C-Reactive Protein Predicts Tumor Necrosis Factor-α Blocker Retention Rate in Axial Ankylosing Spondylitis

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ABSTRACT. ***Objective.*** In ankylosing spondylitis (AS), tumor necrosis factor (TNF) blockers are recommended for patients with high symptomatic disease activity. Few data are available about objective signs of inflammation such as increased C-reactive protein (CRP). We assessed the retention rate of TNF blockers in patients with axial AS, according to baseline CRP and other potentially predictive measures.

Methods. A retrospective study of all patients treated with TNF blockers for axial AS. Retention rate was evaluated using a survival-data analysis technique with discontinuation of the drug because of inefficacy (Kaplan-Meier method). Potential factors explaining the retention rates (demographic and clinical indicators and CRP) were evaluated using log-rank tests and a Cox proportional-hazards regression model.

Results. For axial AS, 175 patients received TNF blockers (men 78%, mean disease duration 12.4 ± 9.1 yrs); 100 patients (of 143 with available data) had an increased CRP (> 10 mg/l). An increased CRP at baseline was the only variable explaining the retention rate in the Cox model (p = 0.003, hazard ratio = 3.3, 95% CI 1.5–7.3).

Conclusion. Interruption for expert opinion of inefficacy was more frequent for patients with low baseline CRP; however, even in these patients retention was high. Increased CRP should not be considered mandatory for proposing TNF blocker treatment in axial AS. (First Release August 15 2007; J Rheumatol 2007;34:2078–81)

Key Indexing Terms:
AXIAL ANKYLOSING SPONDYLITIS
TUMOR NECROSIS FACTOR BLOCKER
C-REACTIVE PROTEIN
RETENTION RATE

Until recently, no slow-acting treatments were available in axial ankylosing spondylitis (AS)[1]. Tumor necrosis factor-α (TNF-α) blocking agents — infliximab, etanercept, and adalimumab — have shown dramatic efficacy in several placebo-controlled trials in AS[2-4]. Given the high cost and the rare but potentially severe risks of these treatments, patients should be carefully selected for treatment. To help in this selection, the international Assessments in Ankylosing Spondylitis (ASAS) working group published a consensus statement for the use of TNF blockers in AS[5]. The consensus requires a positive diagnosis of AS, treatment failure of 2 nonsteroidal antiinflammatory drugs (NSAID), and presence of active disease. Disease activity can be defined on subjective clinical indicators [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[6] ≥ 4 (range 0–10)] and on expert opinion. The expert should consider clinical features (history and examination), but also objective signs of inflammation such as serum acute-phase reactant levels and/or imaging results (radiographs or magnetic resonance imaging). However, acute-phase reactant levels remain to be determined. It is not clear whether the presence of these objective signs of inflammation should be considered mandatory to initiate TNF blocker therapy.

Our objectives were: (1) to confirm the efficacy of TNF blockers in axial AS, assessed through the retention rate; (2) to assess this retention rate according to the presence or absence of objective biologic signs of inflammation at initiation of TNF blocker therapy; and (3) to assess other potentially predictive measures of TNF blocker retention.

MATERIALS AND METHODS

This was a retrospective, observational study in a single-center tertiary-referral clinic.

All patients who were seen for AS in the department between January 1997 and February 2005 were selected through a computer survey of patient files. From these, patients were selected who received treatment with TNF-α blockers for predominantly axial symptoms, i.e., despite concurrent treatment with NSAID, back pain was the main symptom. Patients who received treatment with TNF blockers for main symptoms of arthritis or enthesitis were excluded.

Data collection. Demographic characteristics were collected: sex, birthdate, disease duration, HLA-B27 status, age at start of the first TNF blocker, prior disease modifying antirheumatic drugs (DMARD). The DMARD potentially used before turning to TNF blockers were sulfasalazine and methotrexate. Data of BASDAI, C-reactive protein (CRP, mg/l), and concomitant DMARD were collected at initiation of the TNF blocker.

Only the first course of TNF blocker was analyzed for each patient, i.e.,

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the first TNF blocker prescribed irrespective of the duration of treatment. After a switch from one TNF blocker to another, we considered the treatment as the "second course" and it was not analyzed.

CRP data. Data for this acute-phase reactant were collected in the month before beginning treatment. A positive CRP was defined as a value > 10 mg/l, i.e., the upper limit of normal for our department laboratory and for many laboratories in France at the time of the study.

Statistical analysis. Double data entry was performed. All data were processed anonymously. The retention rate was evaluated using a survival-data analysis technique (Kaplan-Meier product limit estimator) using the delay between initiation and interruption of treatment because of a physician's expert opinion of inefficacy. Inefficacy was defined by an expert opinion to stop treatment because of an insufficient therapeutic effect. Other reasons for discontinuation (side effects, switch to another TNF blocker for reimbursement purposes, patient demand, other reason) were considered as censored data. Patients still undergoing treatment at the time of data collection (April 2005) were also censored.

Potential factors explaining the retention rate were evaluated using log-rank tests, then a Cox proportional-hazards regression model, with all factors with a p value < 0.2 by log-rank analysis entered into the model. The values studied were baseline CRP, age, sex, disease duration, BASDAI score, age at diagnosis, HLA-B27 status, number of previous DMARD, and concomitant DMARD prescription at initiation of the TNF blocker. There was no imputation of missing data.

RESULTS

Patient characteristics. Between 1997 and February 2005, 1161 patients with AS were seen in the department at least once (Figure 1). Among them, 267 (23%) received at least one course of TNF blocker. Treatment was initiated because of axial symptoms in 175 patients. Table 1 shows clinical and demographic characteristics and baseline CRP for these 175 patients. There were 137 men (78%), mean age at initiation of TNF blocker was 39.4 (SD 10.2) years, disease duration at initiation of TNF blocker was 12.4 (SD 9.1) years. HLA-B27 was present in 133 patients (88%). Baseline CRP data were available in 143 patients (82%); it was elevated (> 10 mg/l) in 100 (70% of 143). Baseline characteristics in both groups were comparable except for presence of HLA-B27, which was more frequent in patients with elevated baseline CRP (93% vs 78%; p = 0.02).

TNF blocker retention rate. The percentage of patients who did not discontinue treatment because of insufficient efficacy was 81% ± 3.5% at 1 year (n = 84), 80% ± 3.6% at 2 years (n = 36), and 67% ± 6.7% at 3 years (n = 13).

Factors influencing the retention rate. Log-rank analysis indicated that elevated CRP (p = 0.002) and no concomitant DMARD (p = 0.02) were associated with a higher retention rate (Figure 2). After 1 year of treatment, the number (and percentage by retention rate) of patients who had not discontinued treatment because of insufficient efficacy were the following: 51 (83%) versus 12 (67%) patients with elevated CRP versus normal CRP, and 20 (73%) versus 62 (84%) patients with concomitant prescription of DMARD, yes versus no. Other variables studied (sex, HLA-B27 status, previous use of DMARD, BASDAI before initiation of treatment) were not significantly associated with the retention rate.

In Cox proportional-hazards regression analysis, elevated baseline CRP was found to be the only value associated with the retention rate (p = 0.003, hazard ratio = 3.3, 95% confidence interval 1.5–7.3).

DISCUSSION

Our study confirms the high retention rate of TNF blockers in patients with axial AS, since 80% of patients had not discontinued their treatment for insufficient efficacy after 2 years. The retention rate was higher for patients with elevated CRP at baseline, and this was the only predictive factor revealed by the Cox regression model. However, the retention rate for patients with a normal baseline CRP remained high and clinically relevant.

To our knowledge, this is the largest retrospective observational study of TNF therapy in axial AS. All the patients treated with TNF blockers for axial AS were studied, without selection or exclusion. Our study design focusing on "daily practice" has the advantage of showing the real use of a drug, even if the result may be influenced by factors such as patients' subjectivity in regard to a new drug and physicians' prescription habits. In clinical trials, the inclusion and exclusion criteria select a minority of patients, and evaluation of efficacy is dependent on standard quantitative measures or indices, which are not systematically used in daily practice. In our study, efficacy was evaluated empirically by the physician's opinion, which translated into retention rates[7,8].

The BASDAI is currently used to assess AS clinical activity, a value of at least 4 out of 10 given in the ASAS recommendations as an important clinical requirement for introduction of TNF blockers. In our study, the retention rate of patients with baseline BASDAI < 4 did not differ from patients with BASDAI ≥ 4. These results should be confirmed. Although our results support that CRP is predictive of response in axial AS, the retention rates were also very high for patients without high baseline CRP; thus this indicator should not be considered mandatory for introduction of TNF blocker treatment.

Prediction of treatment response has been examined in a few prospective studies[9-12]. There are some discrepancies between them, resulting from variations in populations and methodologies. Elevated CRP was found to be the only measure predicting response in those studies. Our findings are in agreement with that result, confirming it in a daily-practice population.

Missing data are the major problem of retrospective studies, but few data were missing for our other variables, and the characteristics of the 2 study populations, those with and without elevated CRP, were similar. Only HLA-B27 status was found to differ, and there was no clear explanation for this. The lack of followup data such as CRP measures during treatment is regrettable, but our aim was to assess predictive baseline factors as an aid to clinicians' decisions.

The important issue to date is which patients with axial AS

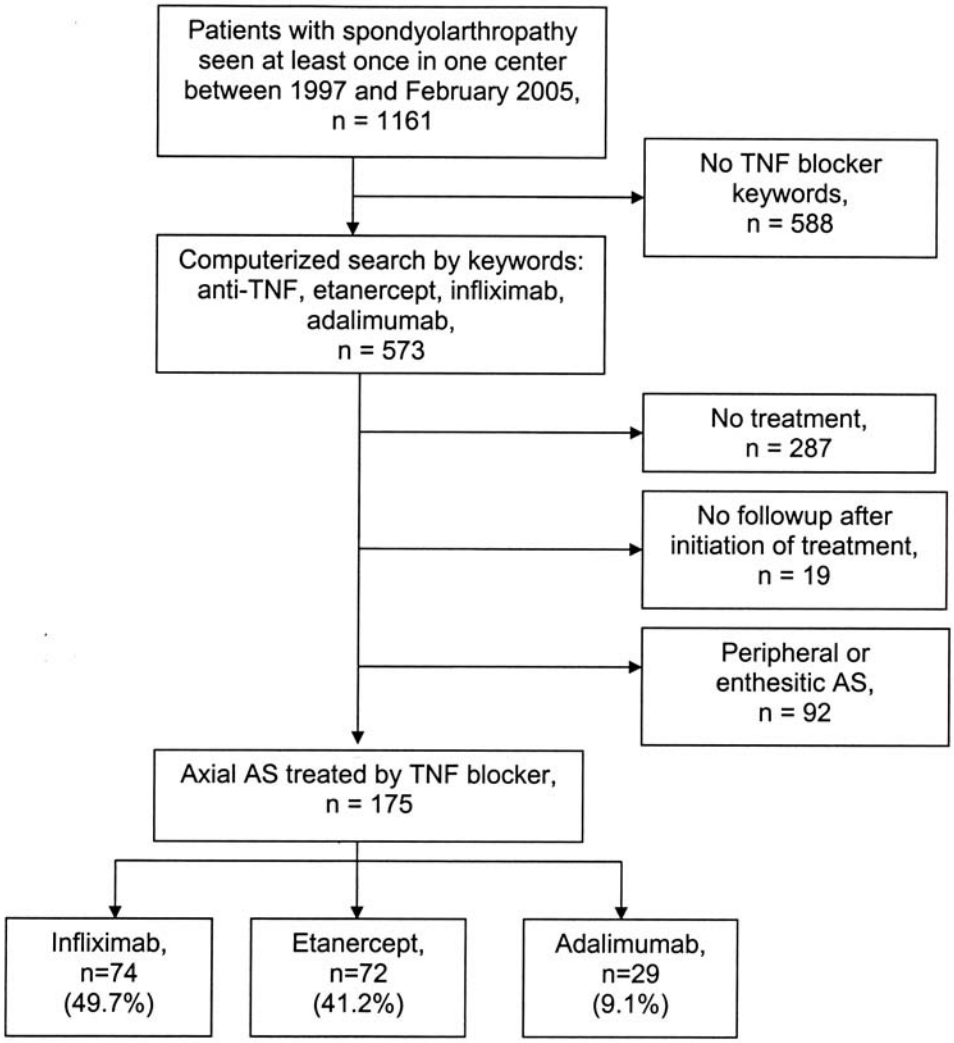

Figure 1. Patient selection. All patients were treated for axial AS using TNF blockers in a single center between January 1997 and February 2005.

Table 1. Characteristics for all patients according to level of baseline C-reactive protein (CRP).

	All Patients, n = 175	Patients with CRP > 10 mg/l, n = 100	Patients with CRP ≤ 10 mg/l, n = 43	p*
Men, no. (%)	137 (78)	80 (80)	33 (77)	0.66
Age at diagnosis, yrs, mean (SD)	27.1 (9.9)	26.4 (9.7)	29.3 (11.5)	0.12
Disease duration, yrs, mean (SD)	12.5 (9.0)	12.0 (8.5)	13.7 (10.1)	0.37
HLA-B27 present/available, no. (%)	133/151 (88)	82/88 (93)	32/41 (78)	0.02
Previous DMARD, yes, no (%)	104 (60.5)	63 (63.6)	23 (53.5)	0.27
No. of previous DMARD, mean (SD)	1.0 (1.1)	1.04 (1.07)	1.02 (1.3)	0.93
BASDAI before treatment (0–10), mean (SD)	5.2 (1.9)	5.2 (2.0)	5.2 (1.7)	0.96
CRP, mg/l, mean (SD)	26.8 (25.7)	35.8 (25.9)	5.9 (2.8)	< 0.0001
History of uveitis, no. (%)	36 (21)	25 (25)	10 (23)	0.82
Concomitant DMARD, no. (%)	44 (25)	32 (32)	12 (28)	0.69
Infliximab treatment, no. (%)	87 (50)	66 (66)	15 (35)	0.002
Etanercept treatment, no. (%)	72 (41)	26 (26)	23 (53)	0.002
Adalimumab treatment, no. (%)	16 (9)	8 (8)	5 (12)	0.002

* Comparing patients with elevated baseline CRP to patients with normal baseline CRP.

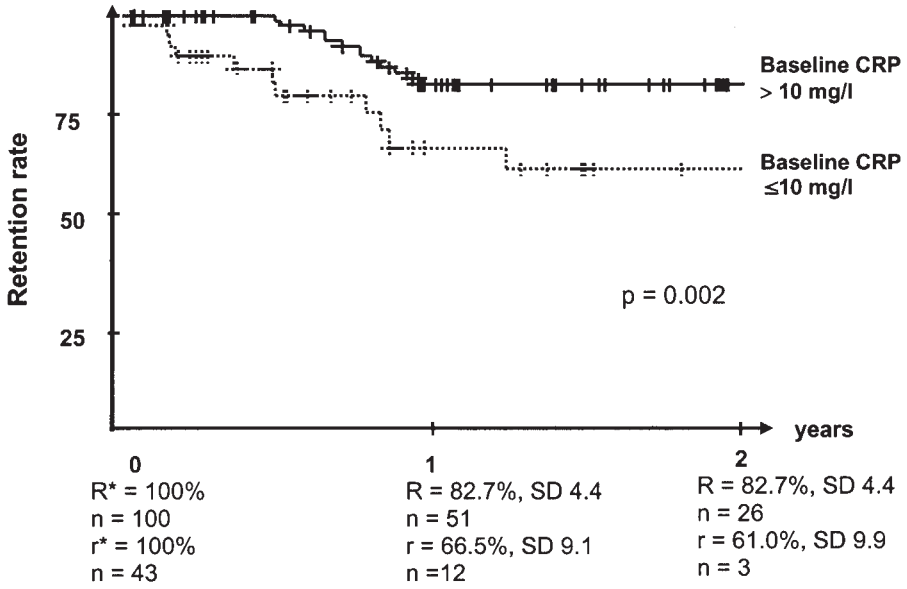

Figure 2. Retention rate in the 2 subgroups, with and without elevated baseline CRP. *R: retention rate in the subgroup with elevated CRP; *r: retention rate in subgroup with normal baseline CRP.

should be treated by TNF blockers. Prediction of treatment response is an interesting perspective. Further prospective studies are necessary to confirm our results. The results could then be integrated into future recommendations, and could also assist physicians in their daily practice.

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