Infliximab is a chimeric, monoclonal antibody against tumour necrosis factor \(\alpha\). 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 interrelated 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 besides 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-posit
Diabetes and sleep problems (54.1%) [4]. In addition, and stiffness (90.2%) but also fatigue (62.4%) important impact, not only of pain (83.1%) compared with the general population, with an withdrawal from work 3.1-times higher in AS approximately 16% higher and 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 sulfasalazine as a disease-modifying, antirheumatic drug (DMARD), but this therapy has no proven effect on axial inflammation. Preliminary studies suggest a possible beneficial effect of pamidronate and thalidomide on axial symptoms [8–10], but this remains to be confirmed in placebo-controlled studies.

Taked 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 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 successfully 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, placebo-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 evaluation 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 hour 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 approximately 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 metabolism 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 occurred 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 BASDAI50 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.

Treated 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<sub>50</sub> 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 occurrence 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 occurring 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 occurring 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 occurred in both groups at the same frequencies. In ASSERT, upper respiratory tract infections occurred 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 occurring 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 pustulosis, 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 insufficient 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 (BASDAI50) [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 occurring 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 management 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 [52,62], 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 structural 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 subjective 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
Infliximab – DRUG PROFILE

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.

37. 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.
39. 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.
**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.


**Extending the previous report, successful 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.


65. Brandt J, Haibel H, Reddig J, Sieper J, Braun J. Successful short-term treatment of severe undifferentiated spondyloarthropy...


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