Efficacy in current practice of switching between anti-tumour necrosis factor-α agents in spondyloarthropathies

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Abstract

Objective. Anti-TNF-α agents are remarkably effective in the treatment of SpAs. However, 30% of patients withdraw from anti-TNF-α agents yearly because of inadequate efficacy or side effects. The objective of this study was to assess in current practice the response to a second and a third anti-TNF-α.

Methods. Retrospectively, all records of patients who had received at least two anti-TNF-α agents have been studied. For axial forms, treatment was considered effective if 3 months after switching the patient had a favourable expert opinion or showed an improvement in BASDAI of at least 2 on a scale of 0–10 or an improvement of 50% (BASDAI 50). For peripheral forms, the treatment was considered effective if the patient had a favourable expert opinion or if a clinical improvement of >30% of the swollen and tender joint counts was established. The reasons for switching were: (i) primary non-responder; (ii) loss of efficacy; and (iii) occurrence of side effects. To identify response predictor factors bivariate analysis was performed.

Results. Three hundred and seventy-seven patients under anti-TNF-α agents were treated and 99 patients had received at least two anti-TNF-α agents. Twenty-eight of these 99 patients had been treated with three anti-TNF-α agents. Following the failure of a first anti-TNF-α, the response to a second agent was satisfactory in 80.8%. Patients who had received a third anti-TNF-α following failure of the first two also showed a satisfactory response in 82.1%. The reason for switching from the first or second agent was not predictive of the response.

Conclusion. In the event of failure or intolerance to anti-TNF-α in the treatment of SpAs, performing a first or second switch produces a satisfactory therapeutic response.

Key words: Ankylosing spondylitis, Psoriatic arthritis, Spondyloarthropathies, Anti-tumour necrosis factor-α agents, Switch.

Introduction

The concept of SpAs encompasses a range of diseases with common characteristics. It includes AS, PsA, articular manifestations of IBDs (SP/IBDs), ReA, juvenile spondylitis and uSpA [1]. Conventional DMARDs have limited effectiveness on axial manifestations [2, 3]. For peripheral forms, conventional DMARDs have demonstrated potential effectiveness particularly in PsA [4–8].

The advent of TNF-α inhibitors (anti-TNF-α) has improved the management of patients with SpA. Many randomized, placebo-controlled clinical trials have demonstrated the efficacy of anti-TNF-α in the treatment of AS and PsA [9–14]. The efficacy of these therapies has also been demonstrated in uSpAs and in SP/IBD [15–17]. Three anti-TNF-α are currently used in the treatment of SpA: etanercept, adalimumab and infliximab. Most of the data have shown that infliximab, etanercept and adalimumab have comparable safety and efficacy profiles. In the absence of comparative head-to-head trials, there is no hierarchy recommended for the first prescription of anti-TNF-α.
Although anti-TNF-α have a dramatic effect on the treatment of SpA, almost 30% of the patients will have to discontinue their treatment prematurely due to loss of efficacy or side effects [18]. For those patients for whom a first anti-TNF-α fails, the alternative is a switch, corresponding to the introduction of a new anti-TNF-α. In RA, experience of switching anti-TNF-α is now substantial [19–21]. In the case of failure of a first anti-TNF-α, the introduction of a new agent permitted a satisfactory response to be obtained in most situations. But if switching to a second anti-TNF-α has been found to be efficient in 64–68%, the lack of efficacy of two anti-TNF-α, due to a primary non-responder, is predictive of ineffectiveness of the third anti-TNF-α [22]. Data regarding the use of this strategy in the management of SpA are limited [23–26]. Delaunay et al. [23] were the first to publish a preliminary study involving only 15 patients. These patients were unresponsive or intolerant to infliximab and etanercept was administered. Cantini et al. [24] reported in a prospective and observational study the efficacy and safety of etanercept in 23 AS patients who were unresponsive or intolerant to infliximab. Conti et al. [25] also conducted a prospective and observational study involving the switching of anti-TNF-α in 23 patients. Coates et al. [26] conducted a retrospective study on 16 SpA patients followed up for 2 years. All these authors found a satisfactory clinical response with a second anti-TNF-α.

The aim of this study was to determine in a large cohort of patients the response to a second anti-TNF-α after the unsuccessful administration of a first anti-TNF-α in patients with SpA. The study data were drawn from ‘real-life’ clinical situations. We also analysed whether the response to the second agent was determined by the reason for switching. Finally, we completed our analysis by studying patients who had received a third anti-TNF-α after the failure of the first two.

Materials and methods

Patients

This was a retrospective study conducted in two departments of rheumatology. All patients with SpA who had been treated with anti-TNF-α (from April 2000 until May 2008) were identified by record review. The records of SpA patients who had been treated with at least two anti-TNF-α agents were analysed. Only those with a minimum follow-up of 3 months after initiation of the last anti-TNF-α were selected.

Patients with AS were classified according to the modified New York Criteria, and patients with PsA according to the CASPAR and/or Moll and Wright criteria [27, 28]. Amor and/or the ESSG criteria were used for the diagnosis of other SpAs (uSpA and SP/IBD) [29, 30]. Patients were also classified according to axial or peripheral form depending on the predominant manifestations of SpA. A standardized form was used to collect data on demographics, effectiveness and adverse events observed during the anti-TNF-α therapy.

Drug administration

Anti-TNF-α used were infliximab (5 mg/kg every 6 weeks), adalimumab (40 mg every 14 days) and etanercept (25 mg twice a week or 50 mg/week). In this study, French Society of Rheumatology (FSR) and Assessment in Ankylosing Spondylitis (ASAS) Working Group recommendations for the use of anti-TNF-α in AS and PsA were followed in most cases [31, 32]. No compliance studies were conducted, and a number of anti-TNF-α prescriptions were produced before the publication of these recommendations.

Evaluation

FSR and ASAS recommendations were also used to assess the effectiveness of anti-TNF-α [31, 32]. For axial forms, treatment was considered effective if 3 months after switching the patient had a favourable expert opinion or showed an improvement in BASDAI of at least 2 on a scale of 0–10 or an improvement of 50% (BASDAI 50). For peripheral forms, the treatment was considered effective if the patient had a favourable expert opinion or if a clinical improvement of >30% of the swollen and tender joint counts was established. For patients who discontinued anti-TNF-α therapy before the scheduled evaluation at 3 months, due to side effects, changes in BASDAI for axial forms, and changes in swollen and tender joint counts for peripheral forms were recorded.

Statistical analysis

Statistical analysis was conducted using SAS software (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at P < 0.05. The results are presented as mean (s.d.) or median [inter-quartile range (IQR)] according to the number of subjects. Qualitative variables are expressed as percentages. Continuous time parameters (BASDAI, swollen and tender joint counts) were analysed using paired Student’s t-test or the Wilcoxon test for paired samples. Bivariate analysis was performed to identify response predictor factors (cause of failure, SpA subtype, axial or peripheral form, association with a DMARD, sex, HLA-B27, duration of disease and type of anti-TNF-α, type of sequence). For qualitative variables, the chi-square test or the Fisher’s exact test was used and for continuous parameters, the Wilcoxon test was used. Survival analysis was performed to study the time until failure of anti-TNF-α using the Kaplan–Meier method. The time to event was defined as the delay between anti-TNF-α start and anti-TNF-α failure and for patients who did not stop the treatment, the observation was censored at the date of maximal follow-up. The log rank test was used to compare cumulative incidences according to the type of anti-TNF-α.

Results

Characteristics of patients

Three hundred and seventy-seven SpA patients under anti-TNF-α agents were seen between April 2000 and May 2008. Two hundred and sixty-seven of these patients
had been treated with only one anti-TNF-α agent and 110 patients had stopped receiving the first anti-TNF-α agent due to primary non-response, loss of efficacy or occurrence of side effects before switching to another anti-TNF-α agent. Eleven of the 110 patients lost to follow-up were excluded. Consequently, the records of 99 SpA patients were assessed for the first switch. Twenty-eight of these 99 patients had been treated with three anti-TNF-α agents. Demographic and clinical characteristics of these patients are summarized in Table 1.

Effectiveness of the second anti-TNF-α in the cohort of 99 patients
For the first anti-TNF-α (number of prescriptions in Fig. 1), various causes of failure were recorded in the cohort of 99 patients (Table 1). The mean (s.d.) duration of the first anti-TNF-α agent before switching was 15 (14) months in the cohort of 99 patients. Forty-six per cent of these patients received their first anti-TNF-α agent due to primary non-response, loss of efficacy or occurrence of side effects before switching to another anti-TNF-α agent. Eleven of the 110 patients lost to follow-up were excluded. Consequently, the records of 99 SpA patients were assessed for the first switch. Twenty-eight of these 99 patients had been treated with three anti-TNF-α agents. Demographic and clinical characteristics of these patients are summarized in Table 1.

Effectiveness of the third anti-TNF-α in the cohort of 28 patients
Various causes of failure were recorded for the second anti-TNF-α in the cohort of 28 patients (Table 1). For the second anti-TNF-α, the number of prescriptions is shown in Fig. 1. The most common treatment sequence used for the first switch was etanercept to adalimumab (31 times), followed by the switch from etanercept to infliximab (22 times). A clinical response based on expert opinion was seen in 80.8% (80/99) of patients for the second anti-TNF-α 3 months after switching. The predominant manifestations were axial for 75 patients. Complete data about BASDAI before switching and 3 months after switching were available for 50/75 patients (before switching 39/50 patients had a BASDAI > 40/100 based on FSR and ASAS recommendations). For axial forms, 80.0% (60/75) responded to treatment based on expert opinion; 42.0% (21/50) vs 48.7% (19/39) based on improvement in BASDAI of at least 2 on a scale of 0–10; and 36.0% (18/50) vs 41.0% (16/39) responded to treatment based on BASDAI 50. Mean (s.d.) BASDAI was initially 55.1 (20) and fell to 41.3 (23) 3 months after switching. A statistically significant difference was found for BASDAI 3 months after switching (P < 0.0001). The predominant manifestations were peripheral for 24 patients. Complete data about swollen and tender joint counts were available for 11/24 patients (before switching only 6/11 patients had swollen joint count >3 and tender joint count >3 based on FSR recommendations). For peripheral forms, 83.3% (20/24) responded to treatment based on expert opinion, 54.5% (6/11) vs 83.3% (5/6) based on clinical improvement of >30% of the swollen and tender joint counts. Median (IQR) swollen joint count was 3.0 (1–6) initially and fell to 0 (0–2) 3 months after switching. Median (IQR) tender joint count was 7.0 (3–16) initially and fell to 2.0 (0–7) 3 months after switching. No statistically significant difference was found for median swollen joint count (P = 0.14) or for median tender joint count at 3 months (P = 0.24).

Effectiveness of the third anti-TNF-α agent in the 28 patients who had received three anti-TNF-α
Various causes of failure were recorded for the second anti-TNF-α in the cohort of 28 patients (Table 1). For the third anti-TNF-α, the number of prescriptions is shown in Fig. 1. A clinical response was seen in 82.1% (23/28)
patients for the second anti-TNF-α 3 months after switching.

The predominant manifestations were axial for 22 patients. Complete data about BASDAI before switching and 3 months after switching were available for 17/22 patients (before switching 16/17 patients had a BASDAI ≥ 40/100 based on FSR and ASAS recommendations). For axial forms, 81.8% (18/22) responded to treatment based on expert opinion, 52.9% (9/17) vs 56.2% (9/16) on improvement in BASDAI of at least 2 on a scale of 0–10 and only 29.4% (5/17) vs 31.2% (5/16) responded to treatment based on BASDAI 50. Mean BASDAI (IQR) was initially 75.0 (46–81) and fell to 43.0 (28–50) 3 months after switching. A statistically significant difference for BASDAI 3 months after switching was observed (P=0.0008).

The predominant manifestations were peripheral for six patients. Complete data about swollen and tender joint counts were available for four out of six patients (before switching only one out of four patients had swollen joint count ≥3 and tender joint count ≥3 based on FSR recommendations). For peripheral forms, 83.3% (5/6) responded to treatment based on expert opinion. No statistical evaluation for the swollen and tender joint counts was conducted due to the small number of patients.

A sub-group analysis was specifically conducted for AS and PsA patients (Table 2) without significant difference in efficacy after 3 months. Only 1 of the 21 patients who switched twice was a primary non-responder for all three anti-TNF-α agents. For the third course of anti-TNF-α, the survival rate was not determined due to the small number of patients (n=28).

### Analysis of predictive factors

Logistic regression analysis failed to distinguish response predictors (Table 3 and Fig. 3).

### Discussion

In this study, which involved 99 patients requiring a second anti-TNF-α agent, we have shown the good effect of switching. After the failure of a first anti-TNF-α agent, the response to a second one was judged satisfactory in 80.8% (80/99) based on expert opinion. For axial forms, a response was seen in 42.0% (21/50) for improvement in BASDAI of at least 2 on a scale of 0–10 and in 36.0% (18/50) for BASDAI 50. For peripheral forms, a response was seen in 27.2% (3/11) based on clinical improvement. The response to this second agent does not seem to be conditioned by the reason for failure of the first anti-TNF-α. Patients who received a third anti-TNF-α after the failure of the first two also presented a satisfactory response in 82.1% (23/28) based on expert opinion. A response was seen in 52.9% (9/17) for improvement in BASDAI of at least 2 on a scale of 0–10 and in 29.4% (5/17) for BASDAI 50. The reason for discontinuing the second agent did not condition response.

### TABLE 2 Response rate to the second and the third anti-TNF-α agent with sub-group analysis for AS and PsA

<table>
<thead>
<tr>
<th>Response rate</th>
<th>Improvement in outcome measures, %</th>
<th>Improvement by expert opinion, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second TNF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS</td>
<td>34</td>
<td>41.1</td>
</tr>
<tr>
<td>PsA</td>
<td>9</td>
<td>44.4</td>
</tr>
<tr>
<td>All SpA</td>
<td>61</td>
<td>34.4</td>
</tr>
<tr>
<td>Third TNF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS</td>
<td>14</td>
<td>42.8</td>
</tr>
<tr>
<td>PsA</td>
<td>3</td>
<td>66.6</td>
</tr>
<tr>
<td>All SpA</td>
<td>21</td>
<td>53.3</td>
</tr>
</tbody>
</table>

Responder: for axial forms, treatment was considered effective if, 3 months after switching, the patient showed an improvement in outcome measure (BASDAI of at least 2 on a scale of 0–10) or based on expert opinion; for peripheral forms, the treatment was considered effective if a clinical improvement of >30% of the swollen and the tender joint counts was established (outcome measure) or based on expert opinion.

The predominant manifestations were peripheral for six patients. Complete data about swollen and tender joint counts were available for four out of six patients (before switching only one out of four patients had swollen joint count ≥3 and tender joint count ≥3 based on FSR recommendations). For peripheral forms, 83.3% (5/6) responded to treatment based on expert opinion. No statistical evaluation for the swollen and tender joint counts was conducted due to the small number of patients.

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Logistic regression analysis failed to distinguish response predictors (Table 3 and Fig. 3).

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### TABLE 3 Logistic regression analysis failed to distinguish response predictors

<table>
<thead>
<tr>
<th>Response predictors</th>
<th>Response to the first agent</th>
<th>Response to the second agent</th>
<th>Response to the third agent</th>
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<tbody>
<tr>
<td>Subtype of SpA</td>
<td>0.97</td>
<td>0.055</td>
<td>0.85</td>
</tr>
<tr>
<td>Axial or peripheral form</td>
<td>0.52</td>
<td>0.72</td>
<td>0.93</td>
</tr>
<tr>
<td>Association with a DMARD</td>
<td>0.54</td>
<td>0.46</td>
<td>0.28</td>
</tr>
<tr>
<td>Sex</td>
<td>0.69</td>
<td>0.73</td>
<td>0.63</td>
</tr>
<tr>
<td>HLA-B27 profile</td>
<td>0.63</td>
<td>0.49</td>
<td>0.52</td>
</tr>
<tr>
<td>Duration of disease</td>
<td>0.78</td>
<td>0.61</td>
<td>0.09</td>
</tr>
<tr>
<td>Type of anti-TNF-α agent</td>
<td>0.33</td>
<td>0.73</td>
<td>0.54</td>
</tr>
<tr>
<td>Cause of failure of the first anti-TNF-α agent</td>
<td>0.96</td>
<td>0.25</td>
<td>0.47</td>
</tr>
<tr>
<td>Cause of failure of the second anti-TNF-α agent</td>
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![FIG. 2 Survival curve; the cumulative probability of continuing the treatment for the second anti-TNF-α agent was 67.0% at 1 year.](https://academic.oup.com/rheumatology/article-abstract/50/4/714/1778263/717)
Failure for the three anti-TNF agents was really rare. Only 1 of the 21 patients was a primary non-responder for all three anti-TNF-α.

The effectiveness of anti-TNF-α in the treatment of SpA has been demonstrated by many randomized, controlled clinical trials. Response rates range from 43 to 71% in AS (assessment on BASDAI 50) and from 62 to 87% in PsA [assessment as PsA responder criteria (PsARC)] [33]. However, controlled clinical trials do not accurately reflect daily clinical practice. Controlled clinical trials are not devoid of bias, including relatively short observational periods, and exclusion and inclusion criteria restricting the size of study groups to a small number of patients, which is unrepresentative of all SpAs. The information provided by open observational studies appears to be more relevant, probably reflecting the reality of medical practice. Delaunay et al. [23] were the first to publish a short series involving 15 patients. Treatment was switched from infliximab to etanercept. Efficacy was evaluated according to BASDAI 50 and American College of Rheumatology (ACR 20) criteria. A satisfactory response was found in 11 patients. Coates et al. [26] conducted a retrospective study on 103 AS patients. Sixteen patients were treated with at least two agents. According to ASAS 20 criteria, the response rate to a second agent was 93%. Coates et al. [34] conducted also a retrospective study on 60 PsA patients. Twelve patients were treated with at least two agents and seven with three agents. According to DAS-28 criteria, the response rate to a second agent was 58.3% and to a third agent 71.4%. In an observation-al study conducted by Conti et al. [25], switching was performed in 23 patients (7 AS and 15 PsA). Twelve out of 16 patients (75%) were considered responders on BASDAI 50 and PsARC when a switch was made from infliximab to etanercept, and four out of seven (57.1%) when a switch was made from etanercept to adalimumab.

In a multicentre, prospective study conducted by Cantini et al. [24] with patients initially treated with infliximab, a satisfactory response, based on ASAS 20 criteria, was observed in 17/23 (74%) at 54 weeks. In these studies, no clinical features were found to predict response. All these results are consistent with those obtained in our study. Moreover, we involved a substantial number of patients; one switch was made in 99 patients and two switches in 28 patients. This is not the first study assessing and confirming the interest of using a third anti-TNF-α agent in the treatment of SpA, but this study includes much larger numbers of patients treated with three anti-TNF-α agents.

The retrospective nature of this study limited the quality of collected data, particularly to assess the response rate to anti-TNF-α using BASDAI, swollen and tender joint counts. For the first switch, complete data about BASDAI were only available for 50/75 patients and before switching only 39/50 patients had a BASDAI ≥ 40/100. This is the reason why the responder rate was so different between expert opinion and BASDAI improvement (36.0% for BASDAI 50 and 42.0% for improvement in BASDAI of at least 2 on a scale of 0–10). For the joint count, complete data were only available for 11/24 patients and before switching only 6/11 patients had swollen joint count ≥ 3 and tender joint count ≥ 3. This is the reason why the responder rate was so different between expert opinion (83.3%) and improvement in joint count (27.2%). For the second switch, the responder rate was also really different between expert opinion, BASDAI and improvement in joint count for the same reason. Another limitation of this study due to its retrospective nature was the proportion on missing data on outcomes. Otherwise, given the limited alternative to anti-TNF-α, patients and physicians may continue treatment despite sub-optimal responses. This is particularly true for the second and the third anti-TNF-α. Indeed, there is no other option available. It may also influence the survival rate of these treatments.

Our data suggest that switching between anti-TNF-α agents is useful for SpA patients who are unresponsive or intolerant to a first and also to a second anti-TNF-α contrary to the results suggested for RA [22, 35, 36]. These results must be interpreted with caution due to the retrospective character of the study. Larger studies involving various switching patterns need to be undertaken before a definite conclusion can be drawn.

<table>
<thead>
<tr>
<th>Rheumatology key messages</th>
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<tbody>
<tr>
<td>- Performing a first or a second switch produces a satisfactory response in the treatment of SpAs.</td>
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<tr>
<td>- Failure of three anti-TNF-α agents is very rare.</td>
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Disclosure statement: The authors have declared no conflicts of interest.
References


