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Infliximab therapy in ankylosing spondylitis: an observational study

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Key Words: Ankylosing spondylitis; Infliximab; Drug survival; BASDAI; ASAS.
Objective: To investigate the efficacy, toxicity, and drug discontinuation in an observational study of patients with ankylosing spondylitis (AS) treated with infliximab.

Methods: Thirty-five AS patients were investigated in this study between June 2001 and December 2003. All patients fulfilled the modified New York criteria of AS. Patients entering into the study had negative tuberculin skin test, were fully informed about the treatment regimen and were followed at predefined times according to a standardized protocol. Infliximab was given intravenously in a loading dose of 5 mg/kg/weight at weeks 0, 2, 6 and every 8 weeks thereafter. Data concerning infliximab tolerability, adverse events, interval and drug discontinuation, were all recorded. In addition, the clinical improvement according to the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Assessment Study group (ASAS) 20%, 40% and ASAS 5/6 response criteria were also recorded.

Results: There were 34 male and one female with a mean age of 42.5 (SD=12.6) years and mean disease duration of 14.5 (SD=8.0) years. Thirty-one patients were HLA-B27 positive. After the first year of treatment, 20 (57.1%) patients achieved the BASDAI 50% response criteria, while the ASAS 20% and 40% were reached by 25 (71.4%) and by 23 (65.7%) patients respectively, and ASAS 5/6 was attained by 18 patients (51.4%). After the second year of treatment, the BASDAI 50% response criteria were achieved by 11 (31.4%) patients. The ASAS 20% was reached by 14 (40.0%) patients, the ASAS 40% by 11 (31.4%), while the ASAS 5/6 by 9 (25.7%) patients. This clinical improvement was associated with an improvement of the Bath Ankylosing Spondylitis Functional Index (BASFI) and a reduction of C reactive protein levels. After the first year of treatment, the “survival rate” of infliximab was 94%, while this rate was 89% after the second year. The treatment was well tolerated with mild adverse events. Three patients discontinued the study. One discontinued because of an immediate hypersensitivity reaction after the third infusion, and two more patients because of drug inefficacy.

Conclusion: Infliximab was effective, safe and well tolerated in patients with AS. After two years of treatment, infliximab survival was 89%.

Running Title: Infliximab therapy in AS.
Ankylosing spondylitis (AS) is a chronic inflammatory disease affecting primarily the axial skeleton, leading to functional disability and premature death.[1] Extensive rationale exists for the use of tumor necrosis factor alpha (TNF-alpha) inhibitors in AS, and a growing body of evidence demonstrates the clinical efficacy of this approach.[2] One of them is infliximab. The efficacy and safety of infliximab has been established in a number of short, open label and randomized controlled trials in AS patients.[3-7] As in rheumatoid arthritis (RA), treatment of AS must be continued because the disease activity returns a few weeks after infliximab is stopped. On the other hand, serious adverse events, including predisposition to bacterial infections, reactivation of tuberculosis, and others, are some of the disadvantages of infliximab therapy.

Thus, rheumatologists and physicians should know: (i) how long infliximab is effective and safe; (ii) which are the most frequent and hazardous adverse events. To address the above questions, we investigated infliximab efficacy, drug survival and reasons for drug discontinuation during the disease course in an observational study of patient with refractory AS.

MATERIALS AND METHODS
From June 2001 until December 2003, 41 AS were recruited. All patients fulfilled the modified New York criteria of AS.[8] Patients were fully informed about the treatment regimen and were followed at predefined times according to a standardized protocol. Infliximab was given intravenously (infusion time >2 hours) in a loading dose of 5 mg/kg at weeks 0, 2, 6 and every 8 weeks thereafter. If the therapeutic response was insufficient, then the interval was shortened to 6 or to 4 weeks. The exclusion criteria have been reported elsewhere.[7]

Data concerning infliximab efficacy, tolerability, concomitant therapy, adverse events and discontinuation were all recorded. Data on clinical improvement according to the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI),[9] as well as the Ankylosing Spondylitis Assessment Study group (ASAS) 20% and 40% and ASAS 5/6 response criteria,[10] were also recorded. All patients had a last follow-up by June 2004.

Definitions
Active disease was defined if patients had BASDAI ≥40/100 [9] and C-reactive protein (CRP) ≥10 mg/l (normal value <6 mg/l). Refractory disease was defined by the failure of at least two non-steroidal anti-inflammatory drugs (NSAIDs) during a single three-month period, failure of intra-articular steroids if indicated, and failure of sulfasalazine in patients with peripheral arthritis. A response to treatment according to ASAS criteria requires improvement of at least 20% and absolute improvement of at least 10 units on a scale of 0-100 in three of the following four domains: a) patient’s global assessment of the disease activity, b) pain, c) function (in this study the Bath Ankylosing Spondylitis Functional Index [BASFI] score),[11] and d) inflammation (in this study the mean duration of the morning stiffness related with the BASDAI, and Visual Analogue Scale 100 mm [VAS] scores) and the absence of deterioration by 20% and by 10% of units in the four domains.[12]

Lack of efficacy was defined as patients not fulfilling the BASDAI 20%, as well as the ASAS 20% response criteria. Failure of drug treatment was defined as patients who stopped receiving the drug for more than two months because of lack of efficacy. Adverse drug reactions were defined as patients who had reactions that required infliximab permanent discontinuation due to life threatening conditions, or because of intolerability. Discontinuation was decided when patients presented failure of drug treatment, or experienced adverse drug reactions.

Monitoring
A complete blood count with differential and platelet count, as well as serum values of liver enzymes, bilirubin, albumin, glucose, creatinine and urine analysis were obtained before treatment and at each patients’ visit. Finally, blood serum from patients were stored for the measurement of antibody profile.

Statistical analysis
Standard methods of survival analysis (Kaplan–Meier) were used, in which infliximab termination due to side effects and/or lack of efficacy, and/or failure of drug treatment were taken as the endpoints.
RESULTS
During the recruitment period 41 AS patients were enrolled. Of these, one refused treatment and 5 were excluded from the study. Thus, 35 patients were investigated. The demographic, clinical and laboratory data at entry are shown in the table.

<table>
<thead>
<tr>
<th>Table</th>
<th>Clinical and laboratory data of patients with ankylosing spondylitis treated with infliximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>35</td>
</tr>
<tr>
<td>Male/Female</td>
<td>34/1</td>
</tr>
<tr>
<td>Age (years) (mean ±SD)</td>
<td>42.5 (12.6)</td>
</tr>
<tr>
<td>Disease duration (year) (mean ±SD)</td>
<td>14.5 (8.0)</td>
</tr>
<tr>
<td>Peripheral arthritis n (%)</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>History of uveitis n (%)</td>
<td>11 (31.4)</td>
</tr>
<tr>
<td>Methotrexate intake n (%)</td>
<td>3 (8.6)</td>
</tr>
<tr>
<td>Sulfasalazine intake n (%)</td>
<td>3 (8.6)</td>
</tr>
<tr>
<td>Prednisone intake (5 mg/day) n (%)</td>
<td>4 (11.4)</td>
</tr>
<tr>
<td>NSAIDs n (%)</td>
<td>35 (100)</td>
</tr>
<tr>
<td>HLA-B27 n (%)</td>
<td>31 (88.6)</td>
</tr>
<tr>
<td>BASDAI (mean ±SD)</td>
<td>57.23 (18.5)</td>
</tr>
<tr>
<td>CRP (mg/l) (mean ±SD)</td>
<td>25.6 (17.0)</td>
</tr>
</tbody>
</table>

NSAIDs, Non steroid anti-inflammatory drug intake; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C reactive protein.

All patients had axial disease, two patients presented with peripheral arthritis and 11 had a history of anterior uveitis. All patients had active disease as this was evaluated by the high BASDAI score and high levels of CRP (table). The mean duration of morning stiffness related to BASDAI was 60.9±27.7 and that related to VAS was 65.0±28.0. The study profile and the response to treatment according to the BASDAI and ASAS criteria are shown in fig 1. After two years of infliximab therapy a significant number of patients achieved the BASDAI and ASAS response criteria. In addition, infliximab therapy resulted in a rapid and significant improvement in BASDAI and BASFI scores and a durable response for 24 months. This clinical and functional improvement was associated with the reduction of acute phase reactants as measured by CRP levels (fig 2). No correlation of BASDAI and CRP was found at baseline and after treatment. Furthermore, no significant improvement in spinal mobility, as measured by Schober test, was noted. After the first year of treatment, the “survival rate” of infliximab was 94%, while this rate was 89% after the second year. The treatment was well tolerated with mild adverse events. Eleven patients (31.4%) experienced adverse events, mainly infections and allergic drug reactions. All these adverse events, except one, resolved without sequelae. One patient withdrew from the study due to an immediate hypersensitivity reaction after the third infusion, and two more patients had to stop because of drug inefficacy. The first was a male with a long-standing history of axial disease and hip involvement, who discontinued the study after the sixth infliximab infusion. The second was also a male with axial disease, and severe scoliosis and kyphosis, who discontinued the study after the ninth infusion. These two patients had no response to treatment since the beginning, thus the interval between infusions had been shortened from 8 to 6 weeks. The first patient’s interval had been shortened after the fourth infusion, while the second after the fifth. No further improvement was achieved. Four more patients’ interval between infusions had been shortened from 8 to 6 weeks. These patients initially responded well to infliximab therapy, however, 10 days before the next infusion they experienced neck pain and stiffness. In one patient the interval had been shortened after the 8th infusion, while in 3 patients after the 10th infusion. All responded well to this treatment strategy. Finally, 8 (22.8%) patients developed positive antinuclear antibodies, with a fine speckled pattern, in titers ranging between 1/160 and 1/640. No other antibodies were detected.

DISCUSSION
AS is a chronic inflammatory rheumatic disease affecting primarily young men, with an estimated prevalence of 0.15-0.8%.[13] TNF-alpha inhibitors have been shown to be highly efficacious in
patients with active AS. Several placebo controlled and open trials have shown a dramatic response of active AS to infliximab.[3-7] As in RA, the treatment of AS must be continued because the disease activity returns a few weeks after infliximab is stopped. On the other hand, serious adverse events may occur during infliximab therapy. One main finding of the present study, during the observation period of 2 years, is that infliximab was effective as measured by the BASDAI 50% and ASAS 20% and 40% and ASAS 5/6 response criteria. The second finding of our results was the significant functional improvement as this was evaluated by the BASFI score, which was associated with the reduction of acute phase reactants. The third point is that 89% of our patients continued to have beneficial effects after the second year of treatment.

The efficacy and safety of infliximab and its survival in the present study of AS patients is greater than expected. The absence of serious adverse events is probably attributed to the strict inclusion criteria used. The drug survival for infliximab therapy in AS has not been reported so far. Loss of infliximab survival may be explained by the generation of human antichimeric antibodies (HACA). These antibodies appeared to be associated with lower serum infliximab concentrations, and may be related to a shorter duration of response after repeated infliximab doses, as reported for RA patients. Concomitant administration of methotrexate appears to reduce HACA formation. However, in our study only 3 patients were taking methotrexate. Another point to take into consideration is the higher infliximab dosage used, as compared to RA patients. Formation of HACA may be inversely related to the infliximab dose. HACA were found in 53, 21 and 7% of patients with RA receiving infliximab 1, 3 or 10 mg/kg respectively, 12 weeks after the last of five infusions of infliximab.[14] It has been suggested that higher doses of infliximab may be associated with immunological tolerance.[14] This may explain the high “survival rate” of infliximab in our AS patients and its beneficial effects for a period of 2 years. Limited data are available regarding the optimal dosage of infliximab in spondyloarthropathies. In a small study it showed that the dose of 5 mg/kg was superior to 3 mg/kg.[15] However, the lower dosage of infliximab seems to work as well.

The results of this observational study suggest that infliximab therapy was effective, safe, and well tolerated in patients with AS. The survival of infliximab after 2 years of therapy was 89%. However, further long-term, controlled and observational studies, with large numbers of patients, are needed to validate our results.
REFERENCES


FIGURE LEGENDS

**Figure 1** Study profile and response to treatment. The lateral arrows represent the patients who did not meet entry criteria or discontinued the study. The middle arrows represent the patients who continued infliximab therapy but were not followed-up for a full 1 or 2 years. Percentages of response are calculated on the basis of 35 patients presented at entry.

**Figure 2** Improvement of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) and reduction of C reactive protein (CRP).
Figure 1

41 patients screened

3 positive tuberculin skin test
1 congestive heart failure
1 restrictive lung disease
1 refused

35 patients studied

6 patients

1 immediate hypersensitivity reaction

27 patients 12 months

BASDAI 50%: 20 (57.1%)
ASAS 20%: 25 (71.4%)
ASAS 40%: 23 (65.7%)
ASAS 5/6: 18 (51.4%)

12 patients

1 drug inefficacy

14 patients 24 months

BASDAI 50%: 11 (25.7%)
ASAS 20%: 14 (40%)
ASAS 40%: 11 (31.4%)
ASAS 5/6: 9 (25.7%)
Figure 2