Adalimumab in clinical practice. Outcome in 70 rheumatoid arthritis patients, including comparison of patients with and without previous anti-TNF exposure

A. N. Bennett, P. Peterson, A. Zain, J. Grumley, G. Panayi and B. Kirkham

Tumour necrosis factor (TNF) blockade has become a standard treatment for severe rheumatoid arthritis (RA). Adalimumab, a fully human anti-TNF-α monoclonal antibody, is the most recently licensed of these therapies in the UK, having been licensed in September 2003. Adalimumab has a comprehensive clinical trial programme [1–3].

The aim of this study was two-fold. First, to compare the outcome of treatment in normal clinical practice to trial outcomes, and secondly to study the efficacy of adalimumab in treating patients who had previously failed other biological therapies.

Data on the switching from one anti-TNF-α drug to another are available but limited [4, 5]. The two published papers provide encouraging data on switching between infliximab and etanercept or vice versa in relatively small numbers of patients. Evidence to support switching from other anti-TNF-α drugs to adalimumab is limited to publications in abstract form and is again limited [6].

Materials and methods

Patients with a confirmed diagnosis of RA who met the British Society for Rheumatology guidelines for anti-TNF-α treatment [7] were prospectively followed if they were started on adalimumab. Seventy patients, from one clinic, were identified and the following information was recorded from routine outpatient follow-up appointments: patient demographics, diagnosis, previous disease-modifying anti-rheumatic drugs (DMARDs), previous prednisolone, previous treatment with and reason for stopping other biological therapy, current DMARDs, dose, frequency and duration of treatment with adalimumab, Disease Activity Score 28 (DAS28) and health assessment questionnaire (HAQ) prior to commencing adalimumab, DAS28 and HAQ at weeks 4, 8, 16, 26 and 52 and the most recent scores, change in DAS28 and HAQ from prior to adalimumab to the most current, European League Against Rheumatism (EULAR) response, remission rate and adverse events.

Informed consent was obtained from the patients. As this project was a departmental audit, local ethical approval was not required.

Statistical analysis

Data were analysed using the statistical package for the social sciences (Norusis/SPSS). The data were assessed for normality by calculating values for kurtosis and skewness, as well as with the Kolmogorov–Smirnov test of normality. The independent t-test and Mann–Whitney test were used to compare differences between groups and paired t-test and Wilcoxon signed rank test were used to compare differences within groups, depending on whether
or not the data were normally distributed. *P* values < 0.05 were regarded as statistically significant.

**Results**

The characteristics of the study population are shown in Table 1. All patients received adalimumab 40 mg subcutaneously once every fortnight. The primary outcome measures were the change in DAS28 and HAQ. EULAR response and achievement of remission. Remission is defined as a DAS28 < 2.6. The EULAR response criteria are displayed in Table 2.

The mean previous number of DMARDs used was 3.4. Twenty-five patients (36%) had previously been on prednisolone. Sixty-nine (99%) had previously been on methotrexate (one patient refused methotrexate therapy). Sulphasalazine, hydroxychloroquine, leflunomide, parenteral gold and azathioprine had been tried in 73, 51, 40, 35 and 21% of patients, respectively.

Eighteen (26%) patients were on monotherapy with adalimumab. Fifty-two (74%) were on combination therapy; six (9%) were on adalimumab with low-dose prednisolone, 31 (44%) were on adalimumab with one other DMARD (26 methotrexate, two leflunomide, two hydroxychloroquine, one azathioprine).

**Table 1. Characteristics of the study population**

<table>
<thead>
<tr>
<th>Total no. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>100</td>
</tr>
<tr>
<td>Female</td>
<td>61</td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
</tr>
<tr>
<td>Mean age: yr (range)</td>
<td>54 (19–77)</td>
</tr>
<tr>
<td>Mean previous DMARD use (range)</td>
<td>3.4 (2–7)</td>
</tr>
<tr>
<td>Previous prednisolone</td>
<td>25</td>
</tr>
<tr>
<td>Previous number of biologicals used (no. of patients)</td>
<td>29 (26)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>23</td>
</tr>
<tr>
<td>Etanercept</td>
<td>5</td>
</tr>
<tr>
<td>Anakinra</td>
<td>1</td>
</tr>
<tr>
<td>Mean duration of treatment with previous biological: months (range)</td>
<td>9 (0.5–24)</td>
</tr>
<tr>
<td>Secondary failure (all infliximab)</td>
<td>13</td>
</tr>
<tr>
<td>Primary failure</td>
<td>8</td>
</tr>
<tr>
<td>Adverse events</td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
</tr>
</tbody>
</table>

**Table 2. EULAR response criteria**

<table>
<thead>
<tr>
<th>DAS28 improvement</th>
<th>Present DAS28</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 1.2</td>
</tr>
<tr>
<td>&lt; 3.2</td>
<td>Good response</td>
</tr>
<tr>
<td>3.2–5.1</td>
<td>Moderate response</td>
</tr>
<tr>
<td>&gt; 5.1</td>
<td>Moderate response</td>
</tr>
</tbody>
</table>

**Table 3. EULAR response and mean DAS28 and HAQ change**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>EULAR response (%) (moderate, good, remission)</th>
<th>Mean DAS change</th>
<th>Mean HAQ change</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>70</td>
<td>77 (51, 26, 19)</td>
<td>−2.1 (<em>P</em> &lt; 0.001)</td>
<td>−0.34 (<em>P</em> &lt; 0.001)</td>
</tr>
<tr>
<td>Previous anti-TNF: naive</td>
<td>44</td>
<td>85 (55, 30, 23)</td>
<td>−2.4 (<em>P</em> &lt; 0.001)</td>
<td>−0.31 (<em>P</em> &lt; 0.001)</td>
</tr>
<tr>
<td>Previous anti-TNF: exposed</td>
<td>26</td>
<td>65 (46, 19, 8)</td>
<td>−1.7 (<em>P</em> &lt; 0.001)</td>
<td>−0.31 (<em>P</em> = 0.01)</td>
</tr>
<tr>
<td>Previous anti-TNF: secondary failures</td>
<td>13</td>
<td>77 (62, 15, 15)</td>
<td>−2.1 (<em>P</em> &lt; 0.001)</td>
<td>−0.26 (<em>P</em> = 0.062)</td>
</tr>
<tr>
<td>Previous anti-TNF: primary failures</td>
<td>8</td>
<td>37.5 (25, 12.5, 0)</td>
<td>−0.7 (<em>P</em> = 0.243)</td>
<td>−0.22 (<em>P</em> = 0.073)</td>
</tr>
</tbody>
</table>

**Outcome**

After a mean treatment duration with adalimumab of 7.3 months (range 1–20), 54 (77%) patients continued adalimumab. Fifty-four (77%) achieved a EULAR response: 18 (26%) had a good response and 36 (51%) a moderate response. Thirteen (19%) were in remission (Table 3).

The mean improvement in DAS28 was 2.1 (6.3–4.2; *P* < 0.001), after a mean of 7.3 months of treatment (Fig. 1). The mean HAQ score improved 0.34 (2.07–1.73; *P* < 0.001) (Fig. 2). A clinically significant decrease in HAQ of greater than 0.22 occurred in 66% of patients.

Sixteen (23%) patients stopped treatment with adalimumab, 10 (14%) because of primary failure, one (1%) because of secondary failure, and five (7%) because of adverse events.

**Previous biological therapy**

Twenty-six patients had previously tried 29 biologicals (23 infliximab, five etanercept, one anakinra). The mean duration of treatment was 9 months (range 0.5–24). The reason for changing biologicals (Table 1) was secondary failure (defined as failure to maintain a EULAR response after a minimum of 3 months of treatment, having initially achieved a response) to infliximab in 45% (13) of cases, primary failure (defined as never achieving a EULAR response) in 27% (8) and adverse events in 21% (6). Of the other two patients, one had previously had a good response to etanercept but had moved from the USA to the UK when etanercept was in short supply, and the other had been successfully treated with infliximab in a drug trial but wished to change to a self-administered form of anti-TNF-α.

After a mean treatment duration of 8.5 months (range 1–19) on adalimumab, 65% of patients responded to adalimumab with a mean decrease in DAS28 of 1.7 (6.3–4.6; *P* < 0.001). Forty-six per cent had a EULAR moderate response, 19% EULAR good response. 8% were in remission and 31% were non-responders (Table 3). One (4%) has not responded yet, but has not been on adalimumab for the recommended 3 months before declaring a failure of treatment.

The improvements in DAS28 and HAQ were significant within the previously anti-TNF-naive and exposed group, but when comparing between groups there was no statistical difference in the change in DAS28 (*P* = 0.069) and HAQ (*P* = 0.88).

**Secondary failures to infliximab**

Of the 13 previous infliximab secondary failure patients previously treated for a mean of 8.9 (range 3–13) months, 77% (10) responded to adalimumab, after a mean treatment duration of 9.6 (range 1–19) months. Sixty-two per cent had a EULAR moderate response, 15% had a EULAR good response and 15% were in remission. Two (15%) have not responded and one (8%) with or without low-dose prednisolone, and 15 (21%) were on adalimumab and two or more DMARDs, with or without low-dose prednisolone.
has not responded as yet but has not been on adalimumab for
3 months.

When analysing the outcome of the subgroups, the improve-
ment in DAS28 in the secondary failure group \((n=13, \text{ all }
\text{infliximab})\) was significantly \((P=0.023)\) better than the DAS28
improvement in the primary failure group \((n=8; \text{ four }
\text{infliximab, four etanercept})\). Figure 3 shows the mean DAS at baseline, most
recent DAS and the mean change in DAS in response to
adalimumab, divided into previously anti-TNF-naive, previous
anti-TNF failure, previous anti-TNF primary failure and
secondary failure groups. Similar data for HAQ outcome are
illustrated in Fig. 4.

**Adverse events**

In total, 12 (17%) patients had adverse events. Five (7%) were
clinically significant and resulted in cessation of treatment with
adalimumab and seven (10%) were mild and treatment was
continued. The significant adverse events that led to withdrawal

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**Fig. 1. Mean DAS28.**

**Fig. 2. Mean HAQ score.**
of treatment included acute shortness of breath of unknown cause in one patient, an anaphylactic-like reaction with severe facial swelling and rash in one patient, a flare of her pre-existing lupus (lupus and RA overlap with predominant erosive arthritis and minimal lupus features) in combination with liver function test abnormalities in one patient, and severe nausea and a flu-like illness in two patients. The mild adverse events, which did not require cessation of treatment, were injection site reactions in four patients, nausea in one patient, new-onset asthma in one patient, and a pretibial soft tissue infection (adalimumab temporarily stopped) in one patient.

Discussion

As clinical trial results often differ from results in normal clinical practice, the first purpose of this study was to compare the efficacy and safety of patients treated with adalimumab in normal clinical practice to the outcome data published in the key adalimumab controlled clinical trials. The trials of particular note for comparison are the ARMADA trial [1], the STAR trial [2] and the Humira DE011 study [3]. All of these trials use anti-TNF-naive patients.

The STAR trial is the best comparison with our cohort, because it compares ‘standard rheumatic therapy’ combined with adalimumab, as in our cohort, with continuing ‘standard rheumatic therapy’ plus placebo. The STAR trial population was larger (318 vs 70) but otherwise the two cohorts were similar with respect to mean age, sex and concomitant DMARD use. The major differences between the STAR trial and our cohort are that 37% of our patients have been on previous anti-TNF therapy and only 36% of patients, compared with 51% in the STAR trial, were on prednisolone. Fifty-three per cent of STAR trial patients achieved an ACR20 response. Our data compare favourably to this, with 77% achieving a EULAR moderate or good response.

The ARMADA trial was an efficacy and safety trial of adalimumab at different doses in combination with methotrexate vs placebo and methotrexate. The characteristics of the patients, in the ARMADA trial arm receiving adalimumab 40 mg
subcutaneously every other week ($n=67$), were similar to those of our patients receiving adalimumab and methotrexate ($n=26$). In the ARMADA trial, the mean improvement in DAS was 2.5 (5.7–3.2) and the mean improvement in HAQ was 0.62 (1.55–0.93) after 6 months of treatment. In our cohort, the mean improvements in DAS and HAQ were 2.0 (6.4–4.4) and 0.45 (2.05–1.6), respectively, after a mean of 7.8 months of treatment. If the 50% of our patients who had been on previous anti-TNF therapy are excluded and only previously anti-TNF-naive patients are analysed, the mean decrease in DAS improves to 2.6 (6.5–3.9) and the mean decrease in HAQ improves to 0.52 (1.84–1.32) after a mean of 6 months of treatment, and is very similar to the results in the ARMADA trial.

Twenty-four of our patients were on adalimumab monotherapy (with or without prednisolone, maximum dose 10 mg daily, as in the DE011 trial) and therefore can be compared with the adalimumab 40 mg fortnightly arm of the DE011 trial ($n=113$). The mean age, percentage female, mean number of previous DMARDs and percentage of patients on corticosteroids was 52.7 yr, 79.6%, 3.8 and 68.1%, compared with 60.5 yr, 92%, 4.0 and 25% in our subgroup of monotherapy patients.

The mean improvement in DAS28 and HAQ in the DE011 study was 1.7 (7.1–5.4) and 0.38 (1.83–1.45), respectively, after 26 weeks compared with 2.1 (6.3–4.2) and 0.23 (2.24–2.01) in our monotherapy cohort after a mean of 32 weeks. The percentage of patients achieving at least a moderate response or a good response in the DE011 study was 55.8 and 8.8% at 26 weeks compared with 70 and 25% after a mean of 32 weeks of treatment in our monotherapy cohort. If the adalimumab monotherapy patients with previous anti-TNF exposure from our cohort are excluded from analysis, the mean DAS decrease improves further to 2.3 (6.4–4.1), 76% achieving at least a moderate EULAR response and 29% achieving a good response.

One of the main aims of the STAR trial was to assess the safety of adalimumab in combination with standard rheumatoid therapy. The rate of overall adverse events was 86.5% and that of adverse events leading to withdrawal was 2.8%. In our cohort the overall rate of recorded side-effects was much lower (17%) but the rate of drug cessation directly related to adverse events was 7%. The dramatically lower rate of recorded adverse events can be explained by the less intensive observation for side-effects in everyday clinical practice, particularly for minor side-effects such as rhinitis, headache and back pain.

The efficacy results of our normal clinical practice cohort are similar to the clinical trial outcomes. Our small numbers might influence the increased percentage of patients withdrawing from therapy; however, this may reflect the less selected population.

The second purpose of this study was to assess the outcome of patients treated with adalimumab who had previously been treated with other biological agents. There are only limited data on the efficacy of switching anti-TNF-α therapy when previously one has failed. Two published papers [4, 5] support the use of switching from one anti-TNF-α drug to another in the event of failure, due to lack of efficacy or adverse events; however, these papers only include switching from infliximab to etanercept and vice versa. Gomez-Puerta et al. [8] reported a small group of patients ($n=12$) who had all stopped infliximab due to inefficacy, predominantly due to secondary failure, and had been switched to etanercept. Of these 12 patients, 10 (83%) had a good (2) or moderate (8) EULAR response with a clinically and statistically significant ($P=0.019$) improvement in DAS28 from a mean (s.d.) of 5.63 (1.1) to 4.3 (0.8).

The evidence for switching from a failed anti-TNF-α drug to adalimumab is limited to publications in abstract form. Buch et al. [6] presented 50 adalimumab patients; 33 had previous exposure to biological agents and 50% of these had failed or had toxicity to infliximab. Of their 33 patients, 44% had a moderate EULAR response and 9% had a good EULAR response, with a mean reduction in DAS of 1.48.

In our cohort, 26 patients had previously been treated with 29 biologicals. Sixty-five per cent had a EULAR response: 46% had a moderate response and 19% a good response, and 8% were in remission.

Although there was a trend towards anti-TNF-naive patients having a better outcome than previous anti-TNF failures, in terms of DAS, this was not significant ($P=0.069$). However, when comparing the subgroups of previous anti-TNF failures, the secondary failures, which were all to infliximab, had a significantly ($P=0.023$) better improvement in DAS than the primary failures.

Our study therefore supports the previously mentioned studies showing that despite previous failures to anti-TNF it is clinically worth switching to another anti-TNF blocker. This is particularly the case for previous secondary failures to infliximab, which supports the findings of Gomez-Puerta et al. [8].

The theory behind secondary failure to infliximab is the development of anti-infliximab antibody (AIA), previously known as human anti-chimeric antibody (HACA). This is an antibody to the murine component of infliximab, which develops some time after initiation of treatment and is thought to be related to the shortened duration of response after repeated infliximab doses, resulting in a decrease in efficacy and failure. This was first described in RA patients by Elliott et al. [9]. HACA is associated with lower serum concentrations of infliximab and is reduced by the concomitant administration of methotrexate, which slows the decline in serum concentration of infliximab [10, 11]. In theory, treatment with the fully humanized adalimumab should not lead to the development of these antibodies. Our clinical experience supports this, with only one secondary failure to adalimumab compared with at least 17 secondary failures to infliximab. This study also suggests, from the poor response to adalimumab in previous primary failures, that there may be a subpopulation of RA patients that does not respond to anti-TNF.

Conclusion
Our clinical experience confirms the clinical trial data showing that adalimumab is an effective and safe drug in the treatment of active RA. Our data also show that patients do respond to adalimumab despite previous failures to other anti-TNF drugs. This is particularly true for patients with previous secondary failure to infliximab.

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References
2. Furst DE, Schiff MH, Fleischmann RM et al. Adalimumab, a fully human anti-tumour necrosis factor-α monoclonal antibody, and concomitant standard antirheumatic therapy for the


