monclonal antibody against tumour necrosis factor α. Extending previous findings in other chronic inflammatory diseases, recent double-blind, placebo-controlled, randomized trials have provided large and consistent evidence that infliximab treatment induces a major clinical benefit in ankylosing spondylitis. Before the introduction of infliximab, physiotherapy and nonsteroidal anti-inflammatory drugs only partially controlled signs and symptoms of this frequent and invalidating form of arthritis, affecting axial and peripheral joints in young adults. Infliximab rapidly and profoundly improves symptoms, suppresses inflammation, ameliorates global disease activity, and leads to an important gain in function, mobility, and ultimately, quality of life. The treatment has a favorable risk/benefit ratio that is maintained over the long term, but discontinuation leads to rapid clinical relapse.

Ankylosing spondylitis (AS) is one of the major forms of chronic inflammatory arthritis and the prototype disease within the concept of the spondyloarthritides (SpAs), a cluster of inter-related and overlapping chronic inflammatory rheumatic diseases which are etiologically and clinically distinct from other inflammatory arthritides. Inflammation of the axial skeleton is the major hallmark of AS, occurring in more than 90% of these patients, and is typically characterized by inflammatory lower back pain and morning stiffness due to sacroiliitis and/or spondylitis. It is strongly related with the presence of human leukocyte antigen (HLA)-B27 and clearly differentiates AS–SpA from other types of chronic autoimmune arthritis such as rheumatoid arthritis (RA). Radiological changes of the axial skeleton include blurring of the sacroiliacal joints followed by pseudowidening and sclerosis of the joint margins with eventual erosions and ankylosis. Similarly, squaring of the vertebral bodies, with progressive bridging by syndesmophytes and ankylosis of the adjacent apophyseal joints leads to complete fusion and 'bamboo-spine' formation.

Beside axial inflammation, AS frequently depicts peripheral synovitis associated, or not, with enthesitis. Peripheral joint involvement is generally oligoarticular, asymmetric, and predominantly affects the joints of the lower limbs. Less prevalent than axial inflammation in AS, it constitutes the key feature of other types of SpA. Although in some patients, peripheral arthritis can become chronic and erosive, the majority exhibit a nonerosive and self-resolving joint inflammation. Extra-articular manifestations, such as clinical or subclinical gut inflammation, eye involvement with acute anterior uveitis (AAU), and skin lesions, can also be encountered in AS. A definite clinical overlap between these different AS features has been observed within a single patient, as well as within family members. A tendency towards familial aggregation is illustrated by the finding that 16% of patients have a first- or second-degree relative with inflammatory axial pain or peripheral synovitis. A strong genetic predisposition is further indicated by the linkage with HLA-B27 – the prevalence of HLA-B27 is 80–90% in AS, whereas the percentage in the overall population is estimated at 8%.

Other entities beside AS belonging to the SpA concept include reactive arthritis (ReA), psoriatic arthritis (PsA), arthritis associated with inflammatory bowel disease (IBD), undifferentiated spondyloarthropathy (USpA), and idiopathic AAU. These diseases are also encountered in childhood as juvenile SpA. Whereas each subtype of SpA has his own characteristic clinical presentation, they all share the same previously described, clinical, radiological and genetic features.

Unmet needs in the treatment of ankylosing spondylitis

Recent prevalence studies indicate that SpA is much more common than previously thought; however there are important racial and geographical differences. In western Europe, prevalence is estimated at 0.49–1.9% in the general population and up to 13.6% in HLA-B27-posi-

Keywords: ankylosing spondylitis, , infliximab, monoclonal antibody, spondyloarthritis, TNF-α

Future Drugs Ltd

tive individuals [1,2], with a clear male preponderance in the AS subgroup (male:female ratio, 3:1). Disease onset occurs relatively early in life, usually starting in the second or third decade of life, which implies a long burden of disease. The impact of the disease on quality of life (QoL) and functional capacity appears to be as important as for RA [3]. The QoL is clearly reduced compared with the general population, with an important impact, not only of pain (83.1%) and stiffness (90.2%) but also fatigue (62.4%) and sleep problems (54.1%) [4]. In addition, structural radiological damage, already reported to occur during the first 10 years of AS, contributes to functional decline and poor QoL. Work disability is appromiately 16% higher and withdrawal from work 3.1-times higher in AS then expected in the general population [5,6]. Collectively, the high prevalence, early age of onset, increased mortality and important impact on function and QoL indicate that AS is not a benign disease and has major medical and socioeconomical consequences.

Together with regular exercise and physiotherapeutic approaches to maintain mobility and posture, nonsteroidal anti-inflammatory drugs (NSAIDs) remain the first line of treatment for symptomatic relief in patients with axial and peripheral joint involvement. Interestingly, continuous use of a fixed dose of NSAIDs might even have a halting effect on radiographic progression in AS [7]. Local injection of corticosteroids can be helpful in treating persistent synovitis and enthesitis, whereas the efficacy of systemic corticosteroid therapy has not been evidenced. AS patients with peripheral synovitis, clinical gut involvement or eye disease can benefit from therapy with sulphasalazine as a disease-modifying, antirheumatic drug (DMARD), but this therapy has no proven effect on axial inflammation. Preliminary studies suggest a possible benefical effect of pamidronate and thalidomide on axial symptoms [8–10], but this remains to be confirmed in placebo-controlled studies.

Taken together, the treatment of AS in clinical practice is largely limited to physiotherapy and symptomatic anti-inflammatory treatment with NSAIDs. Although providing some benefit in most patients, this approach often fails to effectively control axial and peripheral inflammation and does not reverse the major loss in QoL of these patients. Moreover, these treatments are insufficient to halt disease progression and prevent important functional handicap.

TNF-α blockade for the treatment of immune-mediated inflammatory diseases

In the last decade, biological therapies have been developed to block the proinflammatory cytokine tumor necrosis factor (TNF)-α and have been succesfully used in RA and in Crohn's disease. The currently available TNF-α blockers include the chimeric anti-TNF-α monoclonal antibody (mAb) infliximab, the soluble TNF-α receptor fusion protein etanercept, and the fully human anti-TNF-α mAb adalimumab. The present review will focus on the data obtained with infliximab.

The double-blind, placeo-controlled studies with infliximab in RA were the first to demonstrate the efficacy of specific cytokine blockade in human immune-mediated inflammatory diseases [11,12]. Multiple Phase II and III follow-up studies have consistently demonstrated the major impact of treatment with infliximab, mostly in combination with methotrexate, on signs and symptoms in RA [13–15]. This effect is sustained over the longer term and is paralleled by an inhibition of progressive structural damage [16,17]. The classical treatment regimen in RA is infliximab 3 mg/kg at week 0, 2 and 6, followed by an infusion every 8 weeks, in combination with methotrexate.

In active, steroid-refractory Crohn's disease, a clinical remission with endoscopic healing of mucosal ulcers after a single intravenous dose of infliximab was reported in an open-label study [18]. In a multicenter, randomized, double-blind, placebo-controlled trial of infliximab in moderate-to-severe Crohn's disease [19], treatment produced a rapid and profound benefit for all response variables measured, which was correlated with endoscopic improvement. On the basis of an additional randomized controlled trial [20], infliximab was approved by the health authorities in the USA (FDA) and Europe (European agency for the evalution of medicinal products [EMEA]) as a drug for treatment-resistant moderate-to-severe Crohn's disease and fistulizing Crohn's disease

Of interest, Crohn's disease is closely related to AS and SpA in general: arthritis mimicking SpA is the most common extraintestinal manifestation of IBD (2–22%) [21–24] and often resembles SpA [25]. In addition, a high prevalence of subclinical gut inflammation has been reported in the different subtypes of SpA, reaching up to 75% in AS [26]. Repeat ileocolonoscopies indicated a strong relationship between persistent

microscopic gut inflammation and the persistence of joint symptoms [27]. Moreover, the similarities between gut inflammation in Crohn's disease and AS and between gut and joint inflammation in AS have been confirmed by a series of immunopathological observations [28–30]. Considering the major efficacy of infliximab in inflammation in Crohn's disease, this treatment was further assessed for locomotor manifestations in Crohn's disease and, subsequently, for the treatment of SpA and AS.

Infliximab: pharmacological profile

Infliximab targets TNF-α, a proinflammatory cytokine with multiple actions including induction of chemokines and cytokines, recruitment and activation of leukocytes and endothelial cells and stimulation of osteoclasts. TNF-α plays a central role in the inflammatory cytokine cascade, since selective blockade of this cytokine also inhibits other proinflammatory cytokines such as interleukin (IL)-1. Infliximab is a chimeric immunoglobulin (Ig)G1κ mAb with human constant and murine variable regions. By binding to TNF-α with an association constant of 10^{10} mol/l, infliximab neutralizes soluble, as well as transmembrane, TNF-α. It also induces apoptosis of activated lymphocytes and monocytes [31].

The dosage used for infliximab in AS is the same as in Crohn's disease: 5 mg/kg. Distribution is essentially restricted to the vascular compartment and the volume of distribution is 70 ml/kg with a median distribution half-life of 3 days. Infusion of a single dose leads to a median maximum serum concentration of 102 µg/ml within the first hours after administration (median 0.084 days). The schedule, as approved for AS (administration at weeks 0, 2 and 6, followed by an infusion every 6–8 weeks), leads to steady-state serum concentrations from week 22 on, with approximatively 2 µg/ml preinfusion and 100 µg/ml postinfusion. In Crohn's disease, the median elimination half-life is 12.5 days and the median clearance is 5.2 ml/day/kg. However, the exact pathways of metabolization and elimination are unknown.

Pilot observations with infliximab in ankylosing spondylitis

Based on the clinical and pathophysiological link between Crohn's disease and SpA and the efficacy of infliximab in Crohn's disease, the first pilot observations came from patients with overt IBD and active SpA, who received infliximab 5 mg/kg intravenously to treat active IBD symptoms [32]. One patient had AS with severe inflammatory axial symptoms, a second patient had AS with peripheral arthritis, and the two other patients suffered from peripheral arthritis. In all four patients, infliximab induced not only gastrointestinal remission, but also remission of articular symptoms.

Based on this pilot study and on the detection of TNF-α mRNA in the sacroiliacal joints of AS patients [33], two open-label studies were conducted simultaneously. The first study treated 11 AS patients with infliximab 5 mg/kg at week 0, 2 and 6 [34]. One patient withdrew due to urticarial xanthoma. Significant improvement was documented in nine of the ten patients with a median decrease in the Bath AS Disease Activity Index (BASDAI) of 70%. This response lasted for 6 weeks after the third infusion in eight out of ten patients. The second study was performed in 21 patients fulfilling the European Spondylarthropathy Study Group (ESSG) SpA classification criteria, including 11 AS patients, who received three infusions of infliximab (5 mg/kg) at week 0, 2 and 6 [35]. All the evaluated variables (global disease activity, peripheral arthritis assessments, axial assessments, and skin disease) improved significantly, and for most variables statistical significance was achieved already at day 3. The improvement was maintained for up to 6 weeks after the third infusion. No major adverse effects were observed and minor effects, such as nausea and dizziness, did not require interruption or discontinuation of the treatment. Based on the positive results of these two studies, different groups conducted additional open-label trials confirming these observations. More importantly, however, this led to three pivotal, double-blind, placebo-controlled, randomized studies of infliximab in AS and SpA.

Clinical efficacy in placebo-controlled trials

The first double-blind, randomized, placebo-controlled trial included 69 AS patients treated either with infliximab 5 mg/kg or by placebo at week 0, 2 and 6 [36]. At week 12, disease activity (BASDAI) had improved by at least 50% in 53% of the infliximab-treated patients versus 9% of the placebo. This 50% improvement occured within 2 weeks after initiation of therapy in 41% of the infliximab-treated patients. A 20% response according to the Ankylosing Spondylitis Assessment Study (ASAS) criteria (ASAS20) was achieved in more than 80% of the treated patients versus 30% in the placebo

group. In addition, function (Bath AS Functional Index [BASFI]), spinal mobility (Bath AS Metrology Index [BASMI]), inflammatory parameters such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), and health-related QoL were significantly improved in the infliximab group compared with the placebo cohort.

Simultaneously, an independent placebo-controlled Phase II study assessed the same treatment schedule (infliximab 5 mg/kg at week 0, 2 and 6) in 40 SpA patients including 19 AS patients (nine in the infliximab group and ten in the placebo group) [37]. Primary outcomes (patient's and physician's global assessment) as well as the inflammatory parameters (CRP and ESR) and measures of peripheral joint disease showed a significant improvement in the infliximab-treated group from week 1 and up to the end point at week 12. In the subgroup with axial involvement, there was also a significant improvement in BASDAI, BASFI and BASMI.

In the 24-week Ankylosing sPondylitis Study For Evaluation Of Recombinant Infliximab Treatment (ASSERT), AS patients received infliximab 5 mg/kg (n = 201) or placebo (n = 78) at week 0, 2, 6, 12 and 18 [38]. At week 24, ASAS20 criteria were achieved in 61% of the infliximab group versus 19% of the placebo cohort and $BASDAI_{50}$ responses were obtained in 51% of the infliximab-treated patients versus 10.7% of the placebo recipients. As in the previous studies, the clinical response was observed as early as week 2 and was maintained over the 24-week study period. This was paralleled by a significantly greater improvement in infliximab versus placebo recipients for BASDAI, BASFI, BASMI, CRP and QoL.

Taken together, these three double-blind, placebo-controlled, randomized trials provide strong and consistent evidence for a major therapeutic effect of infliximab on disease activity, inflammation, function, mobility and QoL in AS. This effect occurs already after the first administration of infliximab 5 mg/kg and seems to be maintained over at least 24 weeks upon retreatment.

Long-term clinical efficacy

Of the 21 SpA patients included in the open-label trial in SpA [35] 19 were retreated with infliximab 5 mg/kg every 14 weeks and evaluated over a 1-year period [39]. The significant improvement in all parameters of global, axial, and peripheral disease was maintained over this period. However, recurrence of symptoms was noted in a rising number of patients before each retreatment (16% at week 20, 68% at week 34, 79% at week 48), indicating that although the efficacy of the treatment was maintained the treatment interval of 14 weeks is too long to achieve a continuous control of signs and symptoms.

AS patients from the double-blind, placebo-controlled trials in AS [36] were retreated with infliximab 5 mg/kg every 6 weeks for 3 years in an open, observational, extension study. Compared with 53% at week 12, an intention-to-treat analysis indicated a 50% improvement in BASDAI scores in 49% at year 1 [40], 43% at year 2 [41], and 41% at year 3 [42]. Analyzing only those patients electing to continue treatment, a $BASDAI_{50}$ response was achieved in 58% at year 2 and 61% at year 3. Also, the secondary end points such as function, mobility and QoL remained significantly improved over the 3-year period. Collectively, these data indicate that infliximab treatment of AS patients for 3 years induced a durable clinical response without loss of efficacy.

Of interest, in the same patient cohort (n = 42) the treatment was discontinued after 3 years and the occurence of clinical relapse (defined as a BASDAI score and a physician's global assessment > or = 4) was analyzed [43]: 24% showed a relapse within 12 weeks, 90.5% within 36 weeks, and 97.6% within 52 weeks. The mean time to relapse was 17.5 weeks with a mean increase of BASDAI of 3.6. Only one patient remained in durable remission after discontinuation of infliximab. In all other patients, retreatment with infliximab after clinical relapse resulted in a restoration of the clinical improvement to a similar level as before the treatment was interrupted.

Short- & long-term safety

Since adverse events occuring during infliximab therapy have been extensively described in RA and Crohn's disease, the authors will focus on the specific data available in AS and SpA. Globally, infliximab treatment was well tolerated, with most adverse events being mild-to-moderate and occuring at similar frequencies in the infliximab-treated and placebo groups. Serious adverse events were observed in 8–10% of the infliximab recipients and none of the controls in the two Phase II trials with infliximab in AS and SpA, and in 3.5% of the infliximab-treated patients versus 2.5% of the placebo recipients in ASSERT [36–38]. Malignancies, demyelination syndromes and cardiac decompensation, all of which have been previously suggested to be

potentially associated with TNF-α blockade, were not observed. Adverse events that are likely treatment related include infections, infusion reactions, psoriasis and induction of antinuclear antibodies (ANA).

TNF-α plays a major role not only in arthritis-associated inflammation but also in host defense against a variety of microbes. Despite the fear that TNF-α blockade with infliximab may interfere with normal host defense and lead to an increase in mild and/or severe infections, data from the different controlled studies did not show significant differences between treated and placebo cohorts. In the 12-week trial in AS [36], upper respiratory tract infections were observed in 51% in the infliximab group and in 35% in the placebo cohort. In the 12-week trial in SpA [37], minor infections occured in both groups at the same frequencies. In ASSERT, upper respiratory tract infections occured in 13.9% of infliximab recipients versus 14.7% of placebo recipients [38]. Only pharyngitis and rhinitis were observed more than twice as much in the infliximab group. However, it should be noted that two out of five severe adverse events occuring in the 12-week trials and one event in an open extension of these trials [44] were cases of systemic tuberculosis in the infliximab groups. The timing and presentation of these cases was similar to the previously described cases in RA and Crohn's disease [45] and thereby provide further evidence that TNF-α blockade may increase the risk of tuberculosis reactivation and eventually other types of opportunistic infections. Whereas these events are rare and effective screening for tuberculosis can probably decrease this risk (there were no cases of tuberculosis in ASSERT), this should be kept in mind when treating patients at risk or when being confronted with nontypical symptomatology in infliximab-treated AS patients.

With regards to allergic reactions to the product, no infusion reactions or delayed-type hypersensitivity reactions were observed in both 12-week trials [36,37]. In ASSERT, 11% of patients receiving infliximab reported an infusion reaction compared with 9.3% of patients receiving placebo, and the proportion of infusions associated with infusion reactions was low and identical between the treatment groups (2.7%) [38].

A surprising finding is the induction by infliximab of palmoplantar pustulosis and/or psoriasis in a few AS patients without personal or familial history of psoriasis [44,46]. Although this does not represent a major clinical issue and skin lesions mostly subside with topical treatment even without discontinuation of infliximab treatment, this paradoxical side effect may provide important clues to immune alterations induced by anti-TNF-α therapy.

Similarly, all double-blind, placebo-controlled studies have evidenced a pronounced induction of ANA and anti-dsDNA antibodies in infliximab-treated AS patients. Whereas the figures are difficult to compare between the different trials due to differences in detection methods and cut-off values, a recent study has detailed the biological profile and clinical relevance of this finding [47]. The infliximab-treated SpA had high numbers of newly induced ANA (61.8%) and anti-dsDNA antibodies (70.6%) after 1 year, but no further increase between year 1 and 2. Of interest, this induction was clearly less pronounced in etanercept-treated patients, suggesting that this is not a pure class effect of TNF-α blockers. Isotyping revealed almost exclusively IgM or associated IgM/A anti-dsDNA antibodies that disappeared upon interruption of treatment, thereby suggesting short-term, nonpathogenic responses. Accordingly, infliximab did not induce other lupus-related reactivities such as anti-ENA, antihistone or antinucleosome antibodies, and no clinically relevant lupus-like symptoms were observed. Similar to the induction of palmoplantar pustolosis, it thus appears that this phenomenon has no direct major clinical implications but suggests that modulation of humoral immunity may be an important biological aspect of infliximab treatment.

Clinical use & treatment guidelines

Based on the previously described trials, infliximab was approved by the FDA and the EMEA for the treatment of severe axial AS and AS with peripheral arthritis which is unresponsive to conventional treatment. The proposed treatment schedule is 5 mg/kg at week 0, 2 and 6, followed by retreatment every 8 weeks. Several open studies in real-life settings have further confirmed the efficacy data from the described studies and indicate that the improvement in health-related QoL is even larger in AS than in RA patients treated with infliximab [48]. Combination with MTX increases the efficacy of infliximab treatment in RA, possibly by inhibiting the formation of human antichimeric antibodies, but does not appear to provide any benefit in AS [49]. Reducing the dose interval in patients with insuffient response may be beneficial in some patients [50], whereas in other patients lower doses (3 mg/kg) may be effective [51].

An important clinical question is: which patients would benefit most from this treatment and how should their response to treatment be evaluated? A multivariate analysis including AS patients treated with infliximab (n = 69) and etanercept (n = 39) indicated that shorter disease duration, lower BASFI, higher BASDAI and higher CRP at baseline are the best predictors for a major clinical response ($BASDAI_{50}$) [52]. Analysis of the same cohort indicated that a 20% improvement in five of six domains (pain, patient global assessment, function, inflammation, spinal mobility and CRP), with a placebo response of 2.9% and an infliximab response of 67.7%, and a 40% ASAS improvement, with a placebo response of 5.7% and an infliximab response of 64.7%, were the best discriminators for defining a short-term improvement upon infliximab treatment in AS [53]. An independent study confirmed the validity of the ASAS criteria for the detection of improvement in AS patients treated with infliximab, but also indicated that the patient global assessment of disease activity, a measure that can be more easily used across different types of SpA, may be sufficient to monitor the treatment response in these patients [54]. Based on these data, different preliminary sets of guidelines and management recommendations have been developed and need to be validated in the near future [55–59].

Expert commentary

The data presented in this review indicate clearly that AS is a commonly occuring disease with a major impact on health and QoL. Since classical treatment strategies are often insufficient to control signs and symptoms and to halt disease progression, the short experience with infliximab in the treatment of severe AS provides already extensive and robust evidence that TNF-α blockade represents a major breakthrough in the managment of this disease. The data of the clinical trials and the growing clinical experience tend to indicate that the impact of infliximab treatment will be even larger in AS than in previous indications such as RA and Crohn's disease. Several important issues deserve further attention in this context.

First, the data presented in this review are largely restricted to the effect of infliximab on AS and essentially on axial inflammation in AS. There is, however, convincing evidence that infliximab treatment is also very effective for treatment of other manifestations of AS such as peripheral synovitis [37,60,61], enterocolitis [32,62] and uveitis [63,64].

Second, the efficacy of infliximab on these different disease manifestations is not only restricted to the AS subtype of SpA but also extends to other SpA subtypes such as undifferentiated SpA [37,65], PsA [37,66], IBD-associated SpA [32,62], and juvenile SpA [67].

Third, whereas most of the original studies were performed with infliximab, there is now increasing evidence that largely similar results are obtained with other TNF-α blockers [68–70]. In the first double-blind, placebo-controlled study with etanercept in 40 AS patients, 80% of treated patients versus 30% of placebo patients had a treatment response at 4 months [68]. All response parameters improved significantly in the etanercept group, without significant adverse events. These findings were reinforced in two larger follow-up studies, with an ASAS20 response at 6 months of 57% with etanercept versus 22% with placebo [70] and a 50% reduction of BASDAI at 6 months in 57% with etanercept versus 6% with placebo [71]. Although not yet published, preliminary results tend to indicate a similar efficacy of adalimumab.

Finally, infliximab treatment in AS does not only lead to an improvement in signs and symptoms, but also induces disease and possibly structure modification [72]. Immunological and histopathological studies have reported a profound effect on T-cell cytokine profiles [72–74], matrix metalloproteinases [75], Toll-like receptor expression and function [76], and synovial histopathology [60,61,77]. More specifically, in the context of AS and structural damage, magnetic resonance imaging (MRI) studies have reported a pronounced and persistent reduction of spinal inflammation [36,38,78]. Preliminary evidence suggests that this also leads to a deceleration or retardation of radiographical progression [79]. This issue is of particular importance and warrants confirmation in larger trials.

Outlook

Treatment with infliximab and other TNF-α blockers will certainly continue to profoundly change the daily clinical management of AS over the coming years. From a clinical point of view, a major challenge will be to correctly assess the long-term effect on QoL in individual patients and to define patient profiles that allow a rational and individualized treatment choice based on the objective balance between clinical and socioeconomic benefit on the one hand and long-term safety and costs on the other. It is likely that clinical/phenotypical characteristics

will turn out to be insufficient to define these profiles and that additional paraclinical and biological information will become crucial in treatment choice and follow-up. It is also likely that the development of cheaper alternatives for TNF-α blockade will further shift the cost–benefit ratio of this type of treatment, leading to an increased use in less favored socioeconomic groups or countries and in less severe cases of AS.

From a scientific point of view, a first important question to be addressed in the coming years is the impact of TNF-α blockade on structural damage, including cartilage and bone destruction as well as bone formation and ankylosis. This issue has important clinical implications as a major impact on this disease aspect would call for infliximab treatment not only in active AS, defined as AS with severe and refractory inflammation, but also potentially in AS patients with moderate inflammation, but a poor long-term prognosis due to progressive structural deterioration. A second major scientific challenge results from the observation that discontinuation of infliximab treatment leads to short-term relapse in almost all patients, indicating that despite the major therapeutic efficacy we are still not able to induce long-lasting remission in AS. This emphasizes the need for further research on innovative treatments, eventually in combination with TNF-α blockade. However, the major clinical benefit of infliximab treatment in AS also forms an increasing medical and ethical hurdle to perform long-term, placebo-controlled studies in AS and thus confronts the rheumatological community with the challenge to develop creative and acceptable alternatives for the clinical development of new therapies.

Highlights

- Ankylosing spondylitis (AS) is a common form of autoimmune arthritis affecting mainly young adults and leading to severe morbidity and loss in quality of life (QoL).
- Classical treatments, consisting of physiotherapy and nonsteroidal anti-inflammatory drugs, fail in many cases to effectively control signs and symptoms of the disease and to retard or halt disease progression.
- Based on spectacular pilot observations, a number of double-blind, placebo-controlled, randomized trials have provided large and consistent evidence that infliximab treatment induces a rapid and profound clinical benefit in AS. This benefit consists of improvement of axial and peripheral joint symptoms, suppression of inflammation, amelioration of global disease activity. It leads to an important gain in function, mobility and ultimately QoL.
- Infliximab treatment in AS is generally well tolerated and has a favourable global safety profile. Severe, drug-related adverse events are rare. Nevertheless, treating physicians and patients should remain aware of the increased risk for atypical or opportunistic infections.
- Growing clinical experience confirms the efficacy and safety data obtained in the clinical trials. The recommended and approved treatment schedule for severe AS resistance to conventional treatment is infliximab 5 mg/kg intravenously as monotherapy (without methotrexate) at week 0, 2 and 6, followed by a retreatment every 6–8 weeks. Efficacy is maintained in the long term, but discontinuation leads to clinical relapse within a few weeks.

Bibliography

Papers of special note have been highlighted as of interest (•) or of considerable interest (••) to readers.

1. Saraux A, Guedes C, Allain J *et al.* Prevalence of rheumatoid arthritis and spondyloarthropathy in Brittany, France. Societe de Rhumatologie de l'Ouest. *J. Rheumatol.* 26(12), 2622–2627 (1999).
2. Braun J, Bollow M, Remlinger G *et al.* Prevalence of spondylarthropathies in HLA-B27 positive and negative blood donors. *Arthritis Rheum.* 41(1), 58–67 (1998).
3. Sokoll KB, Helliwell PS. Comparison of disability and quality of life in rheumatoid and psoriatic arthritis. *J. Rheumatol.* 28(8), 1842–1846 (2001).
4. Dagfinrud H, Mengshoel AM, Hagen KB, Loge JH, Kvien TK. Health status of patients with ankylosing spondylitis. a comparison with the general population. *Ann. Rheum. Dis.* 63(12), 1605–1610 (2004).
5. Boonen A, Chorus A, Miedema H, van der Heijde D, van der Tempel H, van der Linden S. Employment, work disability, and work days lost in patients with ankylosing spondylitis. a cross sectional study of Dutch patients. *Ann. Rheum. Dis.* 60(4), 353–358 (2001).
6. Boonen A, van der Heijde D, Landewe R *et al.* Work status and productivity costs due to ankylosing spondylitis: comparison of three European countries. *Ann. Rheum. Dis.* 61(5), 429–437 (2002).
7. Wanders A, Heijde D, Landewe R *et al.* Nonsteroidal anti-inflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: a randomized clinical trial. *Arthritis Rheum.* 52(6), 1756–1765 (2005).
8. Maksymowych WP, Jhangri GS, Fitzgerald AA *et al.* A six-month randomized, controlled, double-blind, dose-response comparison of intravenous pamidronate (60 mg versus 10 mg) in the treatment of nonsteroidal anti-inflammatory drug-refractory ankylosing spondylitis. *Arthritis Rheum.* 46(3), 766–773 (2002).
9. Huang F, Gu J, Zhao W, Zhu J, Zhang J, Yu DT. One-year open-label trial of thalidomide in ankylosing spondylitis. *Arthritis Rheum.* 47(3), 249–254 (2002).
10. Wei JC, Chan TW, Lin HS, Huang F, Chou CT. Thalidomide for severe refractory ankylosing spondylitis: a 6-month open-label trial. *J. Rheumatol.* 30(12), 2627–2631 (2003).

11. Elliott MJ, Maini RN, Feldmann M *et al.* Repeated therapy with monoclonal antibody to tumour necrosis factor alpha (cA2)in patients with rheumatoid arthritis. *Lancet* 344(8930), 1125–1127 (1994).
12. Elliott MJ, Maini RN, Feldmann M *et al.* Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. *Lancet* 344(8930), 1105–1110 (1994).
13. Maini RN, Breedveld FC, Kalden JR *et al.* Therapeutic efficacy of multiple intravenous infusions of antitumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum.* 41(9), 1552–1563 (1998).
14. Maini R, St Clair EW, Breedveld F *et al.* Infliximab (chimeric antitumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate. a randomised Phase III trial. ATTRACT Study Group. *Lancet* 354(9194), 1932–1939 (1999).
15. Lipsky PE, van der Heijde DM, St Clair EW *et al.* Infliximab and methotrexate in the treatment of rheumatoid arthritis. AntiTumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N. Engl. J. Med.* 343(22), 1594–1602 (2000).
16. Maini RN, Breedveld FC, Kalden JR *et al.* AntiTumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. *Arthritis Rheum*. 50(4), 1051–1065 (2004).
17. Smolen JS, Han C, Bala M *et al*. ATTRACT Study Group. Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement: a detailed subanalysis of data from the antitumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. *Arthritis Rheum.* 52(4), 1020–1030 (2005).
18. van Dullemen HM, van Deventer SJ, Hommes DW *et al*. Treatment of Crohn's disease with antitumor necrosis factor chimeric monoclonal antibody (cA2). *Gastroenterology* 109(1), 129–135 (1995).
19. Targan SR, Hanauer SB, van Deventer SJ *et al*. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N. Engl. J. Med.* 337(15), 1029–1035 (1997).
20. Present DH, Rutgeerts P, Targan S *et al*. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N. Engl. J. Med.* 340(18), 1398–1405 (1999).
21. Palm O, Moum B, Ongre A, Gran JT. Prevalence of ankylosing spondylitis and other spondyloarthropathies among patients with inflammatory bowel disease: a population study (the IBSEN study). *J. Rheumatol.* 29(3), 511–515 (2002).
22. Salvarani C, Vlachonikolis IG, van der Heijde DM *et al*. European Collaborative IBD Study Group. Musculoskeletal manifestations in a population-based cohort of inflammatory bowel disease patients. Scand. *J. Gastroenterol* 36(12), 1307–1313 (2001).
23. Orchard TR, Wordsworth BP, Jewell DP. Peripheral arthropathies in inflammatory bowel disease: their articular distribution and natural history. *Gut* 42(3), 387–391 (1998).
24. Queiro R, Maiz O, Intxausti J *et al.* Subclinical sacroiliitis in inflammatory bowel disease: a clinical and follow-up study. *Clin. Rheumatol.* 19(6), 445–449 (2000).
25. de Vlam K, Mielants H, Cuvelier C, De Keyser F, Veys EM, De Vos M. Spondyloarthropathy is underestimated in inflammatory bowel disease: prevalence and HLA association. *J. Rheumatol.* 27(12), 2860–2865 (2000).
26. De Keyser F, Elewaut D, De Vos M *et al.* Bowel inflammation and the spondyloarthropathies. *Rheum. Dis. Clin. North Am.* 24(4), 785–813 (1998).
27. Mielants H, Veys EM, Cuvelier C *et al.* The evolution of spondyloarthropathies in relation to gut histology. III. Relation between gut and joint. *J. Rheumatol.* 22(12), 2279–2284 (1995).
28. Van Damme N, De Vos M, Baeten D *et al.* Flow cytometric analysis of gut mucosal lymphocytes supports an impaired Th1 cytokine profile in spondyloarthropathy. *Ann. Rheum. Dis.* 60(5), 495–499 (2001).
29. Demetter P, Baeten D, De Keyser F *et al.* Subclinical gut inflammation in spondyloarthropathy patients is associated with upregulation of the E-cadherin/catenin complex. *Ann. Rheum. Dis.* 59(3), 211–216 (2000).
30. Baeten D, Demetter P, Cuvelier CA *et al.* Macrophages expressing the scavenger receptor CD163: a link between immune alterations of the gut and synovial inflammation in spondyloarthropathy. *J. Pathol.* 196(3), 343–350 (2002).
31. Van den Brande JM, Braat H, van den Brink GR *et al.* Infliximab but not etanercept induces apoptosis in lamina propria T-lymphocytes from patients with Crohn's disease. *Gastroenterology* 124(7), 1774–1785 (2003).
32. Van den Bosch F, Kruithof E, De Vos M, De Keyser F, Mielants H. Crohn's disease associated with spondyloarthropathy: effect of TNF-alpha blockade with infliximab on articular symptoms. *Lancet* 356(9244), 1821–1822 (2000).
33. Braun J, Bollow M, Neure L *et al.* Use of immunohistologic and *in situ* hybridization techniques in the examination of sacroiliac joint biopsy specimens from patients with ankylosing spondylitis. *Arthritis Rheum.* 38(4), 499–505 (1995).
34. Brandt J, Haibel H, Cornely D *et al.* Successful treatment of active ankylosing spondylitis with the antitumor necrosis factor alpha monoclonal antibody infliximab. *Arthritis Rheum.* 43(6), 1346–1352 (2000).
35. Van den Bosch F, Kruithof E, Baeten D *et al*. Effect of a loading dose regimen of three infusions of chimeric monoclonal antibody to tumour necrosis factor alpha (infliximab) in spondyloarthropathy: an open pilot study. *Ann. Rheum. Dis.* 59(6), 428–433 (2000).
36. Braun J, Brandt J, Listing J *et al*. Treatment of ankylosing spondylitis with infliximab: a randomised controlled multicenter trial. *Lancet* 359(9313), 1187–1193 (2002).

•• **Describes the first double-blind, placebo-controlled trial with infliximab in AS. It indicates an impressive effect of this drug on almost all outcome parameters. There were a few serious adverse events, including one case of tuberculosis.**

37. Van den Bosch F, Kruithof E, Baeten D *et al*. Randomized double-blind comparison of chimeric monoclonal antibody to tumor necrosis factor alpha (infliximab) versus placebo in active spondyloarthropathy. *Arthritis Rheum.* 46(3), 755–765 (2002).

•• **This completely independent double-blind study was conducted and published at the same time as** [36]**. Using a similar treatment schedule in AS as well as other SpA subtypes, it reports similar results with a major and rapid improvement in the infliximab group compared to almost no changes in the placebo group.**

38. van der Heijde D, Dijkmans B, Geusens P *et al*. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). *Arthritis Rheum.* 52(2), 582–591 (2005).

•• **This large, multicenter Phase III trial confirms and extends the findings of the smaller Phase II trials. Once again, the major efficacy of infliximab versus placebo is confirmed.**

39. Kruithof E, Van den Bosch F, Baeten D *et al.* Repeated infusions of infliximab, a chimeric antiTNFalpha monoclonal antibody, in patients with active spondyloarthropathy: one year follow-up. *Ann. Rheum. Dis.* 61(3), 207–212 (2002).
40. Braun J, Brandt J, Listing J *et al.* Long-term efficacy and safety of infliximab in the treatment of ankylosing spondylitis: an open, observational, extension study of a three-month, randomized, placebo-controlled trial. *Arthritis Rheum.* 48(8), 2224–2233 (2003).
41. Braun J, Brandt J, Listing J *et al.* Two year maintenance of efficacy and safety of infliximab in the treatment of ankylosing spondylitis. *Ann. Rheum. Dis.* 64(2), 229–234 (2005).
42. Braun J, Baraliakos X, Brandt J *et al.* Persistent clinical response to the anti=TNF-alpha antibody infliximab in patients with ankylosing spondylitis over 3 years. *Rheumatology* 44(5), 670–676 (2005).

•• **Follow-up of the patients included in the original Phase II trial in Germany. Indicates convincingly that the efficacy of the treatment is maintained over a 3-year treatment period.**

43. Baraliakos X, Listing J, Brandt J, Rudwaleit M, Sieper J, Braun J. Clinical response to discontinuation of antiTNF therapy in patients with ankylosing spondylitis after 3 years of continuous treatment with infliximab. *Arthritis Res. Ther.* 7(3), R439–444 (2005).

•• **Extending the previous report, succesful treatment with infliximab was interrupted after 3 years to analyze if the AS patients would retain their clinical improvement. The results clearly indicate that almost all patients developed a disease relapse shortly after discontinuation. Together with the previous report, this calls for continuous treatment with infliximab in AS.**

44. Baeten D, Kruithof E, Van den Bosch F *et al.* Systematic safety follow-up in a cohort of 107 patients with spondyloarthropathy treated with infliximab: a new perspective on the role of host defence in the pathogenesis of the disease? *Ann. Rheum. Dis.* 62(9), 829–834 (2003).
45. Keane J, Gershon S, Wise RP *et al.* Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N. Engl. J. Med.* 345(15), 1098–1104 (2001).
46. Sfikakis PP, Iliopoulos A, Elezoglou A, Kittas C, Stratigos A. Psoriasis induced by antitumor necrosis factor therapy: a paradoxical adverse reaction. *Arthritis Rheum.* 52(8), 2513–2518 (2005).
47. De Rycke L, Baeten D, Kruithof E, Van den Bosch F, Veys EM, De Keyser F. Infliximab, but not etanercept, induces IgM antidouble-stranded DNA autoantibodies as main antinuclear reactivity: biologic and clinical implications in autoimmune arthritis. *Arthritis Rheum.* 52(7), 2192–2201 (2005).
48. Heiberg MS, Nordvag BY, Mikkelsen K *et al.* The comparative effectiveness of tumor necrosis factor-blocking agents in patients with rheumatoid arthritis and patients with ankylosing spondylitis: a six-month, longitudinal, observational, multicenter study. *Arthritis Rheum.* 52(8), 2506–2512 (2005).
49. Marzo-Ortega H, McGonagle D, Jarrett S *et al.* Infliximab in combination with methotrexate in active ankylosing spondylitis. A clinical and imaging study. *Ann. Rheum. Dis.* (2005)(Epub ahead of print).
50. Collantes-Estevez E, Munoz-Villanueva MC, Zarco P *et al.* Effectiveness of reducing infliximab dose interval in non-responder patients with refractory spondyloarthropathies. An open extension of a multicentre study. *Rheumatology* (2005)(Epub ahead of print).
51. Maksymowych WP, Jhangri GS, Lambert RG *et al.* Infliximab in ankylosing spondylitis: a prospective observational inception cohort analysis of efficacy and safety. *J. Rheumatol.* 29(5), 959–965 (2002).
52. Rudwaleit M, Listing J, Brandt J, Braun J, Sieper J. Prediction of a major clinical response (BASDAI 50) to tumour necrosis factor alpha blockers in ankylosing spondylitis. *Ann. Rheum. Dis.* 63(6), 665–670 (2004).
53. Brandt J, Listing J, Sieper J *et al.* Development and preselection of criteria for short-term improvement after antiTNF alpha treatment in ankylosing spondylitis. *Ann. Rheum. Dis.* 63(11), 1438–1444 (2004).
54. Stone MA, Inman RD, Wright JG, Maetzel A. Validation exercise of the Ankylosing Spondylitis Assessment Study (ASAS) group response criteria in ankylosing spondylitis patients treated with biologics. *Arthritis Rheum.* 51(3), 316–320 (2004).
55. Maksymowych WP, Inman RD, Gladman D *et al.* Canadian Rheumatology Association Consensus on the use of antitumor necrosis factor-alpha directed therapies in the treatment of spondyloarthritis. *J. Rheumatol.* 30(6), 1356–1363 (2003).
56. Zochling J, van der Heijde D, Dougados M, Braun J. Current evidence for the management of ankylosing spondylitis: a systematic literature review for the asas/eular management recommendations in ankylosing spondylitis. *Ann. Rheum. Dis.* (2005)(Epub ahead of print).
57. Keat A, Barkham N, Bhalla A *et al.* BSR guidelines for prescribing TNF-alpha blockers in adults with ankylosing spondylitis. Report of a working party of the British Society for Rheumatology. *Rheumatology* 44(7), 939–947 (2005).
58. Zochling J, van der Heijde D, Burgos-Vargas R *et al.* ASAS/EULAR recommentations for the management of ankylosing spondylitis. *Ann. Rheum. Dis.* (2005)(Epub ahead of print).
59. Braun J, Davis J, Dougados M *et al.* First update of the International ASAS Consensus Statement for the use of anti-TNF agents in patients with ankylosing spondylitis. *Ann. Rheum. Dis.* (2005)(Epub ahead of print).
60. Baeten D, Kruithof E, Van den Bosch F *et al.* Immunomodulatory effects of antitumor necrosis factor alpha therapy on synovium in spondyloarthropathy: histologic findings in eight patients from an open-label pilot study. *Arthritis Rheum.* 44(12), 2937–2939 (2001).
61. Kruithof E, Baeten D, Van den Bosch F, Mielants H, Veys EM, De Keyser F. Histological evidence that infliximab treatment leads to donwregulation of inflammation and tissue remodelling of the synovial membrane in spondyloarthropathy. *Ann. Rheum. Dis.* 64(4), 529–536 (2005).
62. Generini S, Giacomelli R, Fedi R *et al.* Infliximab in spondyloarthropathy associated with Crohn's disease: an open study on the efficacy of inducing and maintaining remission of musculoskeletal and gut manifestations. *Ann. Rheum. Dis.* 63(12), 1664–1669 (2004).
63. Smith JR, Levinson RD, Holland GN *et al.* Differential efficacy of tumor necrosis factor inhibition in the management of inflammatory eye disease and associated rheumatic disease. *Arthritis Rheum.* 45(3), 252–257 (2001).
64. Braun J, Baraliakos X, Listing J, Sieper J. Decreased incidence of anterior uveitis in patients with ankylosing spondylitis treated with the antitumor necrosis factor agents infliximab and etanercept. *Arthritis Rheum.* 52(8), 2447–2451 (2005).
65. Brandt J, Haibel H, Reddig J, Sieper J, Braun J. Successful short-term treatment of severe undifferentiated spondyloarthropathy

with the antitumor necrosis factor-alpha monoclonal antibody infliximab. *J. Rheumatol.* 29(1), 118–122 (2002).

66. Antoni CE, Kananaugh A, Kirkham B *et al*. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis. results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). *Arthritis Rheum.* 52(4), 1227–1236 (2005).
67. Tse SM, Burgos-Vargas R, Laxer RM. Antitumor necrosis factor alpha blockade in the treatment of juvenile spondylarthropathy. *Arthritis Rheum.* 52(7), 2103–2108 (2005).
68. Gorman JD, Sack KE, Davis JC Jr. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor α. *N. Engl. J. Med.* 346(18), 1349–1356 (2002).
69. Davis JC Jr, Van Der Heijde D, Braun J *et al*. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis. a randomized, controlled trial. *Arthritis Rheum.* 48(11), 3230–3236 (2003).
70. Brandt J, Khariouzov A, Listing J *et al*. Six-month results of a double-blind, placebo-controlled trial of etanercept treatment in patients with active ankylosing spondylitis. *Arthritis Rheum.* 48(6), 1667–1675 (2003).
71. De Keyser F, Baeten D, Van den Bosch F *et al*. Structure-modifying capcaity of antitumour necrosis factor-alpha therapy in ankylosing spondylitis. *Drugs* 64(26), 2793–2811 (2004).
72. Baeten D, Van Damme N, Van den Bosch N *et al*. Impaired Th1 cytokine production in spondyloarthropathy is restored by antiTNFalpha. *Ann. Rheum. Dis.* 60(8), 750–755 (2001).
73. Zou J, Rudwaleit M, Brandt J *et al*. Downregulation of the nonspecific and antigen-specific T-cell cytokine response in ankylosing spondylitis during treatment with infliximab. *Arthritis Rheum.* 48(3), 780–790 (2003).
74. Baeten D, Vandooren B, De Rycke L, Veys EM, De Keyser F. Effect of infliximab treatment on T-cell cytokine reponses in spondylarthropathy. *Arthritis Rheum.* 50(3), 1015–1016 (2004).
75. Vandooren B, Kruithof E, Yu DT *et al*. Involvement of matrix metalloproteinases and their inhibitors in peripheral synovitis and downregulation by tumor necrosis factor α blockade in spondyloarthropathy. *Arthritis Rheum.* 50(9), 2942–2953 (2004).
76. De Rycke L, Vandooren B, Kruithof E, De Keyser F, Veys EM, Baeten D. Tumor necrosis factor α blockade treatment down-modulates the increased systemic and local expression of Toll-like receptor 2 and Toll-like receptor 4 in spondylarthropathy. *Arthritis Rheum.* 52(7), 2146–2158 (2005).
77. De Rycke L, Baeten D, Foell D *et al*. Differential expression and response to anti-TNFα treatment of infiltrating versus resident tissue macrophage subsets in autoimmune arthritis. *J. Pathol.* 206(1), 17–27 (2005).
78. Sieper J, Baraliakos X, Listing J *et al*. Persistent reduction of spinal inflammation as assessed by magnetic resonance imaging in patients with ankylosing spondylitis after 2 years of treatment with the antitumour necrosis factor agent infliximab. *Rheumatology* (2005)(Epub ahad of print).
79. Baraliakos X, Listing J, Rudwaleit M, Brandt J, Sieper J, Braun J. Radiographic progression in patients with ankylosing spondylitis after two years of treatment with the tumor necrosis factor-alpha antibody infliximab. *Ann. Rheum. Dis.* (2005) (Epub ahead of print).

Affiliation

Dominique Baeten, MD, PhD
Division of Clinical Immunology & Rheumatology,
Academic Medical Center/ University of Amsterdam,
F4-218, Meibergdreef 9,
1105 AZ Amsterdam,
The Netherlands
Tel.: +31 205 662 171
Fax: +31 206 919 658
d.l.baeten@amc.uva.nl