Safety and Efficacy of Readministration of Infliximab After Longterm Continuous Therapy and Withdrawal in Patients with Ankylosing Spondylitis

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ABSTRACT. ***Objective.*** To analyze the safety and efficacy of the anti-tumor necrosis factor agent infliximab in patients with ankylosing spondylitis (AS) after discontinuation of longterm therapy over 1 year and readministration, using clinical and laboratory assessments including serum levels of antibodies to infliximab (ATI).

Methods. Altogether 42/43 patients with AS in a 3-year multicenter trial discontinued therapy after continuous treatment with infliximab (5 mg/kg/6 wks). Infliximab was only readministered in case of a clinical relapse [judged by Bath AS Disease Activity Index (BASDAI) and physician global assessment > 4]. ATI were measured at different timepoints. The primary outcome was safety, and efficacy outcomes were secondary.

Results. One patient dropped out after the eighth infusion after retreatment due to repeated local infections. ATI were detected in this patient only. No other relevant adverse events were observed. One patient remained in clinical remission without therapy for more than 1 year. The other 40 patients (97.6%) were reinfused because of clinical relapse. There was no correlation between ATI and clinical measures. BASDAI 50% responses were seen in 25 (63%) and partial remission in 12 (30%) patients. The mean (± SD) BASDAI score dropped from 6.0 ± 1.4 at the time of relapse to 2.6 ± 2.0, and the median C-reactive protein from 11.2 to 1.8 mg/l after 1 year (all $p < 0.05$).

Conclusion. Readministration of infliximab after discontinuation of longterm treatment was generally safe and efficacious. Ongoing remission after discontinuation was rare. There was only one patient with relevant adverse events. ATI were detected only in this patient, but there was no correlation to clinical data. Formation of ATI seems to be rare after longterm infliximab therapy in AS. (First Release Feb 1 2007; J Rheumatol 2007;34:510–15)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS | INFLIXIMAB | WITHDRAWAL
CLINICAL RELAPSE | REINFUSION | ANTIBODIES TO INFLIXIMAB

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Ankylosing spondylitis (AS) is a chronic immune-mediated inflammatory rheumatic disease that is recognized as the prototype of the spondyloarthritides (SpA). AS is characterized by inflammation in the sacroiliac joints, the axial skeleton, peripheral joints, entheses, the uvea, and other structures[1-3]. Agents targeting the proinflammatory cytokine tumor necrosis factor-α (TNF-a) such as infliximab and others have shown significant efficacy on disease signs and symptoms of patients with AS in randomized clinical trials and in short- and longterm followup studies[4-7]. The clinical results have been confirmed in studies using magnetic resonance imaging of the spine[8,9], and radiographic progression seems to be somewhat decelerated[10]. There is some evidence that infliximab needs to be continuously administered in 6 to 8 week intervals[7,11,12].

Biologic agents containing foreign protein such as the chimeric monoclonal antibody infliximab potentially induce antibody formation[13,14]; this may be associated with adverse

events such as infusion reactions[13-16]. An inverse dose-immunogenicity relationship has been reported in patients with rheumatoid arthritis (RA) and was previously observed in Crohn's disease (CD), indicating that higher doses of infliximab may reduce the incidence of anti-infliximab antibodies[17]. The induction of such antibodies may be reduced by concomitant administration of methotrexate (MTX)[18] and other immunosuppressive agents such as azathioprine[17]. The formation of anti-infliximab antibodies was recently quantitated in patients with CD who had been episodically treated with infliximab[14]. This resulted in a higher rate of infusion reactions and a loss of clinical efficacy. No data on formation of antibodies to infliximab (ATI) have been available in AS patients to date.

In a recent publication we reported for the first time on our experience with withdrawal of longterm infliximab therapy in AS patients[12], concentrating on the time to relapse and on predictive indicators. We now extend our report over more than 1 year and adds the results of ATI formation to correlate the data with the safety and efficacy of the readministration of infliximab.

MATERIALS AND METHODS

Patients and study protocol. All patients included in this study were participants of the extensions[5-7] of the initial placebo-controlled trial on the efficacy of infliximab in patients with active AS[4]. Briefly, all patients had been treated with infliximab over 3 years in a dosage of 5 mg/kg every 6 weeks[4-7]. After finishing the third year of the study (defined as timepoint 1, TP1), all patients (n = 43) had the opportunity to continue for another extension. Of those patients, only one discontinued due to personal reasons. All the other 42 patients were included in the next phase described here. According to the study protocol all patients gave informed consent and agreed to withdraw infliximab treatment after Year 3 of the previous extension. The study was approved by the local ethics committees of each participating center. All patients were then visited regularly in 6-week intervals after withdrawal. For assessment of disease flare, clinical relapse was defined as a Bath AS Disease Activity Index (BASDAI)[19] value ≥ 4 and physician's global assessment (PhysGA) ≥ 4 on a 0–10 numeric rating scale. In case of experiencing a clinical relapse (timepoint 2, TP2), each patient was reinfused with infliximab at 5 mg/kg every 6 weeks and was then followed up for the entire period of the study extension. Clinical data were collected similarly to the previous phases of the study at each visit. Data for the present analysis were collected 24 weeks (timepoint 3, TP3) and 48 weeks (timepoint 4, TP4) after infliximab reinfusion.

Outcome measures. The primary outcome measure was the safety of the patients over 1 year after readministration of infliximab (TP4). In addition, serum concentrations of ATI and the drug serum concentration at the timepoint of clinical relapse (TP2) were determined and correlated to the adverse events (AE) observed. An AE was defined as new onset of any clinical symptom the clinical investigator considered to be related to the treatment with infliximab. Infusion reactions were considered as an AE when they occurred during and/or within 2 h after infusion. The definition of a serious AE included any discontinuation of the study and all cases of hospitalization during the study.

Secondary outcome measures were the proportion of patients with a BASDAI 50% improvement at Week 24 (TP3) and Week 48 (TP4) after infliximab readministration, as compared to the timepoint of clinical relapse (TP2). In addition, the Assessments in AS (ASAS) Working Group criteria for remission[20] and the ASAS "5-out-of-6" improvement criteria[21] were evaluated at the same timepoints. Clinical indicators were assessed using validated measures for disease activity (BASDAI[19]), function (Bath AS Functional Index, BASFI[22]), metrology (Bath AS Metrology Index, BASMI[23]), and patient's (PatGA) and physician's (PhysGA) global assessment and pain (NRS-P) using a numerical rating scale (NRS) ranging from 0 to 10. The laboratory indicators C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured conventionally.

Assessment of antibodies to infliximab and level of infliximab concentration. As part of the study protocol, all patients were asked to have blood drawn for assessment of ATI at 2 timepoints: 6 weeks after withdrawal and at the time of clinical relapse, before infliximab readministration. The presence of serum infliximab was evaluated using a sandwich enzyme immunoassay. The limit of detection was 0.1 mg/ml of infliximab in serum[14]. ATI were assessed by measuring the optical density (OD) of antibodies in serum samples using a double-antigen enzyme immunoassay with infliximab serving as detection and capture reagent, as reported[14,24]. The cutoff for an ATI-positive serum sample was OD ≥ 0.250. As the presence of infliximab in serum samples can interfere with the detection of ATI, samples were classified as inconclusive when infliximab concentrations in patient sera were ≥ 0.1 µg/ml.

Statistical analysis. A completer analysis was performed. The paired t-test was applied to compare mean differences between timepoints. For skewed distributions (CRP and ESR) the corresponding nonparametric test (Wilcoxon test) was used. The McNemar test was used to compare frequencies between different points in time. Patients classified as inconclusive at the timepoint of clinical relapse were excluded from the analysis of correlation between ATI level and clinical outcome.

RESULTS

Overall, 41 of the 42 patients (97.6%) included at the timepoint of withdrawal of infliximab completed Week 48 after readministration. The baseline clinical characteristics of the 41 patients who were considered completers at TP4 are presented in Table 1. One patient dropped out after the 8th infliximab infusion after readministration due to repeated infections

Table 1. Mean baseline values (± SD) of all 40 patients that were considered as completers 48 weeks after infliximab readministration. All values, with exception of the BASMI, differed significantly ($p < 0.001$) between TP1-TP2, TP2-TP3, and TP3-TP4, but not between TP1-TP3, TP1-TP4, and TP3-TP4 ($p > 0.05$). TP1: withdrawal of infliximab treatment, TP2: timepoint of clinical relapse and readministration of infliximab, TP3: 24 weeks after infliximab readministraiton, TP4: 48 weeks after infliximab readministration. NRS-P: numerical rating scale for pain, PatGA: patient global assessment, PhysGA: physician global assessment.

Assessment	TP1	TP2	TP3	TP4
BASDAI	2.5 (± 1.9)	6.0 (± 1.4)	2.7 (± 1.9)	2.6 (± 2.0)
BASFI	2.9 (± 2.4)	5.7 (± 1.8)	3.2 (± 2.4)	3.2 (± 2.5)
BASMI	2.6 (±2.0)	3.4 (± 2.1)	3.0 (± 2.1)	2.7 (± 2.0)
CRP, median (range)	1.0 (0–19)	11.2 (0–126)	1.6 (0–22)	1.8 (0–17)
ESR, median (range)	8 (2–32)	24 (4–150)	6 (2–70)	11 (1–66)
NRS-P	2.7 (± 2.1)	7.2 (± 1.7)	3.1 (± 2.2)	3.0 (± 2.5)
PatGA (0–10 cm)	2.6 (± 2.1)	7.0 (± 1.6)	2.9 (± 2.1)	2.8 (± 2.3)
PhysGA (0–10 cm)	1.6 (± 1.2)	6.3 (± 1.9)	1.9 (± 1.4)	2.0 (± 1.9)
BASDAI 50% response (%)	22 (54)	—	25 (62.5)	25 (62.5)
ASAS 40% response (%)	26 (65)	—	26 (65)	25 (62.5)
5-out-of 6 response (%)	29 (72.5)	—	27 (67.5)	28 (70)
Partial remission (%)	14 (35)	—	10 (25)	12 (30)

(see Safety, below). Of the 41 completers, one patient was still in clinical remission 48 weeks after infliximab readministration. Thus, 40 patients were receiving infliximab treatment at the end of the study.

Safety. Analysis of ATI and infliximab concentrations. Blood was drawn in 27/42 patients (64.3%) and 35/42 (83.3%) patients 6 weeks after infliximab withdrawal (TP1) and at the time of clinical relapse (TP2), respectively. Of those, 24/27 patients (88.9%) and 18/35 patients (51.4%) were classified as inconclusive due to high serum levels of infliximab 6 weeks after TP1 and at TP2, respectively.

The mean infliximab concentration was 2.71 ± 2.56 µg/ml at TP1 and 0.64 ± 1.5 µg/ml at TP2. ATI were detected in only one patient, who had OD = 0.871 with a titer of 1:20 six weeks after TP1. The clinical characteristics of this patient at all assessment times were comparable to all other patients. Further, this patient was an ASAS 40% responder at TP1 and he had also been a BASDAI 50% responder at all visits during the first 3 years of infliximab therapy. The time-to-relapse[12] of this patient was 24.1 weeks — longer than the mean time-to-relapse of 17.5 weeks[12] of the whole cohort.

There were no significant correlations between either the concentration of ATI or infliximab concentration and the clinical measures.

Adverse events. Overall, 18/41 patients (43.9%) reported at least one AE during the entire followup period of 48 weeks (Table 2). The overall incidence of AE was similar to the results of the first 3 years of infliximab therapy in the same patients[4-7]. There was no new patient with development of infusion reactions after infliximab readministration, whereas all patients with known infusion reactions were treated intravenously with hydrocortisone before each single infliximab infusion.

Table 2. Drug related adverse events and serious adverse events that occurred in patients (n = 23) during the second year of the study. Values are the number of patients who experienced at least one adverse event in each category.

Reported Event	
Adverse events (n = 41)	
Upper respiratory tract infection	10
Infection at any site	6
Gum infection	4
Herpes simplex	3
Dry skin with pruritus	2
Infusion reactions	1
Elevation of liver enzymes	1
Nausea	1
Aphthen	1
Tachycardia	1
Swelling of fingers	1
Paresthesia in the forearm region	1
Total	26
Serious adverse events	
Repeated local infections	1
Skin leishmaniosis after injury (recovered after hospitalization)	1
Bicycle accidnet with subdural hematoma (recovered after hospitalization)	1
Total	3

Serious adverse events. In contrast to previous reports[13,14] there was only one patient who experienced AE leading to discontinuation of the study medication. This patient was the only one who had detectable ATI at the withdrawal timepoint. The decision to drop out of the study was made before the results about the ATI were available. There were 2 other AE, which were not treatment-related but were reported as serious AE because the patients had to be hospitalized for other reasons (Table 2).

Efficacy. Patients' clinical indicators at assessment timepoints. Demographic characteristics of all 42 patients included in this study extension have been reported[12]. All 40 retreated patients responded well to resumption of therapy with infliximab, with clear improvement of signs and symptoms (Figures 1, 2). A disease state similar to that before withdrawal was reached by all patients at TP4 (Table 1, Figure 1). All indicators, with the exception of the BASMI, differed significantly ($p < 0.001$) between TP1 and TP2, TP2 and TP3, and TP2 and TP4, but not between TP1 and TP3, TP1 and TP4, and TP3 and TP4 ($p > 0.05$).

Overall, 25/40 (62.5%) and 25/40 (62.5%) patients were BASDAI 50% responders, 26/40 (65%) and 25/40 patients (62.5%) were ASAS 40% responders, and 27/40 (67.5%) and 28/40 (70%) were ASAS 5-out-of-6 responders at TP3 and TP4, respectively, as compared to their disease status at TP2 (Figure 2). Further, there were 10/40 (25%) and 12/40 (30%) patients in partial remission at TP3 and TP4, respectively (Figure 2).

Finally, after 24 weeks and 48 weeks of infliximab readministration, BASDAI values reached very similar levels compared to values before withdrawal (Figure 1), with 34/40 patients (85%) at TP3 and 33/40 patients (82.5%) showing a difference of the BASDAI of at least one BASDAI unit at TP3 and TP4, respectively, compared to TP1.

Correlations of individual clinical measures at relapse or changes 1 year after infliximab readministration. There were no significant differences of the levels of infliximab concentration between patients in ASAS partial remission or BASDAI 50% response and patients not in partial remission or with no BASDAI 50% response at TP1 (data not shown).

DISCUSSION

Our study reports the longterm safety and efficacy over a period of 1 year after readministration of infliximab in patients with AS who had discontinued longterm therapy with this agent. We recently showed that discontinuation of longterm treatment with infliximab leads frequently to a clinical relapse after several weeks[12]. We now extend these observations by reporting on the safety of this procedure, including the development of antibodies to infliximab. In addition we confirm the clinical efficacy of this approach over 1 year.

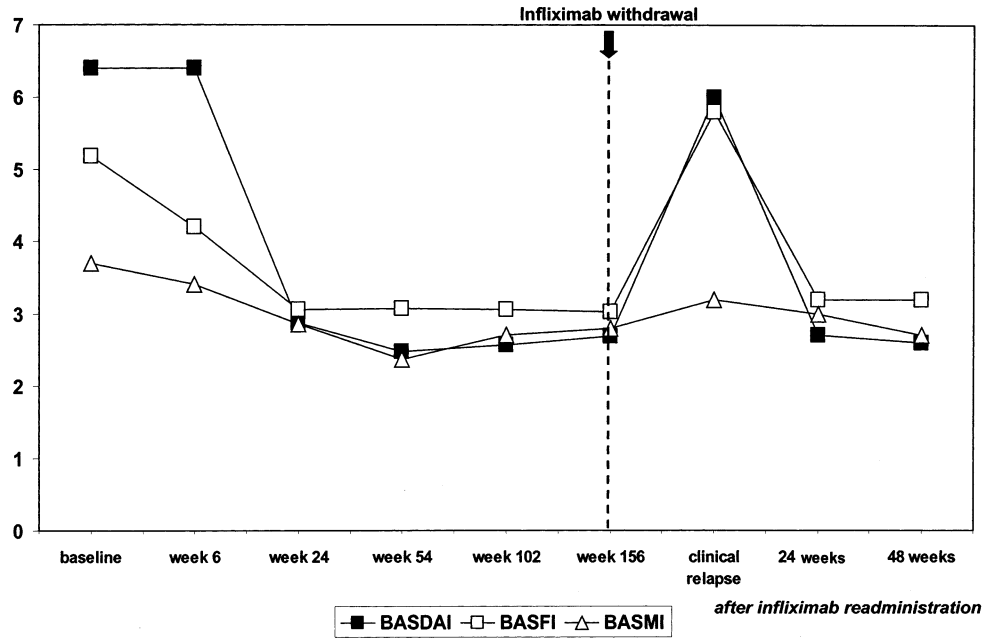

Figure 1. Course of clinical disease measures after 3 years of infliximab therapy, infliximab withdrawal, and readministration. BASDAI: Bath AS Disease Activity Index, BASFI: Bath AS Functional Index, BASMI: Bath AS Metrology Index.

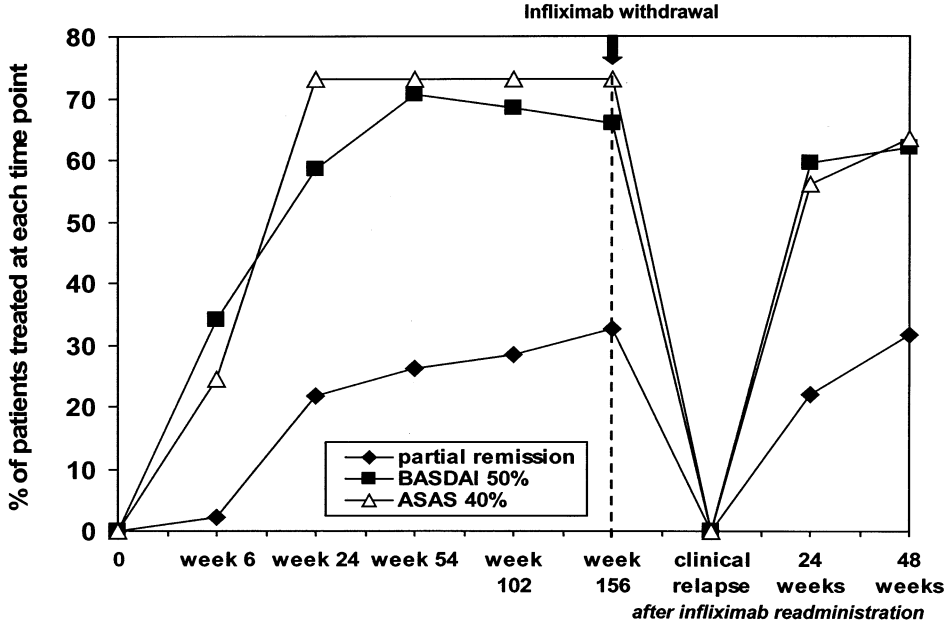

Figure 2. Percentage of patients with BASDAI 50% and ASAS 40% response, and patients in partial remission after 3 years of infliximab therapy, withdrawal, and readministration.

Although we were unable to measure the formation of ATI and infliximab concentrations in all patients, mainly due to technical reasons (see below), it was possible to observe such antibodies in one patient. However, this was of no clinical importance, since this patient had repeated but mild local infections, which are generally not related to formation of ATI. Thus, there is no apparent value to measure ATI in this clinical situation. However, some correlation between ATI, adverse events such as infusion reactions, and lack or loss of clinical response has been reported in patients treated for active Crohn's disease[13]. However, in contrast to our study these patients had been treated not constantly but only episod-

ically, and, as discussed below, the addition of immunosuppressants may be relevant. Thus, our findings argue against a major role of ATI in AS patients treated continuously for several years with a dosage of 5 mg/kg with respect to the safety of such treatment.

While the overall incidence of infusion reactions in patients treated with infliximab has been reported at about 5%, the incidence of ATI has been reported at between 10% and 60%[13,14]. However, the correlation between ATI and AE, such as infusion reactions, does not seem to be very strong[13]. We did not observe any increase in the incidence of infusion reactions after infliximab readministration.

Since no blood sample was drawn at baseline (before start of treatment with infliximab) or at any other timepoint during all extensions of the study to determine ATI, it was not possible to assess the incidence of such antibodies over the entire study period. The reason that significant concentrations of infliximab were still detectable 6 and more weeks after discontinuation is related to the long half-life of infliximab of between 10 and 15 days[15]. This interferes with the measurement of ATI[14]. Considering these data, we cannot clearly state that patients undergoing longterm therapy are less likely to develop ATI, but it is possible on the basis of our results.

The dosage of infliximab used in clinical trials[25] and in daily practice varies between diseases and different studies, and some patients have even been treated episodically according to the presence or absence of symptoms. That the patients in our study had been treated with infliximab without interruption for 3 years may have contributed to the low frequency of ATI and AE reactions reported here. However, it is possible that this led to a preselection of the patients by excluding those who already had developed ATI earlier.

In studies on patients with Crohn's disease[13,14] and RA[17] immunomodulators such as azathioprine and MTX were associated with a lower incidence of ATI and infusion reactions, compared to patients without such treatment. In recent studies of AS patients treated with infliximab plus MTX, no improvement of clinical outcomes was seen compared to patients not treated with this agent[26]. Although doses of MTX used in those studies were slightly lower than those typically employed in RA, there is recent evidence that even with high subcutaneous doses of 20 mg MTX there were no changes of spinal symptoms[27]. In our study with infliximab[4-7], in contrast to those with other anti-TNF agents[28,29], additional immunomodulators were generally not allowed. Thus, this is unlikely to have influenced our results. However, in one study[30], a tendency to a lower incidence of infusion reactions (2 vs 6 patients) in patients treated with MTX was reported. This potential advantage leads to the question of how many AS patients would one have to treat with MTX in order to prevent one infusion reaction — given that there is no further clinical benefit of adding this immunosuppressant, at least not in patients with predominant spinal symptoms. Another interesting finding of this study is that one male patient with AS remained in continuing remission without specific treatment for altogether 2 years. At the timepoint of discontinuation of infliximab, he was in clinical remission, which means complete absence of clinical symptoms, which is even better than the state defined by the ASAS criteria[31]. Of interest, all clinical and laboratory measures did not differ from those of the other patients included in the study at the same timepoint. In our experience, this is the first documented case of an AS patient achieving continuing clinical remission without clinical relapse after longterm therapy with anti-TNF and treatment discontinuation[27]. That remission may be induced in some patients leads to the question whether patients taking anti-TNF therapy should be discontinued at regular intervals in order to make sure that treatment is still necessary. This is also meaningful in regard to the costs and the potential, but rare, risks of this treatment[32]. However, most patients seem to need continuous anti-TNF therapy. Of note, our knowledge about the optimal dose, the optimal infusion interval, and the optimal length of therapy for infliximab is still limited. Clinical experience suggests this is likely to be different in individual patients[11].

In summary, discontinuation of infliximab therapy frequently leads to clinical relapse, but retreatment in the same dosage can be performed safely, and a similar clinical efficacy is achieved as before withdrawal. In this longterm followup 1 year after infliximab readministration, we found no signs of loss of efficacy and no need for an increase of the dose.

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