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# Infliximab in the treatment of active and severe ankylosing spondylitis

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**Key words:** Therapy of ankylosing spondylitis, tumor necrosis factor- $\alpha$ , infliximab, etanercept.

## ABSTRACT

*For treatment of the spondylarthropathies (SpA), of which ankylosing spondylitis (AS) is the prototype, there is no effective disease modifying treatment available. In contrast to rheumatoid arthritis (RA), few studies have been performed on the treatment of patients with AS with disease modifying anti-rheumatic drugs, none of which have proved clearly effective in axial disease. Many patients with AS carry a heavy burden of disease and AS itself is responsible for direct and indirect socioeconomic costs. To find an effective treatment for severe ankylosing spondylitis is therefore thought to be an unmet medical need.*

*In the last four years several pilot studies and recently a few randomised controlled trials have raised good evidence that TNF $\alpha$  blockade is very effective in AS and other SpA. Disease activity, function and quality of life improved upon treatment with TNF $\alpha$  blockers. Thus, biologicals seem to represent a major breakthrough in the treatment of AS and other SpA. Side effects similar to those observed in RA treatment occur. But there is furthermore a need for safety data for long-term treatment with biologicals over several years. In the light of the high costs and the unknown long-term side effects, a definition for patients who might be candidates for such a treatment is needed.*

*This article gives detailed information about current experience with the new treatment options in active and severe AS with anti-TNF $\alpha$  therapy.*

## Introduction

At present, treatment options for patients with severe and active ankylosing spondylitis (AS) are therefore few. Many of them carry a heavy burden of disease, which does not seem to differ much from rheumatoid arthritis (RA), although it lasted longer (1).

Quality of life is reduced in many of these patients (2). The disease itself is responsible for substantial direct and indirect socioeconomic costs (3). Treatment of severe and active ankylosing spondylitis is therefore thought to be an unmet medical need.

Anti-tumor necrosis factor (TNF) therapy with the monoclonal antibody infliximab was shown to be highly effective in patients with RA (4). However, this disease is pathogenetically distinct from AS. Crohn's disease (5) and the arthritic symptoms (6) known to be associated with inflammatory bowel diseases (IBD) can also be effectively treated with anti-TNF treatment. Since patients with Crohn's disease can develop AS and many patients with idiopathic AS have lesions in the intestine that resemble those seen in Crohn's disease, spondylarthropathies (SpA) has been associated with chronic IBD. In addition, anti-TNF agents seem to work also in patients with psoriatic arthritis (7-9). However, not all chronic inflammatory diseases improve on infliximab therapy: multiple sclerosis, for example does not (10). Furthermore, only half of the patients with RA who were treated in large trials showed significant benefit on anti-TNF treatment (4).

Taking advantage of a CT-guided sacroiliac biopsy technique we have shown that TNF is expressed in inflamed sacroiliac joints of patients with AS (11). Taken together, there was reason to assume that infliximab might be an effective agent for the treatment of active and severe AS.

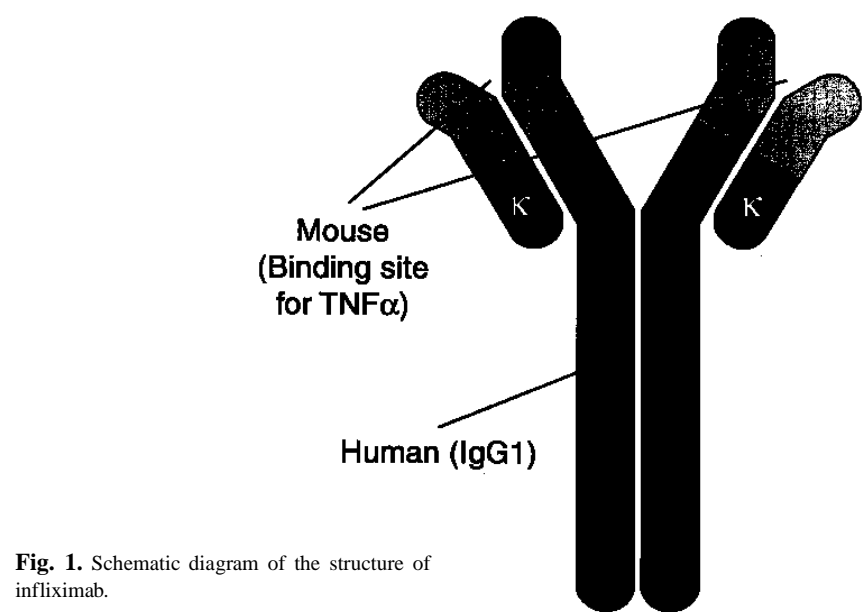
## Open pilot studies with infliximab in the treatment of active AS

In 1999 we conducted the first small pilot study to investigate the assumption that the administration of multiple infusions of infliximab (Fig. 1) (Remicade®) at 5 mg/kg per dose have a beneficial effect on the course of active

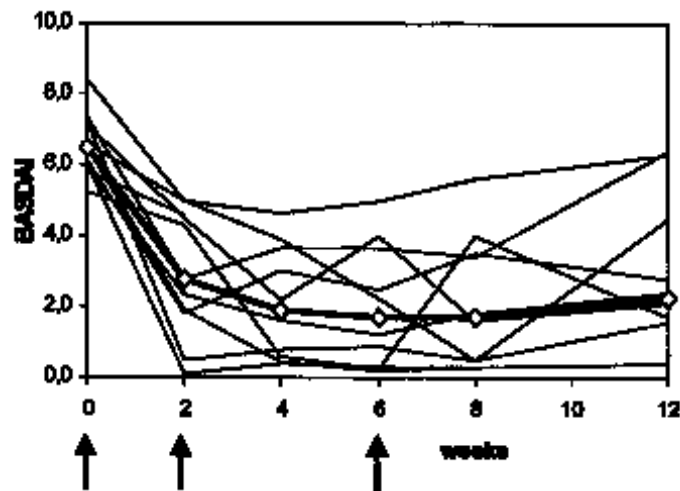
and severe AS (12). Eleven consecutive patients with a median disease duration of 5 years (range 0.5-13 years) who fulfilled the modified New York criteria for AS (13) were included in the trial. These eligible patients had active disease as defined by a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI, 14) score  $> 4$  (0 no activity, 10 strong activity) and a pain score  $> 4$  on a 0 to 10 numeric rank scale (NRS) on to occasions before baseline. Their mean age was 36 years (range 27-56 years), the median disease duration was 5 years (range 0.5-13 years) and ten patients had elevated C-reactive protein (CRP) values ( $> 6$  mg/l), in 3 patients documented several times over at least 1 year. Five patients had AS-relevant radiologic changes of the vertebrae. All patients received infusions with infliximab, an antibody to TNF (cA2, Remicade, Essex Pharma, Munich, Germany), a neutralising chimeric monoclonal antibody of IgG1 isotype (Centocor, Malvern, PA, USA) at week 0, 2 and 6. At that time a dosage of 5mg/kg was chosen for treatment of patients with AS because in patients with RA 3mg/kg were, on the long run, somewhat less effective than 10mg/kg (4) and we had thought that higher doses are necessary to treat spinal inflammation.

Improvement of 50% in disease activity (BASDAI), physical function (BASFI; 15), and pain scores was documented in 9 of 10 patients; the median improvement in the BASDAI after 4 weeks was 70% (range 41 – 94%; see Fig. 2). The median CRP level decreased from 15.5 mg/liter (range  $< 6$  – 90.8) to normal. There was an improvement in quality of life in all 9 SF-36 concepts (16); the improvement was significant for 6 concepts. One patient withdrew from the study due to the occurrence of urticarial exanthema after the first infusion. Our findings in this pilot study strongly indicated that infliximab is very efficacious in the treatment of active AS.

To get an idea of how long infliximab suppresses disease activity, our open pilot study was extended by 3 additional infusions of 5 mg/kg which were only given if the patients had a disease



**Fig. 1.** Schematic diagram of the structure of infliximab.



**Fig. 2.** Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) before during and after treatment of patients with active ankylosing spondylitis with 5 mg/kg infliximab. Each thin line represents the course of BASDAI values of an individual patient; the bold line represents the median of all patients. Arrows indicate the time of infusion.

relapse (17). The relapse was defined as a BASDAI score 80% of the value obtained on day 0 before administration of the first infusion and 60% to get a 5th and 6th infusion.

Ten patients were enrolled in this one-year extension of the study. Four patients dropped out prior to the end of the one-year extension. Two of the four had allergic reactions occurring after the 6th infusion; one of the latter developed high-titer antinuclear antibodies (ANAs) and self-limited symmetric arthralgias. In 1 patient, the AS remained in remission after the 3 loading-dose infusions for now 2 years. The fourth

patient was lost to follow up after the fifth infusion. During the observation period no other serious adverse event or serious infection occurred.

The results showed that the improvement induced by a loading regimen of three infusions of infliximab lasted about 7 weeks before the first symptoms reappeared (Fig. 3). The improvement after the loading regimen lasted longer (median 12 weeks) than after the 3 additional single infusions (median 6 – 8 weeks), despite the lower cut-off used to define relapse. These findings have been taken into account in terms of the dosage used in our still-

ongoing placebo controlled trial, in which 6-week intervals for infusion of infliximab are being used to maintain suppression of disease activity.

In the meantime, there are several open label studies on infliximab in AS (18 - 23). In a Belgian study, 21 spondylarthropathy (SpA) patients including 11 with AS were treated with infliximab with a similar dose regimen but the patients had a longer disease duration (15 years) and the time intervals between the infusions were longer (14 weeks). The spinal and peripheral joint symptoms of all SpA patients improved significantly (18, 19). In Canada there were 24 AS (20), in France 50 AS (21) and in Spain 42 SpA patients (22) who were successfully treated with infliximab, all with a similarly good response in about 80% of the patients. Of interest, in the French study, the bone mineral density of 26 patients with SpA (21 men, 5 women, mean age 40 years, mean disease duration 18 years) increased by  $3.3 \pm 5.5\%$  ( $-6.1, 23.7$ ) at the lumbar spine ( $p < 0.002$ ), and  $1.9 \pm 3.1\%$  ( $-4.9, 10.3$ ) at the femoral neck ( $p < 0.008$ ) after 6 months of infliximab therapy (23).

### Randomized controlled trials with infliximab in the treatment of active AS

The results of the pilot studies were the basis for our placebo-controlled German multicentre trial over 3 months in 70 AS patients (24) with an open extension phase for another 9 months. Patients received infusions of 5 mg/kg infliximab or placebo at week 0, 2, 6 and were observed until week 12. To be included, patients had to fulfil the modified New York criteria for AS (13) and had to have severe and active disease defined by the BASDAI  $\geq 4$  and spinal pain  $\geq 4$  on a 10 cm visual analogue scale.

In this study we could confirm the very good efficacy shown in the open studies: 53% of patients on infliximab had a regression of disease activity assessed with the BASDAI index at week 12 of at least 50% compared to 9% of patients on placebo ( $p < 0.0001$ ; Fig. 4). Function (BASFI) and quality of life (short form 36) also improved sig-

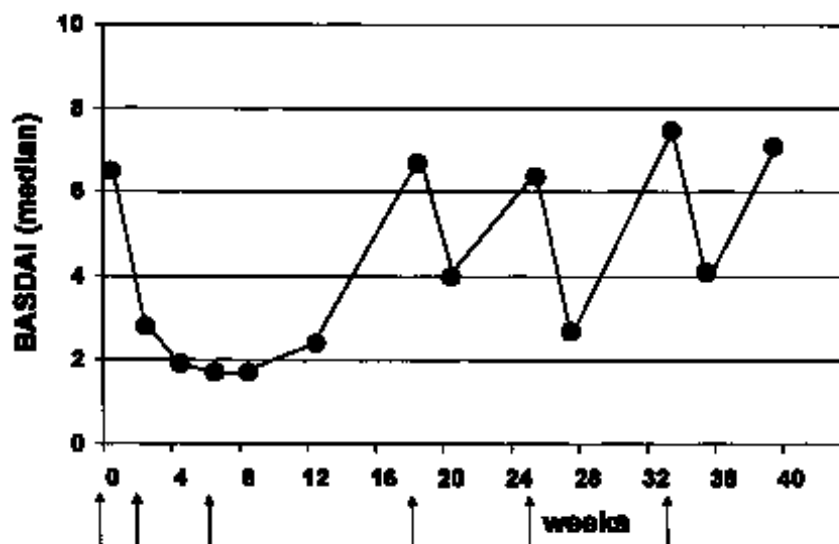


Fig. 3. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores of patients with active ankylosing spondylitis during 36 weeks of treatment with infliximab administered in 5 mg/kg infusions. Arrows indicate the times of infusion.

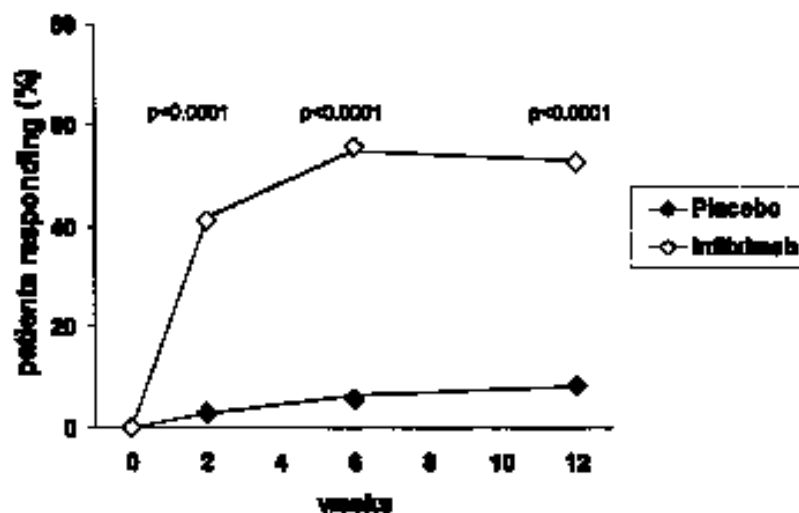


Fig. 4. Percentage of patients with active ankylosing spondylitis responding to therapy with 5 mg/kg infliximab or placebo measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) on the 50% improvement level. p values were calculated by Fisher's exact test.

nificantly on infliximab but not on placebo ( $p < 0.0001$  for function and  $p < 0.0001$  for the physical component score of the SF36, respectively). All individual items of the BASDAI such as fatigue, spinal pain, peripheral joint pain, entheses pain, and morning stiffness improved significantly in the infliximab group compared to the controls (data not shown). Infliximab reduced also the mean number of swollen joints (0.9 at baseline to 0.2 at week 12) and enthesitic regions (1.7 at baseline to 0.7 at week 12) in these patients. Non-steroidal anti-inflamma-

tory drugs (NSAIDs) could be reduced to more than 50% of the baseline value in 56% of the patients on infliximab and were completely stopped by 41% of these patients. So infliximab lead to a relevant reduction of NSAID intake and reduced the risk of their gastric and renal side-effects in patients who normally need continuous treatment with these drugs. Furthermore we used new criteria proposed by the "assessment in AS working group" (ASAS) for response on a 20% and 50% level and for partial remission (25). The differences between the two treatment

groups became even clearer when ASAS criteria were used compared to a similar reduction of disease activity of at least 20%, 50%, and 70% of the BASDAI index (data not shown). A clear response was seen similar to the RA trials also in the acute phase reactants. For example, the mean CRP level in the infliximab group dropped from 24 mg/L to normal at week 12 whereas no change occurred in the placebo group ( $p < 0.0001$ ). In subgroup analysis although the numbers of subgroups were small, those patients with high concentrations of CRP ( $> 10\text{mg/L}$ ) benefited more clearly from treatment, suggesting that these patients should be preferentially considered for infliximab treatment, a finding which has to be confirmed in future studies. Preliminary results from imaging follow ups with spinal magnetic resonance imaging (MRI) assessing both acute and chronic spinal changes, suggest a significant effect of infliximab on disease progression on this basis. Taken together, these data strongly suggest a major breakthrough in the short term therapy of severe AS.

Concerning side effects one serious adverse event in the infliximab group was generalised tuberculosis in the lymph nodes in one patient after the third infusion. TNF is a key cytokine for fighting microbes, especially intracellular bacteria. Thus, as in RA, infections such as tuberculosis are rare, but a possible risk (26). Infections of the upper respiratory tract in general did not differ between the groups. The other two serious adverse events that occurred in patients treated with infliximab were a transient allergic granulomatosis of the lung and an uncomplicated leucopenia (minimal leucocyte count  $2.6 \times 10^9$  per L after the third infusion).

In order to investigate whether infliximab therapy has long-term efficacy in patients with active and severe AS an open extension has followed after week 12 with an extra saturating dose at week 14 for the previous placebo group. Thereafter infusions were given regularly every 6 weeks for all patients until week 54. Recently, first results are available (27). Six weeks after the

initially placebo-treated patients had switched to infliximab they reached similar rates of 50% BASDAI improvement: 49% for the former placebo group compared to 56% for the infliximab group (n.s.). This magnitude of improvement of disease activity was sustained until week 54 with a persistent regression in every outcome measure assessed. Significant adverse events leading to discontinuation in the open extension occurred in another 9 patients: 3 cases of transient symmetric polyarthritis with development of antinuclear antibodies, 1 case of skin lupus, elevation of liver enzymes, herpes zoster and 2 infusion related reactions. In conclusion the results of the open extension showed that treatment with infliximab is very efficacious in patients with active AS over one year.

Very recently, a second randomized double-blind study from Belgium (28) with 40 patients with different subtypes of active SpA, including 19 with AS, 18 with psoriatic arthritis and 3 with undifferentiated spondylarthropathy (uSpA) were treated with the same regimen for three months as in our study (24). The primary outcome measure were the median patient and physician global which showed an impressive improvement of 73% and 76% (67 and 67.5 to 18 and 16.4, respectively). Other assessments for both peripheral and axial disease also showed significant improvements in the infliximab group, but not in the placebo group. As in our trial one patient developed disseminated tuberculosis after the third infusion. Together with the results of the previous open trials (12, 17–23, 29), they indicate that infliximab is highly effective in reducing signs and symptoms in this disease group as a whole.

Regarding the optimal dosage of infliximab in SpA only limited data are available. In a small open study we found the dose of 5 mg/kg superior to 3 mg/kg in 6 patients with uSpA (30). The optimal dosage has to be investigated in future studies.

Studies on etanercept in the treatment of AS have also been conducted (30–35) and are discussed in other chapters of this supplement. Our own experi-

ence with this treatment suggests that etanercept is indeed also very effective in the treatment of AS patients.

## Summary and conclusions

Especially for spinal symptoms of the SpA, of which AS is the prototype, there is no effective disease modifying treatment available. The new TNF-blockers have been proven highly effective in improving the spinal symptoms but also the extra-spinal manifestations of the SpA. Although a direct comparison between RA and AS has not been performed, there is good clinical evidence that TNF-blockade is more effective in AS and other SpA compared to RA. This has also to be seen on the background that 60–80% of patients with active RA can be sufficiently treated with currently available disease modifying anti-rheumatic drugs (DMARDs) while this is not the case for AS. Side effects, mainly infections and allergic reactions, occur similar to those observed in RA treatment. But there is further a clear need for safety-data in case of long-term treatment with biologicals over several years. Currently, there is no reason to combine TNF-blockers with another DMARD for the treatment of AS, mostly because these DMARDs are not effective. Thus, TNF-blockers seems to be a major breakthrough in the treatment of AS and other SpA. Especially in the light of the high costs and the unknown long-term side effects, the patients who are primary candidates for such a treatment have still to be defined. Furthermore, future studies have to show whether these biologicals not only suppress inflammation but also prevent long-term bony damage.

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