

Multicenter open-label study with infliximab in active ankylosing spondylitis over 28 weeks in daily practice

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Abstract

Objective

The aim of this study was to prospectively investigate the therapeutic efficacy and safety of infliximab therapy in NSAID-refractory AS patients, with special emphasis on impact on quality of life in daily practice.

Patients and methods

101 AS patients with active disease (mean Bath ankylosing spondylitis activity index (BASDAI) 6.3, range 4.0-9.8) were enrolled in an open label study. Infliximab 5 mg/kg body weight was administered intravenously at week 0, 2, 6, 12, 18 and 24 followed by a final assessment at week 28. Clinical assessments included quality of life (SF-36, primary endpoint), disease activity (BASDAI), function (BASFI), metrology (BASMI), patients' and physicians' global, pain, work productivity (WPAI) and CRP.

Results

Using an intention to treat (ITT) analysis, the mean SF-36 physical health component improved from 27.6 at baseline to 40.9 at study end ($p < 0.001$), the mean SF-36 mental health component improved from 44.4 at study entry to 53.0 at final assessment ($p < 0.001$). The Assessment of AS (ASAS-) 20 short-term improvement criteria were reached by 80.2% of patients, ASAS 40 by 60.4% and the ASAS criteria for partial remission were reached by 27.7% of patients. A BASDAI 50% improvement was found in 66.3% of patients. Comparable significant improvements were found for mean BASDAI; BASFI, BASMI, patients' and physicians' global, general pain, CRP and WPAI. 11.8% of patients stopped therapy because of side effects.

Conclusions

Infliximab showed high efficacy and safety when used by non-specialised rheumatologists in daily practice.

Key words

Infliximab, ankylosing spondylitis, open-label trial, daily practice.

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Conflict of interest:

Dr. H. Haibel has received honoraria for
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Dr. M. Rudwaleit has received honoraria
for presentations at scientific symposia,
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and financial support for scientific studies;

Dr. S. Hildemann is employed by
Essex-Pharma, the distributor of infliximab
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Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease, which primarily affects the sacroiliac joints (SIJ) and spine in young adults between 20 and 40 years of age. Similar to rheumatoid arthritis (RA) patients, AS is characterized by pain, functional impairment and fatigue which leads to reduced quality of life, high morbidity (1, 2), and loss of work productivity (3). Treatment options are limited in AS (4, 5). Until recently, conventional therapy consisted of symptomatic non-steroidal anti-inflammatory drugs (NSAIDs) and physical therapy. Tumour necrosis factor (TNF)-alpha blocking agents have now been shown to be highly effective and well tolerated in patients with active AS (6-8). Initial studies were conducted with infliximab for this indication (9). The results were confirmed in two placebo controlled studies (7, 10) and infliximab has been approved for the treatment of AS in Europe and the US.

The aim of this study was to investigate the influence of therapy with infliximab over 24 weeks on quality of life, daily activities, and work productivity as well as on efficacy and safety when used in daily practice by rheumatologists in private practices.

Methods

Study design

A 28 week, prospective, multicentre (21 centres) open-label trial started in October 2002. One hundred and one patients (age 18-60 years) with AS according to the modified New York Criteria (11) were included. Inclusion required a Bath Ankylosing Spondylitis Disease Activity index (BASDAI) (12, 14), ≥ 4 and question 2 of the BASDAI for back pain ≥ 4 , despite adequate NSAID therapy. The use of concomitant corticosteroids and disease modifying antirheumatic drugs (DMARDs) were not allowed. Exclusion criteria included evidence of latent tuberculosis (negative chest x-ray during the last 4 weeks before study start and negative 10 IU Mendel Mantoux tuberculine (PPD) skin test), any uncontrolled concomitant disease, pregnancy, breast-feeding or relevant changes according

to clinical and laboratory examinations. Local ethical committee approval and informed consent were obtained prior to enrollment in the study. Patients received infliximab 5 mg/kg body weight at baseline, weeks 2, 6, 12, 18, 24, followed by a follow-up visit at week 28.

Clinical outcome assessments

Quality of life (SF-36) was primary endpoint (13). Secondary endpoints were disease activity (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) (12, 14), general and back pain on a numeric rating scale (NRS), patients and physicians global assessment (NRS), Bath Ankylosing Spondylitis Metrology Index (BASMI) (12, 14), C-reactive Protein (CRP), a 50% improvement in BASDAI, a 20% and 40% improvement according to the AS-assessments in SpondyloArthritis International Society (ASAS) for spondyloarthritis criteria (15), and ASAS partial remission (value of <20 on a 0-100 scale in each of the four ASAS domains). An exploratory endpoint was the work productivity and activity impairment (WPAI-SHP) questionnaire which is based on a questionnaire addressing the status of employment, hours missed at work during the last week because of AS, and how much the disease affected the productivity at work and daily activities (16). The work productivity impairment score measures how much the amount and type of work is impaired because of AS on a 0 to 10 numeric rating scale (0 = no impairment; 10 = maximum impairment).

Statistics

Statistics were performed as an intention-to-treat analysis, last observation carried forward (ITT-LOCF). The non-parametric Wilcoxon signed rank test was used to compare changes between baseline and after-treatment values. A paired *t*-test was used to compare outcomes within different subgroups. Statistical significance was determined as a two-sided $p < 0.05$.

Results

Of 134 patients screened, 101 participated in the treatment phase (for characteristics see Table I) and were analysed

Table I. Patient characteristics (ITT population).

Number of patients, n	101
Male / female	79 / 22
Mean age, years (range)	49.9 (21 – 67)
Mean disease duration, years (range)	15.5 (0.6 – 46)
BASDAI, mean (range)	6.3 (4.0 – 9.8)
HLA-B27 positive (%)	87.1%
History of uveitis (%)	27.7
Psoriasis (present or previous %)	13
IBD (present or previous %)	8
CRP > 10 mg/l (%)	59.4
Number of patients with history of DMARDs (%)	32
Number of patients with previous sulfasalazine (%)	18
Number of patients with previous methotrexate (%)	7

BASDAI: Bath ankylosing spondylitis disease activity index; IBD: inflammatory bowel disease; CRP: C-reactive protein; DMARDs: Disease modifying antirheumatic drugs.

Table II. Primary and Secondary outcome parameters in patients with active ankylosing spondylitis. Mean values.

Outcome parameter	Baseline	Week 2	Week 12	Week 24	Week 28
SF-36					
Physical sum score	27.6	33.0**	39.1**	39.2**	40.9**
Physical function	41.4	53.5**	60.5**	60.3**	64.1**
Physical role function	21.3	28.2*	64.6**	63.1**	69.1**
Physical pain	23.4	35.6**	57.5**	60.4**	62.9**
Vitality	31.3	39.8**	56.4**	56.2**	58.5**
Mental sum score	44.4	45.3**	52.5**	53.1**	53.0**
Emotional role function	57.7	59.7	86.1**	87.8**	86.5**
Social function	52.8	59.8*	76.0**	78.1**	78.5**
Mental well being	58.6	61.7*	73.0**	73.3**	75.1**
Perception of general health	37.5	47.7**	54.5**	55.1**	55.7**
WPAI					
Employed patients (%)	61.4	62.4	67.0	70.0	NA
Missing work hours	4	4	2	2	NA
Work productivity	5.2	3.7**	2.4**	2.3**	2.3**
Daily activities	6.3	4.6**	3.5**	3.3**	2.9**
BASDAI					
Summary Score BASDAI	6.3	4.0**	3.4**	2.9**	2.6**
Fatigue (BASDAI Q1)	6.7	4.8**	3.6**	3.3**	3.1**
BASDAI 50% ***	NA	33.7***	60.4***	58.4***	66.3***
ASAS criteria					
ASAS 20 ***	NA	57.4***	66.3***	80.2***	NA
ASAS 40 ***	NA	38.6***	50.5***	60.4***	NA
ASAS partial remission ***	NA	5.0***	25.7***	27.7***	NA
BASFI	5.9	4.5**	3.7**	3.5**	NA
BASMI	4.7	4.0**	3.4**	3.4**	NA
General pain	7.2	4.4**	3.5**	3.5**	2.8
Patient's global assessment	7.6	4.5**	3.7**	3.0**	NA
Physician's global assessment	6.7	3.8**	2.6**	2.4**	NA

ASA: Assessment in ankylosing spondylitis; BASDAI: Bath ankylosing spondylitis disease activity index; BASFI: Bath ankylosing spondylitis functional index; BASMI: Bath ankylosing spondylitis metrology index; SF-36: Short Form-36;

* $p < 0.05$, vs. baseline; ** $p < 0.001$, vs. baseline; *** % of patients; NA: not applicable.

within an ITT-LOCF. Of these 101 patients 12 patients dropped out before the end of the study because of side effects and one patient because he was lost at follow-up.

Primary endpoint

The SF-36, demonstrated a significant improvement in both the physical and the mental component (physical health: baseline 27.6 vs. 40.9 at week

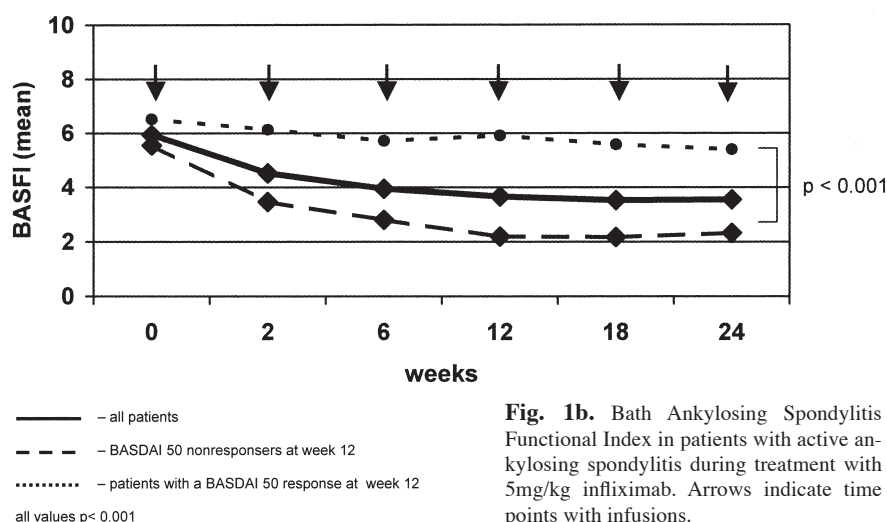
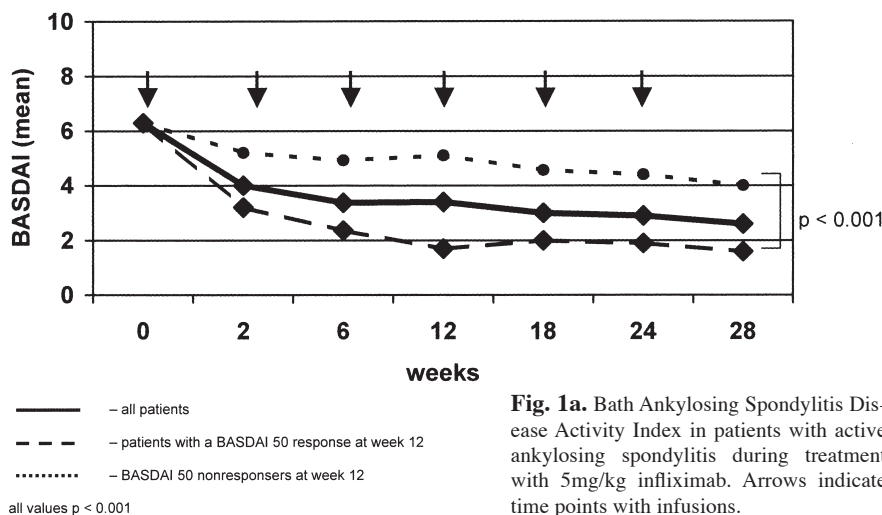
28, $p < 0.001$; mental health: baseline 44.4 vs. 53.0 after 28 weeks, $p < 0.001$). Likewise all subscales of the SF-36 improved significantly (Table II).

Secondary endpoints

For the different questions of the WPAI, at baseline 61.4% ($n=62$) of the patients had been employed compared to 69.3% ($n=75$) at visit 6 ($p < 0.001$). Of the initially 62 patients who were employed at baseline 4 patients did not work at study end (6.5%). The patients who were employed at study entry reported 4 missing work hours due to the disease during the past 7 days at baseline compared to 2 hours at study end ($p=ns$). There was a clear and statistically significant improvement on work productivity from 5.2 at baseline to 2.3 ($p < 0.001$) after 28 weeks and on patients' daily activities from 6.3 at baseline to 2.9 ($p < 0.001$) at study end (Table II).

The mean BASDAI decreased from 6.3 to 2.6 ($p < 0.001$) for the whole group of patients (Table II). Similarly, after 28 weeks a BASDAI 50% improvement could be observed in 66.3% of patients (Table II). Likewise, the ASAS response criteria confirmed the significant improvement at week 24 (80.2% ASAS 20, 60.4% ASAS 40 and 27.7% ASAS criteria for partial remission, Table II). For the other secondary outcome parameters see Table II and Figure 1.

Focussing on the subgroup of patients who reached a BASDAI 50 improvement at week 12 (69.4% of patients of the whole group) the mean BASDAI decreased from 6.3 at baseline to 1.6 at week 28 ($p < 0.001$) compared to the subgroup of patients who did not reach a BASDAI 50 improvement. In the latter group the mean BASDAI decreased only from 6.2 at baseline to 4.0 at week 28, but still reaching significance ($p < 0.001$) (Fig. 1a). It is of special interest that there was also a significant and considerable decrease of the BASFI from 5.6 to 2.2, $p=0.000$) (Fig. 1b) and even of the BASMI (from 4.3 to 2.7; $p=0.000$) in the BASDAI responder subgroup. In this responder group the physical component of the SF-36 also improved clearly (from 29 to 46, $p=0.000$), while this was not as clear



the mental part of the SF-36 (from 44 to 55, $p=0.000$). Similar differences could be observed when looked in the ASAS responder group (data not shown). Sixty-six patients (81%) who reached BASDAI 50 at week 6 also reached BASDAI 50 at study end and of the patients who did not reach a 20% improvement of their initial BASDAI at week 6 only one patient (5%) reached BASDAI 50 at study end.

When comparing the subgroup of patients who were employed at baseline with the subgroup of patients who were not employed, both had a similar BASDAI at baseline (6.00 vs. 6.64, $p=0.02$), but the BASFI was significant lower in the employed group (4.2 vs. 6.4, $p<0.001$). At study end patients who were employed at baseline had a significant lower BASDAI (2.1 vs. 3.4, respectively, $p<0.001$) and BASFI (2.7

vs. 4.9, respectively, $p<0.001$) compared to those who were not employed. For the SF-36, there was less improvement for the physical component (24 at baseline vs. 35 at study end, $p<0.001$) for patients who were unemployed compared to patients who worked (29.6 at baseline vs. 44.4 at study end, $p<0.001$). This difference could not be observed for the mental component (unemployed patients: 45 at baseline vs. 53 at study end; employed patients: 43 at baseline vs. 51 at study end, $p = ns$).

Safety: A total of 223 adverse events occurred in 76 patients (74.5%). An increase of liver enzymes was the most common side effect with 22 reported events followed by nasopharyngitis (20 events), headache (13 events), and diarrhoea (10 events).

Serious adverse events occurred in 12 patients (11.8%) and resulted in a

withdrawal from the study in 5 cases: allergic infusion related reactions in 2, pneumonia in 2 and toxic hepatitis in one patient. Further reasons for discontinuation of the study were: 4 additional patients with elevation of liver enzymes, 2 because of inefficacy and one unknown reason.

Discussion

In this 24-week, prospective, open-label trial with infliximab in 101 patients with active AS, given in daily practice in non-specialised rheumatological clinics and private practices, the quality of life in the majority of patients highly improved by therapy.

Measured by both the physical and the mental component of the SF-36, there was significant improvement at the final examination. This was similar to the results observed in the placebo controlled trial with infliximab (17) where also significant results for the physical and mental health after 24 weeks could be observed. In contrast, in the second placebo controlled trial with infliximab, the ASSERT study (10, 18), and the recent adalimumab trial in AS (19) there was no significant improvement for the mental component in the active groups after 24 weeks. Similarly, in a placebo controlled trial with etanercept (20) no significant improvement of the SF-36 was observed after 16 weeks of treatment, but there was efficacy for all subscales after 48 weeks. When compared with the age matched German database (21) the SF-36 for the physical health at baseline was highly impaired compared to the normal population (27.6 versus 51.0) in the present study but improved considerably (40.9). Interestingly in the present clinical trial patients started with a lower level for the mental component (44.4) than an age matched normal population (51.4), but after treatment the score for the mental component was even higher (53.0) after 28 weeks compared to the normal population (21).

With respect to effects on signs and symptoms, a BASDAI 50% improvement at week 28 was reached by 66.3% of patients. This is better than that observed in the registration trials with infliximab, where a response in the infliximab group

in 52.9% (7) and 51.0% (10, 18) of patients was seen. This observation is concordant with another open label trial with 50 patients showing an even higher improvement after 3 infusions (22), with an ASAS 50 response at week 16 in 86% of patients. But in contrast to the present study, only patients with elevated CRP levels were included suggesting that these patients are prone to a higher response rate. We recently reported that a BASDAI 50% response rate can be achieved in AS patients treated with TNF-blockers in 70% or more if selected for shorter disease duration, better function or elevated CRP (23, 24). Thus, these data suggest that a good or very good response can be expected in up to two-thirds of patients in daily clinical practice if the right patients are chosen for treatment.

It has been shown that the cost of AS increases with higher disease activity, functional impairment and reduced quality of life (25, 26). These factors also contribute to unemployment (3). In our study, work productivity improves significantly after 24 weeks of therapy with infliximab as shown by the single components of the WPAI-SHP score. Most of the patients were within an employable age between 18 and 60 but less patients were employed compared to AS patients with the same disease duration from the German Database (27). This is most probably due to higher disease activity and greater functional impairment in the AS patients included in our trial. The physical but not the mental component of the SF-36 was also significantly lower in unemployed in comparison to employed patients. Interestingly, there was a substantial increase in employment from 61.4% to 70% in patients before and after treatment. Among the group of patients who were employed at baseline there was a significantly higher improvement of BASDAI and BASFI compared to the group who were not employed at baseline indicating that employed patients might rank a similar level of efficacy higher. Also in the group of patients who had been employed at start of the study the missing hours at work during the past 7 days decreased by 50%. It was reported before that after one year

of therapy with infliximab there is a decrease in days of sick leave by more than 50% (28), which is in line with our results.

Our study confirms that infliximab given in a dose of 5 mg per kg body weight has a rapid onset of action and efficacy. This seems to be faster compared to the other two TNF-blockers etanercept and adalimumab (6, 29) although no head to head study between the drugs has been performed until now. The most likely reasons for this difference between the drugs at the start of treatment are the intravenous route of administration and the higher loading dose in case of infliximab treatment.

Recent recommendations on the treatment of AS with TNF-blockers suggest to continue treatment after 12 weeks only if a BASDAI 50 improvement or a decrease of at least 2 points of the BASDAI 0 – 10 scale was achieved (30). In this subgroup of patients with a BASDAI 50 improvement after 12 weeks there was a dramatic drop in both the BASDAI, BASFI (Figs. 1a and 1b) and even the BASMI which would correspond to a considerable increase in the quality of life (31, 32). Because it is only recommended to treat these patients long term with TNF-blockers future socioeconomical analyses should preferentially concentrate on this group.

Taken into account the high costs for TNF-blocker treatment, it would be helpful if such a decision about continuation/ discontinuation of treatment were made even earlier. Here we show that only 6% of patients not reaching BASDAI 20 after 6 weeks of treatment with infliximab (thus after 2 infusions) will reach BASDAI 50 improvement after 12 weeks, suggesting a decision might be made that early for AS patients treated with infliximab. However, a BASDAI 50 improvement after 6 weeks cannot be used as a cut-off because 10% still reached BASDAI 50 after 12 weeks who did not reach this level of improvement after 6 weeks. Furthermore, in the present study we observed an increase in the number of patients reaching a BASDAI 50 response later than 12 weeks in only 6% at week 28, supporting the current ASAS recommendations.

The number and pattern of adverse events and serious adverse events did not differ from those known from the placebo controlled trials (7, 10) indicating that therapy of AS patients with infliximab is also safe when given in non-specialised centres for biological therapy in AS.

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