Prospective Observational Analysis of the Efficacy and Safety of Low-Dose (3 mg/kg) Infliximab in Ankylosing Spondylitis: 4-Year Followup

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ABSTRACT. ***Objective.*** Although there are now compelling data that infliximab is effective for the treatment of AS, most studies have evaluated a dose of 5 mg/kg rather than the 3 mg/kg dose recommended for patients with RA. We assessed the effectiveness and safety of a 3 mg/kg dose of infliximab in normal clinical practice over several years of followup.

Methods. All consecutive patients with AS starting infliximab therapy at 3 mg/kg IV at 0, 2, and 6 weeks and q 2 months between April 2000 and December 2004 were included. Data were systematically collected at baseline, at 14 weeks, and every 6 months thereafter to 4 years or withdrawal. Data included demographic characteristics, Bath AS indices, adverse events, and reasons for withdrawal. Survival taking low-dose infliximab was analyzed by the Kaplan-Meier method with withdrawal for lack of efficacy and/or adverse events and requirement for dose escalation constituting the endpoint.

Results. Thirty-four patients (M:F = 26:8), mean age 44.9 years, mean disease duration 17.1 years, and mean BASDAI of 6.4, were studied, of whom 17 had active peripheral synovitis. Median duration of treatment with low-dose infliximab was 1507 days. Fourteen discontinued therapy after a median of 91 days, 6 for adverse events, 6 for lack of efficacy, and 2 were lost to followup. Five (14.7%) patients required dose escalation. Effectiveness demonstrable at 1 year was maintained over 4 years. We did not identify any significant baseline predictors of maintenance on low dose infliximab for ≥ 2 years.

Conclusion. Low-dose (3 mg/kg) infliximab therapy is associated with sustained effectiveness in patients with AS in the real-world setting. (J Rheumatol 2006;33:558-61)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS INFLIXIMAB TREATMENT

Tumor necrosis factor-α (TNF-α) inhibition with infliximab has been shown to induce sustained amelioration of symptoms and signs of ankylosing spondylitis (AS). A 3-year open extension analysis of 69 patients originally recruited to a placebo-controlled trial of infliximab in AS showed that about 50% of patients had a 50% or greater reduction in disease activity as recorded by the Bath AS Disease Activity Index (BASDAI) that was maintained over the treatment period[1,2]. The only dosage evaluated in clinical trials of AS has been 5 mg/kg at 0, 2, and 6 weeks with maintenance every 6–14 weeks, which is substantially higher than the 3 mg/kg dose every 8 weeks recommended for maintenance therapy of rheumatoid arthritis (RA)[3,4].

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We reported on a prospective observational inception cohort study of real-world clinical practice use of low dose infliximab (3 mg/kg at 0, 2, and 6 weeks, and every 8 weeks thereafter) in 21 patients with AS[5]. The initial 14 week evaluation demonstrated short-term safety and efficacy of low dose 3 mg/kg infliximab with significant improvement in disease activity, function, and metrology indices as well as acute phase reactants. These observations may have major cost-benefit implications for the use of infliximab in AS, which may impact access to treatment. Consequently, in view of the limited available data on the effectiveness of the 3 mg/kg maintenance dose we now present the longterm followup of this cohort up to 4 years with data from additional patients that received this regime of treatment.

MATERIALS AND METHODS

Patients. Thirty-four consecutive patients with AS seen by the Alberta Capital Health Region rheumatologists (5 university based, 7 community based) were recruited to the study between April 2000 and December 2004. Men and women aged 18 or older were eligible if they met the modified New York criteria for AS and were judged by the referring rheumatologist to have active disease despite maximum and/or tolerated doses of nonsteroidal antiinflammatory drugs (NSAID). Since the study evaluated real-world clinical practice, there were no formal entry criteria. NSAID, disease modifying antirheumatic drugs (DMARD), prednisone, and analgesics were continued through the study if medically indicated, and patients were asked to maintain stable dosing.

Study protocol and endpoints. Data were systematically collected at baseline, 14 weeks, and 1 year, and every 6 months thereafter up to 4 years. Primary outcomes were the Bath AS Indices [BASDAI[6], Bath AS Functional Index (BASFI)[7]]. Infliximab was infused at 3 mg/kg at time 0, 2 weeks, and 6 weeks, and every 8 weeks thereafter. All patients had tuberculosis screening that included a chest radiograph and tuberculin skin test at baseline. Dose escalation and/or increased frequency of infusions were permitted according to the discretion of the attending rheumatologist.

Withdrawal and adverse events. All adverse events were systematically recorded according to the recommendations of the OMERACT toxicity working group[8]. Reasons for withdrawal were documented, and a final assessment was performed where possible.

Statistical analysis. Survival on a regime of 3 mg/kg every 8 weeks was analyzed using the Kaplan-Meier method. Data were censored either at the time the patient discontinued infliximab for loss of efficacy and/or adverse events or at the time the patient received a higher dose. Logistic regression analysis (univariate and multivariate) was used to analyze age, sex, disease duration, baseline BASDAI, baseline BASFI, and baseline acute phase reactants as potential predictors of maintenance on low dose infliximab for a period ≥ 2 years. A p value < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics. Thirty-four patients have entered the study cohort of whom a relatively high proportion had active peripheral synovitis (56%) and most had disease of relatively long duration (Table 1). The data on 21 of these patients that had been followed for a mean of 47.5 weeks (range 10–77) have been described[5]. A substantial minority had previously received second line therapy for NSAID-refractory peripheral arthritis (n = 16, 47.0%). Patients had active disease as indicated by a mean BASDAI of 6.4 of whom 85.3% (29 patients) had a BASDAI ≥ 4.

Treatment survival. Median duration of low-dose infliximab treatment is 1507 days (95%CI [1086-1928 days] (Figure 1). Fourteen (41%) patients discontinued the study after a mean of 169.6 days: 6 (17.6%) discontinued because of adverse events and 6 (17.6%) discontinued for lack of efficacy (Table 2). One patient moved to another province and one was lost to followup. Adverse events leading to treatment withdrawal included infusion reactions (n = 4), hypersensitivity reaction (n = 1), and septic osteomyelitis of the talus (n = 1). The latter patient had been treated for septic arthritis of the same ankle joint several years previously and was considered cured of infection. There were no cases of tuberculosis, lymphoma or other malignancy, or demyelination.

Table 1. Baseline characteristics of AS patients (n = 34) started on low-dose (3 mg/kg) infliximab. Values are No. of patients (%) unless otherwise indicated.

Age, yrs, mean (SD)	42.0 (10.9)
Male, %	76
Disease duration, years, mean (SD)	18.0 (7.4)
Peripheral synovitis, No (%)	19 (56)
No. of swollen joints, median (range)	2.0 (0.0–7.0)
Psoriasis	3 (9)
Inflammatory bowel disease	3 (9)
Prior methotrexate	7 (20.6)
Prior sulfasalazine	4 (11.8)
Prior Pamidronate	9 (26.5)
Concomitant NSAID	28 (82.3)
Concomitant methotrexate	6 (17.6)
Concomitant sulfasalazine	5 (14.7)
Concomitant prednisone	3 (8.8)
BASDAI, mean (SD) [median (range)]	6.4 (1.3) [6.6 (3.3–8.9)]
BASFI, mean (SD) [median (range)]	5.6 (2.0) [6.4 (1.7–8.9)]
BASG, mean (SD) [median (range)]	5.8 (2.1) [6.3 (1.0–8.5)]
BASMI, mean (SD) [median (range)]	2.7 (2.4) [0 (0–9.0)]
ESR, mean (SD) [median (range)]	35.6 (17.5) [38.0 (4.0–70.0)]
CRP, mean (SD) [median (range)]	61.9 (53.3) [52.6 (1.4–175.0)]

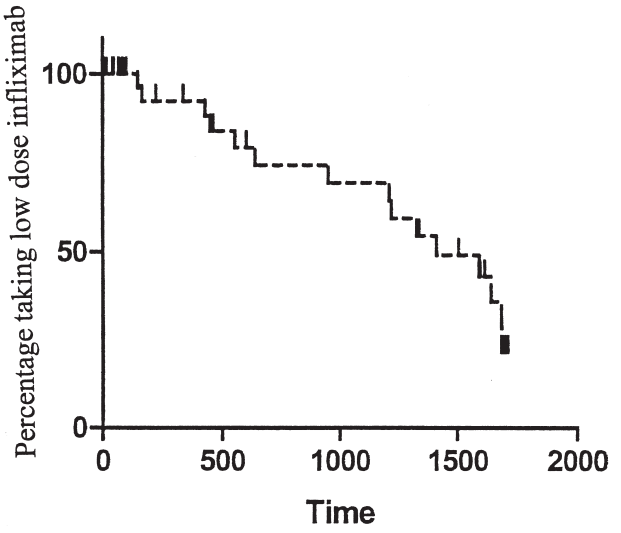

Figure 1. Kaplan-Meier survival plot for low-dose infliximab (3 mg/kg) in patients with AS.

Five patients (14.7%) have had their dose escalated from low-dose infliximab therapy and are still receiving treatment at either 3 mg/kg every 6 weeks (n = 3) (median duration = 1507 days) or 5 mg/kg every 8 weeks (n = 2) (median duration = 1661 days).

Efficacy. The mean BASDAI decreased from 6.4 at baseline to 3.2 at 1 year, 2.4 at 2 years, and 2.2 at 3 years, while the mean BASFI decreased from 5.6 at baseline to 2.2, 2.7, and 1.1 at 1, 2, and 3 years, respectively. Regression analysis revealed no significant baseline predictors of maintenance on low-dose infliximab therapy for ≥ 2 years (data not shown). After 12 months, 8 out of 24 patients (33%) were in complete remission; these patients all remained in remission at month 24.

DISCUSSION

Survival data in real-world clinical practice indicates that low-dose infliximab therapy is effective and well tolerated for a sustained period of time, with median duration of treatment just over 4 years. Although our study was observational and designed to evaluate real-world experience with infliximab in AS, the baseline features of our patient population resemble those of patients recruited to randomized clinical trials. Thus, most patients had a BASDAI ≥ 4 and about one-third had been exposed to DMARD. Further, the baseline characteristics

Table 2. Treatment withdrawals for AS patients starting therapy with lowdose infliximab (3 mg/kg).

No. (%) of Patients	Reason for Withdrawal	Dose at Discontinuation	Duration of Treatment (days) Median (range)	Mean (SD)
3 (8.9)	Infusion reaction	3 mg/kg q 8 wks × 2 patients 3 mg/kg q 6 wks × 1 patient	451.0 (67.0–602.0)	373.3 (275.8)
1 (2.9)	Anaphylaxis after 3rd dose	3 mg/kg q 8 wks	84	84
1 (2.9)	Osteomyelitis after 3rd dose	3 mg/kg q 8 wks	42	42
1 (2.9)	Delayed hypersensitivity	3 mg/kg q 8 wks	14	14
5 (14.7)	Loss of efficacy	3 mg/kg q 8 wks	98 (42–340)	149.2 (129.7)
1 (2.9)	Loss of efficacy	6 mg/kg q 4 wks	42	42
1 (2.9)	Continuing treatment in another province	5 mg/kg q 6 wks	1690	1690
1 (2.9)	Lost to followup	3 mg/kg q 8 wks	NA	NA

NA: not available.

reflect those features identified by members of the Assessment in Ankylosing Spondylitis International Working Group of experts in AS as being influential in their selection of patients for anti-TNF-α therapies[9]. These features included the presence of peripheral arthritis and high acute phase reactants.

Adverse events were typical of infliximab therapy, and treatment was generally well tolerated. Of the over 56 patient years of treatment in our cohort, only one infection was documented in a patient who had septic arthritis several years previously and was considered cured of infection. Although reactivation of dormant tuberculosis is well documented in patients treated with anti-TNF-α therapies, the possible reactivation of other dormant bacteria has been less well recognized. The incidence of infusion and hypersensitivity reactions (14.4%) was somewhat higher than that noted in a recent pivotal trial of infliximab in AS (2.3%)[4]. The primary reason for this difference may be different treatment durations, with patients in our observational cohort receiving therapy for a median duration of 1507 days, while data from the pivotal trial were available for only 156 days. Further, one infusion reaction requiring discontinuation of treatment was noted at 602 days after the start of treatment in our study. Other studies have reported an incidence of 5–10%[10,12].

We found 2 additional reports that described the use of low-dose infliximab in AS. One study reported benefit in 9 patients[12] and a second study, reported in abstract form[13], reported that two-thirds of patients required dose-escalation although only 10 patients actually had AS, and it was not clear how many of these required dose escalation.

Larger numbers of patients and continued followup are needed to determine the cost implications of low-dose infliximab therapy for AS. A recent cost-effectiveness analysis in the United Kingdom recognized the need to evaluate the short- and longterm cost benefits of infliximab when pitted against the economic consequences of lost quality of life, loss of work productivity, and other non-medicinal costs[14]. This, in turn, may influence access to therapy for patients with AS, which is still limited in many parts of the world.

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