Dosage Adjustment of Anti-Tumor Necrosis Factor-α Inhibitor in Ankylosing Spondylitis Is Effective in Maintaining Remission in Clinical Practice

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ABSTRACT. ***Objective.*** While remission is possible in patients with ankylosing spondylitis (AS), it is often unclear what attitude should be adopted once remission has occurred. We investigated whether dosage adjustment is an effective means of maintaining remission.

Methods. This was a retrospective study drawn from clinical situations. Remission was defined using clinical measures [Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≤ 20/100 and no peripheral joint disease] and biological measures [C-reactive protein (CRP) levels ≤ normal value]. The tumor necrosis factor-α (TNF-α) inhibitors used were infliximab, adalimumab, and etanercept. Response predictors of remission were evaluated by logistic regression (age, CRP, HLA-B27 positivity, sex, duration of disease, and anti-TNF-α naivety). CRP and BASDAI were evaluated before and after dosage adjustment at about 6, 12, 24, and 36 months.

Results. One hundred eighty-nine patients with AS were included in the study, with a mean followup of 43.5 (± 17.9) months after the introduction of the first anti-TNF-α inhibitor. Mean age was 45.6 (± 12.5) years. Remission had occurred in 65 patients (35%). Significant response predictors of remission were male sex ($p = 0.003$) and anti-TNF-α naivety ($p < 0.001$). Dosage adjustment was observed 49 times, and progressively reducing treatment frequency was effective to maintain remission in a large number of patients for 36 months. The cumulative probability of continuing anti-TNF-α after dosage adjustment was 79.0% at 12 months, 70.5% at 24 months, and 58.8% at 36 months.

Conclusion. Remission had occurred in 35% of the patients with AS under anti-TNF-α inhibitor therapy. Dosage adjustment and progressively reducing treatment frequency was effective in maintaining remission. (J Rheumatol First Release June 15 2012; doi:10.3899/jrheum.111337)

Key Indexing Terms:
TUMOR NECROSIS FACTOR INHIBITOR ANKYLOSING SPONDYLITIS REMISSION

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease characterized by predominant axial manifestations. Conventional disease-modifying antirheumatic drugs have limited effectiveness on axial manifestations[1,2]. The advent of tumor necrosis factor-α inhibitors (anti-TNF-α) has improved the management of patients with AS. Many randomized, placebo-controlled clinical trials have demonstrated the efficacy of anti-TNF-α in the treatment of AS[3,4,5]. Most data have shown that infliximab (IFX), etanercept (ETA), and adalimumab (ADA) have comparable safety and efficacy profiles[3,4,5]. In the absence of comparative head-to-head trials, there is no recommended ranking for the prescription of anti-TNF-α inhibitors.

A very good clinical response is possible under anti-TNF-α. Improvements in Bath Ankylosing Spondylitis Disease Activity Index scores (BASDAI 50) and in Assessment of SpondyloArthritis International Society (ASAS) guidelines measures of partial remission — between 45.2% and 51.0%, and 22.1% and 22.4%, respectively — have been reported in randomized, placebo-controlled clinical trials[4,5,6]. Comparable results have been found in an open-label study[7]. As in rheumatoid arthritis (RA), remission is possible for AS but it is unclear what attitude should be adopted once remission has occurred. Very few data are available on the maintaining effect of anti-TNF-α dosage adjustment in AS, and discontinuing treatment leads to relapse in almost all patients with AS within weeks or a few months[8,9,10,11]. Our aim was to determine whether, in current practice, anti-TNF-α dosage adjustment was an effective means of maintaining remission in patients with AS. The study data were drawn from real-life clinical situations.

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MATERIALS AND METHODS

Patients. This was a retrospective study conducted in a Department of Rheumatology. All patients with AS who had been treated with anti-TNF-α from April 2001 to August 2010 were identified by record review. Patients with axial AS were classified according to the modified New York criteria and/or ASAS criteria[12,13]. Extraarticular manifestations associated with AS, such as inflammatory bowel disease (IBD), were also recorded. Only AS patients with predominant axial manifestations were selected, but associated peripheral manifestations, such as enthesitis and/or arthritis, were also recorded. The records of patients with AS who had attained remission under anti-TNF-α treatment were analyzed. The ASAS partial remission criteria[6] were not used because some of the measures, such as Bath Ankylosing Spondylitis Functional Index (BASFI), were frequently missing. It is for this reason that remission was defined using clinical measures (BASDAI < 20/100; no peripheral joint disease such as arthritis and/or enthesitis) and biological measures [C-reactive protein (CRP) levels less than or equal to normal values], according to recent reports[8,9]. In the case of AS-associated IBD, remission was considered attained only if IBD was also in clinical remission. Only those patients with a minimum followup of 6 months after dosage adjustment were selected. Administration of low doses and/or changes of dose intervals were considered dosage adjustments. Because this was a retrospective observational study, the dosage adjustment methodology could not have been planned, and was based on the physician's discretion. A standardized form was used to collect data on demographics and remission measures observed during anti-TNF-α treatment. Prebiological and concomitant medications were recorded, such as nonsteroidal antiinflammatory drugs (NSAID), corticosteroids, sulfasalazine, leflunomide, and methotrexate.

Drug administration. The anti-TNF-α inhibitors used were IFX (5 mg/kg every 6 weeks), ADA (40 mg every 14 days), and ETA (25 mg twice a week or 50 mg/week). French Society of Rheumatology (FSR) and ASAS Working Group recommendations on the use of anti-TNF-α in AS were followed in most cases[14,15]. No compliance studies had been conducted, and a number of anti-TNF-α prescriptions had been issued before the publication of these recommendations.

Evaluation. FSR and ASAS recommendations were also used to assess the effectiveness of anti-TNF-α treatment[14,15]. Treatment was considered effective if, after 3 months, the patient's BASDAI score had improved by at least 2 points on a scale of 0–10, or had improved by 50% (BASDAI 50), with a favorable expert opinion. Data were recorded for each patient who had attained remission. Response predictors of remission (mean age, CRP levels, HLA-B27 positivity, sex, mean disease duration, and anti-TNF-α naivety) were evaluated. Maximum followup after remission had been attained was 36 months. CRP and BASDAI were recorded before and after dosage adjustment at about 6, 12, 24, and 36 months. Changes in BASDAI and CRP were also recorded in patients for whom anti-TNF-α treatment was discontinued before the scheduled evaluation at 6, 12, 24, and 36 months. We also recorded whether concomitant medications had been left unchanged, reduced, or discontinued. We evaluated the number of patients worsening after dosage adjustment, and we determined whether remission was attained again after dose escalation in those patients.

Statistical analysis. Measurement distributions were summarized by mean, SD, median, minimum, and maximum. All qualitative measures were summarized in contingency tables displaying frequencies and corresponding percentages. Logistic regressions were performed to explain remission. Continuous measures were classified according to median. All statistical tests were performed at a 5% significance level. A survival analysis (continuing anti-TNF-α) was performed using the Kaplan-Meier method, with its associated survival curve. The log-rank test was used to compare the 3 anti-TNF-α inhibitors.

RESULTS

Characteristics of patients. The study began with 206 patients with AS under anti-TNF-α inhibitor therapy who were seen between April 2001 and August 2010. Of those patients, 17 were lost to followup and therefore excluded. Consequently, the records of 189 patients with AS were assessed. Mean age was 45.6 (± 12.5) years, and mean disease duration before the introduction of the first anti-TNF-α was 12.7 ± 10.0 years. AS-associated IBD was found in 25 of the 189 patients. Forty-five patients (23.8%) had some form of joint disease, such as arthritis and/or enthesitis. Remission had been attained in 65 patients (35.0%; 10 of whom had IBD). Remission was attained 6 months (range 3–25) after the introduction of anti-TNF-α. For these 65 patients, mean BASDAI before and 3 months after the introduction of anti-TNF-α therapy was 53.8 (± 17.2) and 17.7 (± 17.3), respectively. The patients' demographic and clinical characteristics are summarized in Table 1. NSAID and corticosteroids had been used as prebiological medications in 96.1% and 20.4% of the patients, respectively. DMARD, essentially sulfasalazine, had been used in 49.7% of the patients, and the mean number of DMARD used before the introduction of anti-TNF-α was 0.9 (± 1.3).

Analysis of predictive factors. Logistic regressions were performed to distinguish response predictors of remission. Only male sex ($p = 0.003$) and anti-TNF-α naivety were found to be predictive factors of remission ($p < 0.001$; Table 2).

Prescription sequences. One hundred eighty-nine patients had been treated with 1 anti-TNF-α, 72 with 2, and 23 with 3, which corresponded to 284 prescription sequences. Mean followup was 43.5 (± 17.9) months after the introduction of the first anti-TNF-α. IFX was prescribed 109 times, ADA 78 times, and ETA 97 times. With the first anti-TNF-α course, remission was observed 58 times (30.7%), as opposed to 4 times (5.6%) with the second (OR 7.5; 95% CI 2.6–21.6; $p < 0.001$). Remission was observed 5 times (21.7%) with the third anti-TNF-α course (Table 2). Concerning remission, no differences were observed among the 3 anti-TNF-α, particularly in the first sequence ($p = 0.845$; Table 3).

Anti-TNF-α dosage adjustment. Remission was observed 67 times (2 patients had attained remission twice). Loss of followup was observed 3 times and no dosage adjustment, 15 times. Dosage adjustment after remission was therefore observed 49 times. Remission was attained between 3 and 25 months (median 6) after the introduction of anti-TNF-α therapy, and dosage adjustments were made between 0 and 35 months (median 5) after remission had been attained. Dosage adjustments were made 23 times in the first 3 months after remission had been attained. For IFX, administration of low doses was not observed, but dose intervals were adjusted. The interval between infusions was extended from 7 to 15 weeks and the results are expressed as the mean interval in weeks between infusions of IFX (5 mg/kg) at 6, 12, 24, and 36 months (Table 4). For ADA, administration of low doses was not observed, but dose intervals also were adjusted. The results are expressed as the mean interval in weeks between injections of ADA (40 mg). The most frequent dosage adjust-

Table 1. Demographic and clinical measures of patients with remission and without remission. Remission was defined using clinical measures (Bath Ankylosing Spondylitis Disease Activity Index ≤ 20/100 and no peripheral joint disease) and biological measures (C-reactive protein levels less than or equal to normal value).

Characteristics	Total	With Remission	Without Remission
No. patients	189	65	124
Male, n (%)	121 (64.0)	51 (78.5)	70 (56.5)
Mean age, yrs, ± SD	45.6 ± 12.5	45.0 ± 13.8	45.9 ± 11.9
Mean disease duration, yrs, ± SD	12.7 ± 10.0	13.9 ± 10.1	12.1 ± 10.0
HLA-B27-positive (%)	77.1	79.5	76.0
C-reactive protein ≥ normal values (%)	64.2	69.2	62.5

Table 2. Analysis of predictive factor: anti-tumor necrosis factor-α (TNF-α) naivety.

Remission	First Anti-TNF, n = 189 (%)	Second Anti-TNF, n = 72 (%)	Third Anti-TNF, n = 23 (%)
No	131 (69.3)	68 (94.4)	18 (78.3)
Yes	58 (30.7)	4 (5.6)	5 (21.7)

p < 0.001. First anti-TNF vs second anti-TNF: OR 7.5, 95% CI 2.6–21.6, p < 0.001. Third anti-TNF vs second anti-TNF: OR 5.2, 95% CI 1.7–16.6, p = 0.0049. First anti-TNF vs third anti-TNF: OR 1.4, 95% CI 0.6–3.7, p = 0.449.

Table 3. Remission results for the 3 anti-tumor necrosis factor-α drugs IFX, ADA, and ETA during the first prescription sequence.

Remission	IFX, n = 86 (%)	ADA, n = 33 (%)	ETA, n = 70 (%)	Total, n = 189 (%)	p
No	58 (67.4)	24 (72.7)	49 (70.0)	131 (69.3)	0.845*
Yes	28 (32.6)	9 (27.3)	21 (30.0)	58 (30.7)	

* Chi-squared test. IFX: infliximab; ADA: adalimumab; ETA: etanercept.

Table 4. Dosage adjustment for the 3 anti-tumor necrosis factor-α drugs.

Drug	6 Months, n = 49	12 Months, n = 39	24 Months, n = 29	36 Months, n = 20
Infliximab, 5 mg/kg	n = 27	n = 25	n = 20	n = 13
Interval between infusions, weeks (SD)	8.3 (± 1.1)	8.8 (± 1.5)	9.4 (± 2.2)	9.7 (± 2.6)
Etanercept				
Total no. patients	n = 17	n = 10	n = 7	n = 7
Patients taking 25 mg	n = 14	n = 8	n = 7	n = 6
Interval between SC injections, days (SD)	6.6 (± 0.5)	7.1 (± 1.3)	9.0 (± 4.2)	8.0 (± 3.5)
Patients taking 50 mg	n = 3	n = 2	No data	n = 1
Interval between SC injections, days (SD)	12.3 (± 2.5)	15.0 (± 0.0)		10.0
Adalimumab, 40 mg	n = 5	n = 4	n = 2	n = 0
Interval between SC injections, weeks (SD)	3.1 (± 0.2)	3.6 (± 0.5)	3.5 (± 0.7)	No data

SC: subcutaneous.

ment for ADA was 40 mg every 3 weeks. For ETA, administration of low doses (50 mg to 25 mg) and dose-interval adjustment were both observed. The most frequent dosage adjustments were 25 mg once a week and 50 mg every 10 to 14 days. Progressively reducing treatment frequency was effective in maintaining remission for 36 months but the condition of some patients had worsened during maintenance therapy after dosage adjustment, so a dose escalation was required for most of them to improve disease activity.

Infliximab. At 6 months, dosage adjustments were successful in maintaining remission in 26 patients (26/27) and failed in 1 patient (1/27). For the patient who failed, a dose escalation was necessary, and infusions were stepped up from every 8 weeks to every 6 weeks. Followup was < 12 months in 1

patient (1/26). At 12 months, dosage adjustments were successful in maintaining remission in 22 patients (22/25) and failed in 3 patients (3/25). Dose escalations were necessary for the 3 patients who failed; infusions were stepped up from every 8 weeks to every 6 weeks in 2 patients, and from every 12 to every 11 weeks in 1 patient. Followup was under 24 months in 2 patients (2/22). At 24 months, dosage adjustments were successful in maintaining remission in 17 patients (17/20) and failed for 3 patients (3/20). Of the 3 patients who failed, 2 required a dose escalation to maintain remission, and infusions were stepped up from every 8 weeks to every 6 weeks; 1 patient switched from IFX to ADA. Followup was under 36 months in 4 patients (4/17). At 36 months, dosage adjustments were successful in 13 patients (13/13). Dose escalation was not necessary.

Etanercept. At 6 months, dosage adjustments were successful in maintaining remission in 12 patients (12/17) and failed in 5 patients (5/17). Of the 5 patients who failed, 4 required a dose escalation (ETA: 25 mg once a week to 25 mg twice a week), and 1 patient under ETA remained at 25 mg once a week but was not considered in remission. Followup was under 12 months in 2 patients. At 12 months, dosage adjustments were successful in maintaining remission in 9 patients (9/10) and failed in 1 patient (1/10). For the patient who failed, the dose was escalated from 25 mg once a week to 25 mg twice a week. Followup was under 24 months in 2 patients (2/9). At 24 months, dosage adjustments were successful in maintaining remission in all the patients (7/7). At 36 months, dosage adjustments were successful in maintaining remission in 4/7 and failed for 3 patients (3/7). For 2 patients, dose escalation was necessary to maintain remission (25 mg once a week to 25 mg twice a week) and 1 patient under ETA switched to IFX.

Adalimumab. At 6 months, dosage adjustments were successful in maintaining remission in 5 patients (5/5). Followup was under 12 months in 1 patient. At 12 months, dosage adjustments were successful in maintaining remission in 4 patients (4/4). Followup was under 24 months in 2 patients (2/4). At 24 months, dosage adjustments were successful in maintaining remission in 2 patients (2/2), and followup was under 36 months for those 2 patients.

Concomitant medications. For the group of 49 patients, concomitant medications reported after dosage adjustment were corticosteroids (9 times) and DMARD (6 times) — leflunomide 1 time and methotrexate 5 times. After dosage adjustment, corticosteroids were discontinued 8 times and reduced once to 5 mg/day. For DMARD, data were available for only 5 patients, for whom methotrexate and leflunomide were discontinued. Only a few data were available concerning NSAID. When remission had occurred, NSAID were used in 58.2% of cases (39/67). Six months after dosage adjustment, NSAID were used in only 7.7% of cases (3/39). No data were available concerning increases in NSAID dose or frequency to maintain remission. Anti-TNF-α dosage adjustment was effective in maintaining remission even when concomitant medications were discontinued. During relapse and anti-TNF dose escalation, corticosteroids and DMARD were not used, but NSAID were often added.

Survival curve. There was no difference between the 3 anti-TNF-α ($p = 0.07$) in cumulative probability of continuing therapy (Figure 1). The cumulative probability of continuing anti-TNF-α therapy after dosage adjustment was 87.8% at 6 months (n = 49; mean BASDAI = 14.0 ± 12.3), 79.0% at 12 months (n = 39; mean BASDAI = 12.0 ± 11.2), 70.5% at 24 months (n = 29; mean BASDAI = 16.0 ± 14.5), and 58.8% at 36 months (n = 20; mean BASDAI = 14.6 ± 13.8; Figure 1). There was no difference between the 3 anti-TNF-α ($p = 0.07$) in cumulative probability of continuing therapy (Figure 2).

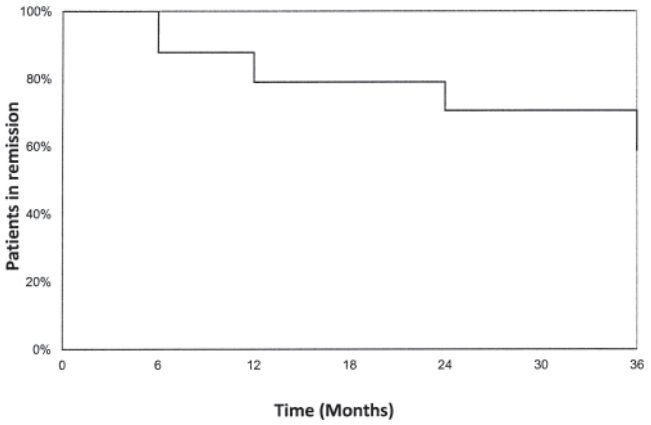

Figure 1. Kaplan-Meier combined survival curve showing percentage of patients in remission after dosage adjustment of the anti-TNF-α drugs adalimumab, etanercept, and infliximab at 6, 12, 24, and 36 months.

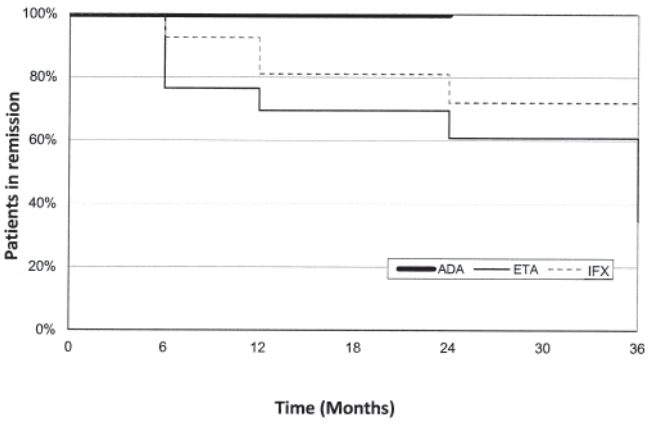

Figure 2. Separate Kaplan-Meier survival curves showing percentage of patients in remission after dosage adjustment of adalimumab (ADA), etanercept (ETA), and infliximab (IFX) at 6, 12, 24, and 36 months.

DISCUSSION

Our retrospective study has shown that remission had been attained in 35% of 189 patients with AS undergoing anti-TNF-α therapy, and those predictive factors of remission were male sex and anti-TNF-α naivety. Dosage adjustment and progressively reducing treatment frequency were effective in maintaining remission. To our knowledge, this is the first study on dosage adjustment in patients with AS involving the 3 anti-TNF-α agents used in current practice, with a prolonged followup.

Over the past decade, use of anti-TNF-α drugs in randomized, placebo-controlled clinical trials has led to ASAS partial remission in 20% to 30% of patients with AS[4,5,6,16,17]. Comparable results were found in an open-label study in which ASAS partial remission had occurred in 27.7% of the patients[7]. It is important to note that partial remission criteria were developed by the ASAS working group on the basis of clinical trials with NSAID. In our study, these criteria were not used because BASFI measures were not available for a large number of patients, and because ASAS partial remission criteria are not easily applicable in current practice. It is for these reasons that remission was defined according to pragmatic clinical and biological measures[8,9].

In one study, important predictors of good clinical response such as ASAS partial remission were younger age, greater CRP concentration, HLA-B27 positivity, and anti-TNF-α naivety[7]. In our study, only male sex and anti-TNF-α naivety were found to be clinical predictors of remission. The discrepancies between this study and other studies regarding prediction of response can be partly explained by the fact that the outcomes were not the same. The remission criteria we used were pragmatic and not comparable with the other criteria generally used (such as BASDAI 50 and partial remission criteria). However, it is surprising that remission was more successful with the third course of anti-TNF-α therapy than with the second. This finding should be interpreted with caution given the small number of patients in the study who were exposed to a third anti-TNF-α, and the fact that this was the last treatment available for patients.

In almost all the patients with AS who attained remission, discontinuing IFX and ETA led to a relapse within weeks or a few months[16,18,19,20]. The relapse rate following the discontinuation of IFX was almost 100%[18,19]. Mean time to relapse was 17.5 ± 7.9 weeks (range 7–45). All the patients with AS who were taking ETA relapsed after the treatment was discontinued. Median time to recurrence after discontinuation was 6.2 ± 3 weeks[16]. To our knowledge, no data are available for ADA.

The recommended and licensed dose of ETA for treating AS is 50 mg/week, administered by subcutaneous injection. For IFX and ADA, the recommended and licensed doses are 5 mg/kg every 6 weeks and 40 mg every 14 days, respectively. Some studies have been conducted on low-dose ETA and low-dose IFX, and on dose-interval adjustment[8,9,10,21,22,23,24]. No data on low-dose ADA were available. An open-label study involving 23 patients with active AS has shown that treatment with ETA 25 mg/week is effective enough to maintain remission after treatment with ETA 50 mg/week for 12 weeks[10]. Only 1 patient's condition worsened during maintenance therapy at 25 mg/week. In another open-label study involving 20 patients with AS treated with IFX, the interval between infusions was extended to 8 ± 1 week (minimum 7; maximum 10). The change in interval occurred between 12 and 142 weeks (median 21) of treatment. Mean followup after changing the therapeutic regimen was 86 ± 45 weeks. An adequate response was maintained in 65% (13/20) of the patients[21]. The effectiveness and safety of a 3 mg/kg dose of IFX in current practice over several years of followup were evaluated in 34 patients[22]. Median duration of treatment with low-dose IFX was 1507 days (about 4 years). Therapy was discontinued in 14 patients after a median of 91 days: in 6 patients for adverse events and in 6 for lack of efficacy; 2 patients were lost to followup. Dose escalation was required in 5 patients[22].

Our study was too small to draw general conclusions about patients with AS in remission. However, our findings suggest that there are good grounds to consider that dosage adjustment for IFX, ETA, and ADA could be effective to maintain remission. The retrospective design of our study limited the quality of the collected data, particularly to assess whether concomitant medications (NSAID in particular) had been left unchanged, reduced, or discontinued. Another limitation of our study was the definition of remission. Clinical and biological measures were used but duration of remission before dosage adjustment was not included. It could be interesting to consider that 3 or 6 months are necessary before dosage adjustment. Another limitation is the retrospective design: the dosage adjustment methodology could not have been planned and was at the physician's discretion.

As more effective therapies for AS become available, disease remission is increasingly regarded as an appropriate therapeutic goal. There is a need to further define and evaluate current proposals concerning the definition of remission in AS and to determine the best attitude to adopt once patients have attained remission. A new disease activity score in AS (ASDAS score) is now available[25]. ASDAS scores < 1.3 are indicative of disease inactivity and could be used for the definition of remission.

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