Concise Report

Lack of efficacy of a third tumour necrosis factor α antagonist after failure of a soluble receptor and a monoclonal antibody

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Objective. Some studies have highlighted the potential benefits of switching from infliximab to etanercept, or after failure of one or the other treatment. To our knowledge, no study has assessed the potential benefits of using the three anti-TNF-α agents that are currently available. The objective of this retrospective study was to assess the response to treatment in RA patients who had received the three anti-TNF-α agents, namely infliximab, etanercept and adalimumab.

Methods. Among a cohort of 364 patients undergoing biological treatments since the year 2000, 284 had been treated with only one anti-TNF-α agent. Our assessment focused on the records of 70 patients who had received at least two anti-TNF-α agents. Twenty of the 70 patients had received all three anti-TNF-α agents (infliximab, etanercept and adalimumab). Effectiveness was assessed using the 28-joint Disease Activity Score (DAS28), and adverse events were reported for each anti-TNF-α treatment.

Results. Of the 70 patients who had received two anti-TNF-α agents, 32 had switched from an antibody to a soluble receptor; 45% of them had a good clinical response to the soluble receptor. Thirty patients had switched from a soluble receptor to an antibody; 45% of them had a good clinical response to the antibody. Only eight patients had switched from an antibody to another antibody with an efficiency score of 33%. Of the 20 patients who had received three anti-TNF-α agents, seven had stopped receiving the third anti-TNF-α agent due to lack of effectiveness. In this group of non-responders to the third anti-TNF-α treatment, all patients except one had stopped receiving the two previous anti-TNF-α agents, without adverse events, for lack of effectiveness. These patients were deemed resistant to anti-TNF-α therapy.

Conclusions. Resistance to anti-TNF-α agents is rare. The lack of effectiveness of a soluble receptor and of one of the anti-TNF-α antibodies predicts the lack of effectiveness of the third anti-TNF-α treatment.

KEY WORDS: Rheumatoid arthritis, Anti-TNF-α agent, Switch, Etanercept, Infliximab, Adalimumab.

Anti-TNF-α agents have been available for the treatment of rheumatoid arthritis (RA) since the year 2000. The first anti-TNF-α agent available was infliximab. Anti-TNF-α therapy has been shown to significantly improve the course of the disease, modifying the probability of remission in some patients and reducing and even stopping articular destruction [1].

Today, three anti-TNF-α agents are available for the treatment of RA: infliximab [2], etanercept [3] and adalimumab [4]. The clinical effectiveness of anti-TNF-α therapy in patients who are non-responders to methotrexate is between 60 and 70% American College of Rheumatology 20% [ACR] response [5]. In early RA, and before methotrexate treatment, effectiveness can reach 70% [6, 7]. Thus, at least 30% of patients do not respond to the first anti-TNF-α treatment. Despite molecular differences [8], these three anti-TNF-α agents show similar degrees of effectiveness when combined with methotrexate [5, 9].

Some studies have explored the effectiveness of treating patients who failed to respond to infliximab with etanercept, and vice versa [10–12], showing an interest in changing from one anti-TNF-α agent to another when adverse events or inefficiencies occur.

To our knowledge, no studies have been conducted in which patients were treated successively with all three anti-TNF-α agents. The objective of this study was to analyse the potential efficacy of a third anti-TNF-α treatment after the first two had failed.

Patients and methods

Patients

Patients who had been diagnosed with RA, fulfilling the American College of Rheumatology (ACR) criteria [13], and who had been treated with at least one anti-TNF-α agent between July 2000 and August 2005 in the rheumatology department of a university hospital were identified by record review. The records of RA patients who had been treated with at least two anti-TNF-α (inflimab, etanercept or adalimumab) agents were analysed. Eighty patients were identified following a review of 364 records. A standardized form was used to collect data on demographics, effectiveness and adverse events observed during the anti-TNF-α therapy.
Evaluation

Demographic data included age, sex, rheumatoid factor, anti-citrullinated protein antibodies (CCP) as detected by enzyme-linked immunosorbent assay (ELISA) and disease duration. Previous DMARD therapy was recorded if known. Effectiveness criteria included tender and swollen joint counts (28-joint counts), morning stiffness (min), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Subjective data on global patient assessment were also available (rated from 0 to 100). The Disease Activity Score including 28 joints (DAS28) [14] was calculated on the basis of these criteria before the start of anti-TNF-α therapy and again 3 months later. The change in DAS28 indicated the difference between the DAS28 before the anti-TNF-α treatment and after 3 months of treatment. For patients who had stopped receiving the anti-TNF-α treatment before the end of the 3-month interval, on account of the occurrence of adverse events, the change in DAS was calculated using the DAS28 at the moment the treatment was stopped. When the change in DAS was <1.2 at 3 months, or when the DAS 28 remained >5.1, treatment was considered to be ineffective. Safety criteria included laboratory data (complete blood count, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), albumin and creatinine) before anti-TNF-α treatment and after switching to another anti-TNF-α agent, the number and severity of infusion reactions, infections, hospitalizations, other side-effects, and death.

Statistics

Data on the 80 patients were analysed using the SPSS program. Continuous variables were expressed as mean and standard deviation (s.d.). Owing to the small size of the samples, the Mann–Whitney test was used for intergroup comparisons. Statistical significance was defined as P < 0.05.

Results

Characteristics of patients

One thousand two hundred and twenty-three RA patients were seen in a university hospital rheumatology department between July 2000 and August 2005. Infliximab was the first anti-TNF-α agent available in July 2000. Etanercept, which was initially available in 2000 and 2001, was finally authorized for prescription in February 2002 and adalimumab was available in February 2003. Of the 223 RA patients, 364 patients who had received anti-TNF-α treatment were recorded. Two hundred and eighty-four (78%) of these had been treated with only one anti-TNF-α agent and 80 patients (28%) had stopped receiving the first anti-TNF-α agent due to adverse events or ineffectiveness before switching to another anti-TNF-α therapy. Of these 80 patients, 55 (68%) continued being treated with the second anti-TNF-α agent and 25 had stopped receiving the treatment on account of adverse events or ineffectiveness, and switched to a third anti-TNF-α agent. For 10 of the 80 patients, data were incomplete. Consequently, the records of 70 RA patients were assessed. Fifty of these patients had been treated with two anti-TNF-α agents and 20 of them with all three. The characteristics of these 70 patients are shown in Table 1. No difference was observed between the patients who had received two or three of the anti-TNF-α agents as regards erosive disease, positivity for rheumatoid factor or anti-citrullinated protein antibodies and mean number of DMARDs before anti-TNF-α therapy. All of the 70 patients had active disease. Patients who had received two anti-TNF-α agents had an initial DAS28 (before anti-TNF-α treatment) of 5.97 (s.d. 0.93), and those who had received all three anti-TNF-α agents had an initial score of 6.02 (s.d. 0.93).

Effectiveness of the second anti-TNF-α agent in the cohort of 70 patients who had received two anti-TNF-α agents

Thirty-two patients had received infliximab first, 30 etanercept first and eight adalimumab first.

Thirty-two patients had switched from an antibody to a soluble receptor, with a good clinical response being observed in 45% of the patients. Thirty patients had switched from a soluble receptor to an antibody, again with a good clinical response being observed in 45% of the patients. Only eight patients had switched from an antibody to another antibody, with an efficiency score of 33%. The changes in DAS28 for the first and second anti-TNF-α agents were 0.59 (s.d. 1.21) and 1.16 (s.d. 1.62), respectively.

Effectiveness of anti-TNF-α therapy in the 20 patients who had received three anti-TNF-α agents

Effectiveness and adverse events with infliximab. In 12 of the 20 patients, anti-TNF-α treatment began with infliximab as this was the first treatment available. DMARDs were associated with the anti-TNF-α agent in 18 of the 20 patients (methotrexate in 15 cases and leflunomide in three cases). Infliximab was discontinued due to inadequate response in 65% of the patients. Of the eight patients who had stopped receiving the treatment due to adverse events, five had an allergic reaction, one had a pulmonary infection and one had a cutaneous reaction. The mean duration of treatment was 12.5 months (range 3–42).

Effectiveness and adverse events with etanercept. In six of the 20 patients, anti-TNF-α treatment began with etanercept, whereas in 11 of the patients etanercept was second in the sequence of treatments. DMARDs (methotrexate) were associated with the anti-TNF-α agent in 12 of the 20 patients. Etanercept was discontinued due to inadequate response in 85% of the patients. Three adverse events, one allergic reaction, one headache and one cutaneous reaction, were observed. One patient is still on the treatment. The mean duration of treatment was 5.36 months (range 3–8).

Effectiveness and adverse events with adalimumab. Adalimumab was the last in the sequence of treatment in 12 of the 20 patients. Only two of the patients began the anti-TNF-α treatment with adalimumab. DMARDs were associated with the anti-TNF-α agent in 12 of the 20 patients (methotrexate in eight cases and leflunomide in four cases). Adalimumab was discontinued due to inadequate response in

Table 1. Characteristics of the 70 patients who had received at least two anti-TNF-α agents

<table>
<thead>
<tr>
<th>Age, mean (yr)</th>
<th>Patients treated with two anti-TNF-α agents (n = 50)</th>
<th>Patients treated with three anti-TNF-α agents (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>58</td>
<td>52.63</td>
<td></td>
</tr>
<tr>
<td>Sex ratio (F/M)</td>
<td>43/7</td>
<td>17/3</td>
</tr>
<tr>
<td>Rheumatoid factor</td>
<td>81%</td>
<td>81.1%</td>
</tr>
<tr>
<td>Anti-CCP antibodies</td>
<td>82%</td>
<td>87%</td>
</tr>
<tr>
<td>Erosive disease</td>
<td>82%</td>
<td>90%</td>
</tr>
<tr>
<td>Mean disease duration (yr)</td>
<td>15.42</td>
<td>13.02</td>
</tr>
<tr>
<td>Mean initial DAS28</td>
<td>5.97</td>
<td>6.02</td>
</tr>
<tr>
<td>Mean number of DMARDs used before anti-TNF-α agents</td>
<td>4.02</td>
<td>4.3</td>
</tr>
<tr>
<td>First anti-TNF-α agent used</td>
<td>Etanercept</td>
<td>24</td>
</tr>
<tr>
<td>Infliximab</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>
TABLE 2. Comparison between responders and non-responders to the third anti-TNF-α agent

<table>
<thead>
<tr>
<th></th>
<th>Responder to the third anti-TNF-α agent (n=7)</th>
<th>Non-responder to the third anti-TNF-α agent (n=13)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (yr)</td>
<td>44</td>
<td>61</td>
<td>0.016</td>
</tr>
<tr>
<td>Disease duration (yr)</td>
<td>10</td>
<td>19</td>
<td>0.107</td>
</tr>
<tr>
<td>Number of previous DMARDs</td>
<td>3.71</td>
<td>4.83</td>
<td>0.239</td>
</tr>
<tr>
<td>Mean initial DAS28</td>
<td>6.04</td>
<td>6.04</td>
<td>0.812</td>
</tr>
<tr>
<td>Number of side-effects with the two previous anti-TNF-α agents</td>
<td>1.28</td>
<td>0.16</td>
<td>0.004</td>
</tr>
</tbody>
</table>

In bold = \( P < 0.05 \).

47% of the patients. Three adverse events (two allergies and one infection) were observed. Seven of the patients are still taking adalimumab. The mean duration of treatment for the nine patients who had stopped was 4.54 months (3–8).

**Benefits of treatment with a third anti-TNF-α agent after failure of one antibody and one soluble receptor.** Of the 20 patients, seven showed a good response to the third anti-TNF-α agent and constituted group 1. In the 13 remaining patients, no response was observed and the treatment was discontinued due to lack of effectiveness. These 13 patients constituted group 2.

When the characteristics of the two groups were compared, it was interesting to note that all of the group 1 patients save one had adverse events with one of the two initial anti-TNF-α treatments. On the other hand, all except two of the group 2 patients had no adverse events but discontinued the anti-TNF-α treatment (i.e. one anti-TNF-α antibody and the soluble receptor) due to lack of effectiveness. In this group, switching to another anti-TNF-α agent did not contribute to improving effectiveness. The number of adverse events occurring with the three anti-TNF-α agents was compared between groups 1 and 2 and the difference was statistically significant \( P = 0.004 \). Moreover, in the group 2, in which RA was refractory to anti-TNF-α therapy, the age of the patients was significantly higher than in group 1, although other parameters such as initial DAS28 and the number of DMARDs before anti-TNF-α treatment were not different (Table 2).

**Discussion**

Three anti-TNF-α agents, one soluble TNF- receptor (etanercept [3]) and two anti-TNF-α antibodies (infliximab [2] and adalimumab [4]), are available for the treatment of RA. In this retrospective study we observed that patients who had failed to respond to the soluble TNF-receptor and to one of the two anti-TNF-α antibodies on account of their ineffectivity, and who had not shown side-effects, did not respond to the other anti-TNF-α antibody. On the other hand, most of the patients who had stopped receiving one of the first two anti-TNF-α agents due to the occurrence of adverse events showed a good response to the third anti-TNF-α agent. Moreover, patients in the anti-TNF-α-refractory group were older than those in the other group but did not differ, in terms of activity or previous treatment, from the group that responded to the third anti-TNF-α treatment. To our knowledge, this is the first study that has assessed patients who were refractory to three anti-TNF-α therapies.

When we analysed the entire population of RA patients who had received anti-TNF-α treatment between 2000 and 2005, we observed that 68% of patients had discontinued a second anti-TNF-α agent after a mean follow-up of 11.81 months (s.d. 8.01). This result is consistent with the literature as several studies have reported the benefits of using infliximab after etanercept [10, 11] or etanercept after infliximab [12, 15–18]. When adalimumab (a second anti-TNF-α antibody) was available, reports on its effectiveness after etanercept or infliximab were published [19, 20]. The ineffectiveness of two anti-TNF-α agents is not an infrequent event; 35% of patients monotherapy treatment. Thus, most of the patients benefited from a change in anti-TNF-α agent when they had initially been receiving only one.

Our population of anti-TNF-α-refractory patients is rather limited as it represents only 8.8% of all of the RA patients (284) treated with anti-TNF-α agents in the last 5 yr. Although most of the data show that all three anti-TNF-α agents are similarly effective [2–4] and that switching anti-TNF-α agents is effective regardless of the molecule used [21], our study shows that the third anti-TNF-α agent was effective in only 35% of the patients. Moreover, when responders were compared with non-responders, we observed a lack of effectiveness without adverse events with the first two anti-TNF-α agents in most of the non-responders, although all of the patients in the responders group had one adverse event with at least one of the first two anti-TNF-α agents, suggesting that the previous anti-TNF-α agent should have been effective in the absence of this complication.

In conclusion, RA patients who are refractory to all three anti-TNF-α agents are rare. The ineffectiveness of two anti-TNF-α treatments, one soluble receptor and one antibody, predict the ineffectiveness of the third anti-TNF-α agent.

The authors have declared no conflicts of interest.

**References**