Remission in ankylosing spondylitis treated with anti-TNF-\(\alpha\) drugs: a national multicentre study

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Abstract

Objective. The primary objective of this retrospective study was to investigate the possibility of achieving partial remission (PR) in AS patients treated with anti-TNF-\(\alpha\) antagonists, such as adalimumab (ADA), etanercept (ETA) and infliximab (INF), in a real clinical practice setting. Predictors of PR were also evaluated.

Methods. A retrospective study was conducted in patients with AS treated with ADA, ETA and INF from 2000 to 2012. Kaplan–Meier survival curves were plotted to determine the rates of PR during the treatment with anti-TNF-\(\alpha\) drugs.

Results. A total of 283 patients with AS were treated with ADA (18.7%), ETA (26.8%) and INF (54.4%) as first anti-TNF-\(\alpha\) drugs, with a PR rate of 57.6%. The probability of obtaining PR with ADA, ETA or INF was not significantly different among all anti-TNF-\(\alpha\) patients. AS patients treated with a second anti-TNF-\(\alpha\) drug had a PR rate of 40.5%, but after switching for lack of response, the probability of obtaining PR with a second anti-TNF-\(\alpha\) drug was significantly lower from that of the first anti-TNF-\(\alpha\) drug (\(P = 0.0039\)). The probability of obtaining PR in patients with enthesitis (\(P = 0.04\)) or psoriasis (\(P = 0.0016\)) or low levels of CRP (\(P = 0.0225\)) was significantly lower compared with that of patients without these manifestations at baseline.

Conclusion. Our real-life study on PR confirmed the effectiveness of ADA, ETA or INF as first or second anti-TNF-\(\alpha\) drugs. The presence at baseline of enthesitis or psoriasis or low CRP values yielded a lower probability of obtaining PR.

Key words: ankylosing spondylitis, remission, anti-TNF-\(\alpha\) drugs.

Introduction

The TNF-\(\alpha\) antagonists infliximab (INF), etanercept (ETA) and adalimumab (ADA) have been demonstrated to be effective in controlling symptoms in AS [1]. A good clinical response to anti-TNF-\(\alpha\) drugs in AS can be defined by at least a 50% improvement in the BASDAI (BASDAI50) [2]. Assessment of SpondyloArthritis international Society (ASAS) response criteria [3, 4] and AS Disease Activity Score (ASDAS) [5]. The differentiation between complete clinical remission and a status of low disease activity has not been well defined and for this reason partial remission (PR) is the term normally used when ASAS remission criteria are applied. PR criteria, widely used in clinical trials, showed that PR can be achieved in about 20–40% of patients with AS treated with anti-TNF-\(\alpha\) drugs [6]. Nevertheless, to our knowledge few studies have addressed whether certain clinical/laboratory characteristics predict PR with TNF antagonist therapy in patients with AS [7–9]. Moreover, PR has not been considered as a primary endpoint in clinical trials, with no direct comparisons among TNF-\(\alpha\) blockers [10–12].
The primary objective of this retrospective study was to investigate the possibility of achieving PR in AS patients treated with anti-TNF-α antagonists, such as ADA, ETA and INF, in a real clinical practice setting. Clinical and laboratory features at baseline associated with PR were also evaluated.

Patients and methods

Study design

A retrospective study was conducted in six Italian secondary referral rheumatology centres (Rome, Campobasso, Milan, Padua, Potenza and Reggio Emilia) involved in research studies of AS. Patients’ written consent were obtained according to the Declaration of Helsinki when they were first entered into the database for treatment. This study was approved by the local ethical committee (Sapienza – University of Rome). We collected data on efficacy and safety of patients with AS treated with TNF-α blockers with a minimum of 6 months of follow-up from June 2000 to March 2012. Each patient met the modified New York criteria for the classification of AS [13].

ADA (40 mg every other week) and ETA (25 mg twice weekly or 50 mg/week) were given subcutaneously; INF was administered intravenously at 3–5 mg/kg at weeks 0, 2 and 6, then every 6–8 weeks, although the treating physician could increase or decrease this dose or schedule when warranted. At the time of initiation and during the follow-up of anti-TNF-α treatment, patient data were collected, including age, sex, diagnosis, disease duration, extra-articular manifestations (EAMs) (i.e. uveitis, IBD, psoriasis), BASMI [14], BASDAI [15], BASFI [16], patient’s visual analogue scale (VAS) on global disease activity (spinal pain), (iii) function (measured by the BASFI) and (iv) inflammation (mean of intensity and duration of morning stiffness, from the BASDAI) [3, 4].

Details of past and present anti-rheumatic therapies, such as DMARDs, corticosteroids, NSAIDs or analgesics, and current comorbidities were also recorded.

Statistical analysis

Categorical variables were analysed by χ² test with Yates’s correction or Fisher’s exact test. Kaplan–Meier (KM) survival curves were plotted to determine the rates of PR during treatment with anti-TNF-α drugs (ADA, ETA or INF). In KM survival curve calculations, we entered the time until the subject was censored or the event occurred. The difference between survival curves were determined by the log-rank test. The results were expressed as (median/25th–75th percentile). P < 0.05 was considered significant.

Results

From June 2000 to March 2012 (range of follow-up 6–142 months), a total of 283 patients with AS were treated with ADA (n = 53; 18.7%), ETA (n = 76; 26.8%) and INF (n = 154; 54.4%) as the first anti-TNF-α drug. The baseline characteristics of this cohort of patients are shown in Table 1.

At 12 weeks of exposure to the first anti-TNF-α drug, PR was achieved in 75 patients (26.5%). The percentage of PR among patients remaining on therapy continued to increase (n = 163; 57.6%) after a median (25th–75th percentile) interval of 4 (3–9) months. The median (25th–75th percentile) duration of PR was 32 (12–57) months. In these patients PR was lost in 33 patients (20.2%) after a median interval (25th–75th percentile) of 12 (6.5–22.5) months.

The KM life table for PR during treatment with ADA, ETA and INF in 283 patients with AS is shown in Fig. 1. Log-rank tests to compare survival curves showed that the probability of obtaining PR with ADA, ETA or INF was not significantly different among all anti-TNF-α patients.

The overall rate of discontinuation after the first anti-TNF-α drug was 19.8% (n = 56), of which 36 patients (12.7%) stopped the drug due to LR and 20 (7.1%) due to an AE. Thirty-seven (LR = 25; AE = 12) of the 56 AS patients started a treatment with a second anti-TNF-α drug, with a PR rate of 40.5%. The KM life table for PR during treatment with ADA, ETA and INF in 283 patients with AS is shown in Fig. 1. Log-rank tests to compare survival curves showed that the probability of obtaining PR with ADA, ETA or INF was not significantly different among all anti-TNF-α patients.

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<th>Table 1 The main demographic and clinical features of AS patients at baseline treated with TNF-α blockers</th>
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treatment with a first \((N = 283)\) or second anti-TNF-\(\alpha\) drug after switching for LR \((n = 25)\) or AE \((n = 12)\) in patients with AS is shown in Fig. 2. Log-rank tests to compare survival curves showed that the probability of obtaining PR with a second anti-TNF-\(\alpha\) drug, after switching for LR, was significantly lower than for the first anti-TNF-\(\alpha\) drug \((P = 0.0039)\). The group treated with a second anti-TNF-\(\alpha\) drug included patients switching from ADA to ETA \((n = 7)\) or INF \((n = 3)\), ETA to ADA \((n = 2)\) or INF \((n = 2)\), and INF to ADA \((n = 7)\) or ETA \((n = 16)\). Patients switching from ADA/INF to ETA \((n = 23)\) compared with patients switching from ADA/INF to INF/ADA \((n = 10)\) had a significantly \((P = 0.02)\) higher PR rate \((66.5\% \text{ vs } 10\%)\). The PR rate of patients switched from ETA to ADA/INF \((n = 4)\) was 25%.

CRP results were categorized into low \((<0.6 \text{ mg/dl})\), moderate \((0.6-2 \text{ mg/dl})\) and high \((>2 \text{ mg/dl})\) values according to Vastesaeger et al. [9]. The KM life table for PR during treatment with anti-TNF-\(\alpha\) drugs in AS patients with low \((n = 57)\), moderate \((n = 125)\) or high \((n = 101)\) CRP values at baseline is shown in Fig. 3. Log-rank tests to compare survival curves showed that the probability of obtaining PR in patients with high CRP values was significantly higher than that of patients with low CRP values \((P = 0.0225)\) at baseline.

The KM life table for PR during treatment with anti-TNF-\(\alpha\) drugs in AS patients with \((n = 95)\) or without \((n = 188)\) enthesitis, defined as spontaneous pain or tenderness at examination of the site of enthesis at baseline, is shown in Fig. 4. Log-rank tests to compare survival curves showed that the probability of obtaining PR in patients with enthesitis was significantly lower than that of patients with an absence of enthesitis \((P = 0.04)\) at baseline.

The KM life table for PR during treatment with anti-TNF-\(\alpha\) drugs in AS patients with psoriasis \((n = 37)\), IBD \((n = 30)\), uveitis \((n = 45)\) or absence of EAM \((n = 173)\) at baseline is shown in Fig. 5. Log-rank tests to compare survival curves showed that the probability of obtaining PR in patients with psoriasis at baseline was significantly lower than that of
patients with an absence of EAM (P < 0.0016) or IBD (P < 0.0028) at baseline. Twenty-seven patients with psoriasis had moderate (n = 20) and high (n = 7) CRP values. Survival curves for PR were not affected by parameters assessed before treatment, such as age (< or >40 years), disease duration (< or >10 years), peripheral arthritis (presence or absence), BASFI (<4.5, 4.5–6.5 or >6.5) or HLA-B27 (presence or absence).

Discussion

The concept of disease remission in AS should consider different aspects of the disease, such as clinical disease activity (including articular and extra-articular manifestations and associated diseases such as uveitis, psoriasis or IBD), objective inflammation (i.e. raised CRP) or active inflammation on MRI (i.e. function and structural damage). Nevertheless, true disease remission defined by the complete absence of disease activity, loss of function and damage is an important target in the management of AS patients classified according to the modified New York criteria.

In this context, the ASAS identified four domains (patient global assessment, pain, physical function and inflammation) for defining PR as a measure of low or minimal disease activity rather than of true disease remission [6]. This composite measure, giving a dichotomous result of the absence or presence of PR, has been validated by expert opinion and in clinical trials [18, 19]. In particular, anti-TNF-α therapy clinical trials have shown similar PR rates of around 20–40% for active therapy, regardless of which biologic agent is used and <5% in placebo groups [6]. In our real-life study we confirmed the usefulness of anti-TNF-α therapy with PR rates of 43.4%, 60.5% and 60.4% of patients treated with ADA, ETA and INF, respectively. In our study, the PR rate was higher than the PR rate of previous randomized controlled trials, suggesting that long-term follow-up permits the detection of PR in a larger group of patients. In fact, at 12 weeks of exposure to the first anti-TNF-α drug, the PR rate was 26.5% and continued to increase (57.6%) after a median (25th–75th percentile) interval of 4 (3–9) months. The probability curve of obtaining PR with ADA, ETA or INF was not significantly different among all anti-TNF-α patients. These results confirm previous studies reporting similar PR rates among ADA, ETA and INF, even if a direct comparison has not been performed [20–26]. Nevertheless, the different dosages of INF vs the fixed dosages of ADA and ETA could determine a difficult direct comparison among these anti-TNF-α drugs. However, a significant proportion of AS patients discontinue the therapy because of failure or poor tolerability [27–32]. In these patients, switching to another anti-TNF-α drug seems to be a feasible option [33–37], but the achievement of PR has not been analysed. Our study showed that the probability curve of obtaining PR with a second anti-TNF-α drug, after switching for LR, was significantly lower than that of the first anti-TNF-α drug. Nevertheless, a PR rate of 40.5% in these resistant patients to a first anti-TNF-α drug should be considered an important success that confirms the validity of switching to another anti-TNF-α drug in AS. In our study, switching from an anti-TNF-α receptor to an anti-TNF-α monoclonal antibody or vice versa cannot be compared because of the small sample size, while switching from one monoclonal antibody to another monoclonal antibody did not seem to achieve a high percentage of PR.

Although a retrospective study has methodological limits for identifying predictors of response, we also investigated which of the parameters assessed before treatment were associated with PR. In fact, few studies have addressed whether certain clinical or laboratory characteristics predict a clinical response to TNF-α antagonist therapy in patients with AS [7–9]. Our study showed that in the presence of high CRP values at baseline, the probability curve of obtaining PR was increased. This result agrees with a study showing that important predictors of good clinical response (BASDAI 50, ASAS40 and PR) after 12 weeks of ADA treatment in patients with AS included not only younger age, HLA-B27 positivity and TNF-α antagonist naiveity, but also higher CRP concentration [11]. The predictive value of CRP at baseline is confirmed by a recent study showing that CRP is a predictor of outcome resulting from anti-TNF-α and conventional therapy in various AS subpopulations [9].

Our analysis of different patterns of articular involvement (i.e. peripheral arthritis, enthesitis) showed that in the presence of enthesitis the probability curve of obtaining PR was reduced. A previous study evaluating predictors of a major clinical response to TNF-α blockers in AS reported an odds ratio for enthesitis of 1.02 for BASDAI50 response [8]. This study also reported that a shorter disease duration, younger age and a lower BASFI are predictors of a major clinical response to TNF blockers in active AS [8]. These results were obtained from data of two 12-week placebo-controlled randomized trials with INF and ETA [38, 39]. Recently the role of enthesitis as a predictor of the outcome of AS therapy was well defined [9]. With regard to the EAM at baseline (IBD, uveitis, psoriasis), the presence of psoriasis at baseline yielded a lower
probability of obtaining PR than the absence of EAM. To our knowledge, data about EAM as a predictor of response during anti-TNF-α treatment in AS are poor. However, at week 12, Rudwaleit et al. [11] showed in adalimumab-naive patients that the presence of psoriasis was associated with a good clinical response, but the data were not shown, while in another study no difference was found [40]. In our study, age, disease duration, BASFI and HLA-B27 did not affect survival curves for PR. The discrepancy of some of our results with previous studies can be explained by different outcome measures, study designs and follow-up, and show that observational studies might yield findings different from those coming from randomized controlled trials. Moreover, the impact of EAMs on domains included in the definition of PR has not been defined. In fact, the domains included in the PR (patient global assessment, spinal pain, function measured by the BASFI, inflammation measured by morning stiffness on the BASDAI) are more involved in the articular components of the disease and it could not perceive the impact of some other extra-articular ones.

In conclusion, we acknowledge that this real-life study has some limits, such as the retrospective design and the lack of information available on radiographic changes and MRI. Despite these limitations, these results on PR, obtained from clinical practice, are a reliable indicator of the sustained effectiveness of anti-TNF-α treatment in AS. The predictors of PR should probably be better defined to optimize treatment with TNF-α blockers. The achievement of clinical remission, defined by some crucial domains of the disease, should be the management target for patients with AS.

Rheumatology key messages

- The partial remission rate is similar in patients in Italy for AS treated with adalimumab, etanercept or infliximab.
- The presence at baseline of enthesitis or psoriasis or low CRP values yielded a lower probability of obtaining partial remission in Italy.

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