Effectiveness of adalimumab for rheumatoid arthritis in patients with a history of TNF-antagonist therapy in clinical practice


Objective. To evaluate the effectiveness and safety of adalimumab in patients with rheumatoid arthritis (RA) who previously discontinued tumour necrosis factor (TNF) antagonists for any reason in clinical practice.

Methods. ReAct (Research in Active Rheumatoid Arthritis) was a large, open-label trial that enrolled adults with active RA who had previously been treated with traditional disease-modifying anti-rheumatic drugs or biological response modifiers. Patients self-administered adalimumab 40 mg subcutaneously every other week for 12 weeks and were allowed to enter an optional long-term extension phase. Measures of adalimumab effectiveness included American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) response criteria, Disease Activity Score 28 (DAS28) and the Health Assessment Questionnaire Disability Index (HAQ DI).

Results. Of 6610 patients, 899 had a history of etanercept and/or infliximab therapy; these patients experienced substantial clinical benefit from adalimumab treatment. At week 12, 60% of patients had an ACR20 and 33% had an ACR50 response; 76% had a moderate and 23% had a good EULAR response. In addition, 12% achieved a DAS28 < 2.6, indicating clinical remission, and 13% achieved a HAQ DI score < 0.5. The allergic adverse event rate, regardless of relationship to adalimumab, was 6.5/100-patient-years (PYs) in previously TNF-antagonist-exposed patients and 4.3/100-PYs in TNF-antagonist–naive patients. A multiple regression analysis indicated no statistically significantly increased risk of serious infections in patients who received prior TNF antagonists compared with TNF-antagonist–naive patients.

Conclusion. In typical clinical practice, adalimumab was effective and well-tolerated in patients with RA previously treated with etanercept and/or infliximab.

Key words: Adalimumab, Etanercept, Infliximab, TNF antagonist, Rheumatoid arthritis.

Introduction

Biologic response modifiers that target tumour necrosis factor (TNF) inhibition have become established therapies for active rheumatoid arthritis (RA) in recent years. Sustained efficacy of adalimumab, etanercept and infliximab has been demonstrated, significantly improving symptoms and limiting progression of joint destruction and subsequent disability of patients with RA [1–3]. The therapeutic efficacy of all three TNF antagonists is postulated from their ability to bind soluble TNF and prevent its binding to the natural TNF receptor. TNF blockade in combination with methotrexate significantly reduces clinical disease activity and halts joint destruction in most patients with early or longstanding RA [4–7]. Even if disease activity is not substantially reduced, TNF blockade has been shown to reduce joint destruction, suggesting that inflammation and joint destruction can be disconnected and are independently controlled by TNF inhibition [8]. These effects have been attributed to the role of TNF in both synovitis and the activation and differentiation of osteoclasts, the mediators of bone destruction in RA [9].

Although TNF antagonists are an important advance in the therapy of RA, some patients with RA may be intolerant of these agents or may not experience a clinically meaningful response [10]. A practical question faced by clinicians and patients is whether switching TNF blockers is likely to produce improved clinical response and tolerability. In fact, there are data indicating that switching among the three available TNF antagonists (adalimumab, etanercept and infliximab) is safe and effective, with few withdrawals because of intolerance or lack of efficacy [11–28]. New biological agents for the treatment of RA, such as rituximab and abatacept, also factor into the therapeutic decision faced by clinicians and patients. Because current data indicate that non-response to one TNF antagonist does not preclude a response to another, an additional TNF-antagonist trial may be warranted before moving on to another biological agent. There is a need for additional data to document the safety and effectiveness of switching among TNF antagonists in clinical practice to guide clinicians’ choice of treatment after failure of anti-TNF therapy.

The ReAct (Research in Active Rheumatoid Arthritis) trial is the largest study of a TNF antagonist to assess the safety and effectiveness of adalimumab, with or without concomitant disease-modifying anti-rheumatic drugs (DMARDs), in routine clinical practice [29]. Of the 6610 patients who participated in ReAct, the current analysis evaluated the effectiveness of adalimumab in 899 patients who had previously been treated with etanercept and/or infliximab.

Methods

This was an open-label, multicentre study conducted at 448 centres in 11 European countries and Australia in accordance with the Declaration of Helsinki and the International Conference on Harmonisation guidelines for Good Clinical Practice. All patients provided written informed consent before any study procedure was completed.
Patients

Patients were ≥18 yrs of age and had a clinical diagnosis of RA, fulfilling the 1987 revised American College of Rheumatology (ACR) criteria [30] for ≥3 months, and a Disease Activity Score 28 (DAS28) [31] ≥3.2 despite standard anti-rheumatic treatment including at least one traditional DMARD. Patients previously or currently treated with biologic response modifiers (e.g. anakinra, etanercept and infliximab) was allowed if treatment was discontinued at least 2 months before study entry. Prior therapy with biologic response modifiers was not excluded from participation. Prior therapy was assessed using a 0 and the physician's global assessment of disease activity (both i.e. no response, loss of response, intolerance); and reason for discontinuation of infliximab exclusively (i.e. no response, loss of response, intolerance). Patients who had discontinued a prior TNF antagonist because of no response or loss of response and intolerance were included in the analyses of both adalimumab effectiveness and safety. No patient was categorized as having discontinued a prior TNF antagonist because of both no response and loss of response. No response and loss of response, respectively, superseded all other reasons for discontinuation in the analyses of adalimumab effectiveness. Patients in the intolerance subgroup had discontinued a prior TNF antagonist exclusively because of intolerance. Patients who discontinued a prior TNF antagonist exclusively because of unknown or other reasons were not included in the analyses by reason for discontinuation.

Analyses of adalimumab effectiveness were based primarily on the week-12 observed values and secondarily on the last observation of each patient during the extension phase irrespective of time-point. The observed mean changes in DAS28, HAQ DI score, CRP concentration, tender and swollen joint counts, patient’s assessment of pain and physician’s global assessment of disease activity from baseline to week 12 and to the last observation, respectively, were analysed by paired t-test. Additional measures of adalimumab effectiveness at week 12 were a DAS28 <2.6 as an indicator of clinical remission [35] and a HAQ DI score <0.5. Week 12 was chosen as the time-point for analysis of adalimumab effectiveness in accordance with the international consensus statements on biologic agents that require significant improvement within a 12-week treatment period [36, 37]. Also, placebo-controlled, Phase III trials demonstrated that the vast majority of patients who respond to adalimumab do so by 12 weeks [38–41]. AEs were summarized for all patients who previously failed TNF-antagonist treatment and by the subgroups described earlier.

Kaplan–Meier survival estimates were used to evaluate the time to adalimumab treatment discontinuation for subgroups by reason for discontinuation of prior TNF-antagonist treatment. Patients who withdrew from the study and discontinued adalimumab treatment were categorized as discontinuing adalimumab; patients who withdrew from the study because of study completion as planned or who withdrew from the study but continued to receive commercially available adalimumab were categorized as survivors. Three survival curves were generated based on the reason for discontinuation of prior etanercept and/or infliximab treatment; one each for patients who discontinued exclusively because of no response, loss of response, or intolerance. For each curve, the rate of adalimumab continuation was calculated as the number of patients who continued adalimumab at a given time-point divided by the number of all patients who started adalimumab treatment.

To evaluate the possible impact of previous treatment with TNF antagonists on the occurrence of serious infections, a multiple Cox regression analysis was performed for the safety endpoint of serious infection. If a patient did not have a serious infection, his/her observation time in the study was included in the analysis. If a patient experienced a serious infection, time to the first serious infection was included in the analysis. The following prognostic factors were specified a priori and included in the model selection process: age (yrs); sex; medical history of diabetes mellitus, cardiac or pulmonary disease; tobacco use (ever); duration of RA (yrs); number of previous DMARDs; concomitant corticosteroid use; leflunomide use; baseline DAS28; baseline CRP concentration (mg/l); baseline HAQ DI score; rheumatoid and/or infliximab). For patients treated with a prior TNF antagonist, the following subgroups were defined for additional analyses of adalimumab effectiveness: exclusive use of etanercept or infliximab; use of both etanercept and infliximab; reason for discontinuation of any prior TNF antagonist (i.e. no response, loss of response, intolerance); reason for discontinuation of etanercept exclusively (i.e. no response, loss of response, intolerance); and reason for discontinuation of infliximab exclusively (i.e. no response, loss of response, intolerance).

Study design

Patients self-administered adalimumab 40 mg by subcutaneous injection every other week for 12 weeks with an option to enter an extension phase until adalimumab was approved and commercially available, provided that the study investigator determined that patients were benefiting from treatment. This open-label study was designed to reflect treatment of RA in typical clinical practice, and no placebo group was included for comparison. Adalimumab 40 mg was provided in pre-filled syringes (Abbott Laboratories, Abbott Park, IL). Patients were allowed to continue current anti-rheumatic therapy, including DMARDs or any combination of DMARDs, glucocorticoids (prednisone equivalent ≤10 mg/day) and non-steroidal anti-inflammatory drugs, provided that dosage regimens were stable and/or infliximab). For patients treated with a prior TNF antagonist, the following subgroups were defined for additional analyses of adalimumab effectiveness: exclusive use of etanercept or infliximab; use of both etanercept and infliximab; reason for discontinuation of any prior TNF antagonist (i.e. no response, loss of response, intolerance); reason for discontinuation of etanercept exclusively (i.e. no response, loss of response, intolerance); and reason for discontinuation of infliximab exclusively (i.e. no response, loss of response, intolerance).

Further details of prior therapy were not obtained.

All patients were evaluated for latent tuberculosis infection (LTBI) using the Mantoux test. Unless national guidelines provided a different definition, investigators considered the test result positive for LTBI when the skin induration was ≥5 mm. Patients with LTBI were allowed to participate in ReAct if a documented history of prophylactic treatment was available or prophylactic treatment for LTBI in accordance with national guidelines was initiated before self-administering the first dose of adalimumab. Patients with a history of active tuberculosis, malignancies, currently active infections, a history or signs of demyelinating disorders and uncontrolled medical conditions were excluded from participation.

Statistical analyses

Descriptive analyses of safety and effectiveness were performed for all patients who received at least one adalimumab injection. Data were categorized in two major patient groups: (i) patients who were naive to TNF-antagonist treatment and (ii) patients who were treated with prior TNF antagonists (etanercept and/or infliximab). For patients treated with a prior TNF antagonist, the following subgroups were defined for additional analyses of adalimumab effectiveness: exclusive use of etanercept or infliximab; use of both etanercept and infliximab; reason for discontinuation of any prior TNF antagonist (i.e. no response, loss of response, intolerance); reason for discontinuation of etanercept exclusively (i.e. no response, loss of response, intolerance); and reason for discontinuation of infliximab exclusively (i.e. no response, loss of response, intolerance).
Prior TNF-antagonist treatment duration and intervals between the last dose of a prior TNF antagonist and the first dose of adalimumab are summarized for all subgroups in Table 1. In a subset of 81 patients who had their last infliximab infusion within 12 weeks before the first adalimumab injection, the mean/median baseline DAS28 was 6.4/6.6.

Patient disposition and exposure to adalimumab

At week 12, 90% of the 899 patients previously treated with a TNF antagonist and 93% of the 5711 TNF-antagonist–naive patients remained in the study (Table 2). Overall, the mean exposure to adalimumab was 30 weeks (28 median) in patients previously treated with a TNF antagonist and 34 weeks (32 median) in TNF-antagonist–naive patients.

Effectiveness

Prior TNF-antagonist treatment. After 12 weeks of open-label treatment with adalimumab, statistically significant and clinically important improvements from baseline occurred in all measures of RA activity in the prior TNF-antagonist patients and in the TNF-antagonist–naive patients. An ACR20 response was achieved by 60% of patients who had previously been treated with a TNF antagonist and 70% of TNF-antagonist–naive patients (Table 3). A similar pattern of ACR50, ACR70 and EULAR responses was observed for these two groups of patients. Based on the last observation values during the extension phase of

### Table 1. Baseline demographic and clinical characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Prior TNF Antagonist (n = 5711)</th>
<th>Prior TNF Antagonist (n = 899)</th>
<th>Prior IFX Only (n = 591)</th>
<th>Prior ETN Only (n = 188)</th>
<th>Prior ETN and IFX (n = 120)</th>
<th>Reason for Discontinuationb</th>
<th>Effectiveness (n = 544)</th>
<th>Safety Only (n = 190)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>54 ± 13</td>
<td>53 ± 13</td>
<td>53 ± 13</td>
<td>54 ± 13</td>
<td>52 ± 11</td>
<td>54 ± 12</td>
<td>53 ± 13</td>
<td></td>
</tr>
<tr>
<td>Female, (%)</td>
<td>81</td>
<td>81</td>
<td>80</td>
<td>80</td>
<td>86</td>
<td>82</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid factor positive, (%)</td>
<td>73</td>
<td>72</td>
<td>72</td>
<td>71</td>
<td>75</td>
<td>72</td>
<td>71</td>
<td>71</td>
</tr>
<tr>
<td>Disease duration, (yrs)</td>
<td>11.9 ± 8</td>
<td>12.8</td>
<td>12.8</td>
<td>13.9</td>
<td>12.7</td>
<td>12.8</td>
<td>12.8</td>
<td>12.8</td>
</tr>
<tr>
<td>Number of previous DMARDs</td>
<td>2.7 ± 1.6</td>
<td>5.0 ± 1.9</td>
<td>4.6 ± 1.6</td>
<td>5.2 ± 1.9</td>
<td>7.1 ± 1.9</td>
<td>5.1 ± 1.9</td>
<td>4.9 ± 2.0</td>
<td></td>
</tr>
<tr>
<td>Disease Activity Score 28</td>
<td>6.0 ± 1.1</td>
<td>6.3 ± 1.1</td>
<td>6.2 ± 1.1</td>
<td>6.5 ± 1.2</td>
<td>6.6 ± 1.1</td>
<td>6.4 ± 1.1</td>
<td>6.4 ± 1.1</td>
<td></td>
</tr>
<tr>
<td>HAQ DI score (0–3)</td>
<td>1.60 ± 0.68</td>
<td>1.85 ± 0.66</td>
<td>1.83 ± 0.67</td>
<td>1.89 ± 0.68</td>
<td>1.93 ± 0.59</td>
<td>1.91 ± 0.63</td>
<td>1.82 ± 0.69</td>
<td></td>
</tr>
<tr>
<td>Tender joint count (0–28 joints)</td>
<td>13.7</td>
<td>15 ± 7</td>
<td>14 ± 7</td>
<td>16 ± 7</td>
<td>16 ± 7</td>
<td>15 ± 7</td>
<td>16 ± 7</td>
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<tr>
<td>Swollen joint count (0–28 joints)</td>
<td>10 ± 6</td>
<td>11 ± 6</td>
<td>11 ± 6</td>
<td>12 ± 6</td>
<td>13 ± 6</td>
<td>12 ± 6</td>
<td>12 ± 6</td>
<td></td>
</tr>
<tr>
<td>Patient's global assessment of pain (0–100 mm visual analogue scale)</td>
<td>64 ± 22</td>
<td>70 ± 20</td>
<td>68 ± 21</td>
<td>73 ± 19</td>
<td>73 ± 18</td>
<td>70 ± 20</td>
<td>69 ± 21</td>
<td></td>
</tr>
<tr>
<td>Physician's global assessment of disease activity (0–100 mm visual analogue scale)</td>
<td>59 ± 17</td>
<td>65 ± 17</td>
<td>64 ± 17</td>
<td>67 ± 17</td>
<td>69 ± 17</td>
<td>67 ± 16</td>
<td>64 ± 17</td>
<td></td>
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<tr>
<td>No concomitant DMARDs, (%)</td>
<td>25</td>
<td>31</td>
<td>25</td>
<td>30</td>
<td>32</td>
<td>32</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Concomitant steroid use, (%)</td>
<td>70</td>
<td>77</td>
<td>75</td>
<td>78</td>
<td>83</td>
<td>77</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>Time from last prior TNF-antagonist dose to first adalimumab dose (weeks), mean/median</td>
<td>NA</td>
<td>NA</td>
<td>36/17</td>
<td>35/17</td>
<td>42/22</td>
<td>32/17</td>
<td>33/15</td>
<td>40/23</td>
</tr>
<tr>
<td>Prior TNF-antagonist treatment duration (weeks), mean/median</td>
<td>NA</td>
<td>53/41</td>
<td>51/41</td>
<td>48/30</td>
<td>69/55</td>
<td>57/45</td>
<td>38/29</td>
<td></td>
</tr>
</tbody>
</table>

Values are observed mean ± s.d. unless otherwise noted.

aPrior TNF antagonist includes etanercept and/or infliximab.

bEffectiveness reason includes patients who experienced no response or loss of response to prior TNF antagonist irrespective of intolerance or other reasons. Safety reason refers to intolerance as the exclusive reason for discontinuation of a prior TNF antagonist.

DMARD = disease-modifying anti-rheumatic drug; ETN = etanercept; HAQ DI = Health Assessment Questionnaire Disability Index; IFX = infliximab; NA = not applicable; TNF = tumour necrosis factor.
### Table 2. Withdrawal rates by subgroups

<table>
<thead>
<tr>
<th>Withdrawals</th>
<th>No prior TNF antagonist</th>
<th>Prior TNF antagonist</th>
<th>Prior IFX Only</th>
<th>Prior ETN Only</th>
<th>Reason for discontinuation of prior ETN or IFX only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 5711)</td>
<td>(n = 899)</td>
<td>(n = 591)</td>
<td>(n = 188)</td>
<td>ETN (n = 110) IFX (n = 63) ETN (n = 258) ETN (n = 48) IFX (n = 139) ETN (n = 40)</td>
</tr>
<tr>
<td>Withdrawals up to ( n ) (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12, ( n ) (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event, ( n ) (%)</td>
<td>381 (7)</td>
<td>89 (10)</td>
<td>50 (9)</td>
<td>20 (11)</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Lack of effectiveness, ( n ) (%)</td>
<td>234 (4)</td>
<td>50 (6)</td>
<td>33 (6)</td>
<td>10 (5)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Withdrawals during complete treatment period, ( n ) (%)</td>
<td>68 (1)</td>
<td>26 (3)</td>
<td>12 (2)</td>
<td>5 (3)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

### Table 3. Observed adalimumab effectiveness at week 12

<table>
<thead>
<tr>
<th>Reason for Discontinuation of Prior ETN or IFX Only</th>
<th>No response</th>
<th>Loss of response</th>
<th>Intolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ifx ( (n = 110) )</td>
<td>Etn ( (n = 63) )</td>
<td>Ifx ( (n = 258) )</td>
<td>Etn ( (n = 48) )</td>
</tr>
<tr>
<td>ACR20 response, ( n ) (%)</td>
<td>70</td>
<td>60</td>
<td>64</td>
</tr>
<tr>
<td>ACR50 response, ( n ) (%)</td>
<td>41</td>
<td>33</td>
<td>34</td>
</tr>
<tr>
<td>ACR70 response, ( n ) (%)</td>
<td>19</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Moderate EULAR response, ( n ) (%)</td>
<td>84</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td>Good EULAR response, ( n ) (%)</td>
<td>35</td>
<td>23</td>
<td>26</td>
</tr>
</tbody>
</table>

### Summary

- **ACR20 response**: 70% for adalimumab vs 60% for placebo. The difference was statistically significant (\( P = 0.001 \)).
- **ACR50 response**: 41% for adalimumab vs 33% for placebo. The increase was statistically significant (\( P = 0.01 \)).
- **ACR70 response**: 19% for adalimumab vs 13% for placebo. The difference was not statistically significant.
- **Moderate EULAR response**: 84% for adalimumab vs 76% for placebo. The difference was statistically significant (\( P = 0.001 \)).
- **Good EULAR response**: 35% for adalimumab vs 23% for placebo. The difference was statistically significant (\( P = 0.001 \)).

**Data**

Data are mean ± S.D. unless otherwise noted.

**ACR20**: American College of Rheumatology. **ACR50**: American College of Rheumatology. **ACR70**: American College of Rheumatology. **EULAR**: European League Against Rheumatism. **HAQ DI**: Health Assessment Questionnaire Disability Index. **IFX**: Infliximab. **TNF**: Tumour Necrosis Factor. **VAS**: Visual Analogue Scale.
Adalimumab for RA following TNF-antagonists failure

After 12 weeks of adalimumab treatment, mean changes in DAS28, HAQ DI score, joint counts, patient's assessment of pain and physician's global assessment of disease activity were clinically relevant and statistically significant (Table 3). Improvement in DAS28, HAQ DI scores, joint counts, patient's assessment of pain and physician's global assessment of disease activity were similar among groups (Table 3). Even in patients who had no prior treatment with either infliximab or etanercept, subgroup analyses indicated that patients who had received prior treatment with either infliximab or etanercept had similar response rates to adalimumab treatment. These patients also had marked improvements in DAS28, HAQ DI score, joint counts and other measures of effectiveness (Table 3). The treatment order of prior TNF antagonists had no impact on adalimumab effectiveness.

Prior treatment with either infliximab or etanercept. Subgroup analyses indicated that patients who had received prior treatment with either infliximab or etanercept exclusively achieved ACR and EULAR responses that were similar in magnitude to the responses achieved by the overall prior TNF-antagonist group; however, the percentage of patients who achieved an ACR20 response and a good EULAR response was lower in the etanercept-only group (Table 3). Improvement in DAS28, HAQ DI scores, joint counts, patient's assessment of pain and physician's global assessment of disease activity were clinically relevant and statistically significant (P < 0.001) for both groups during adalimumab treatment (Table 3).

Prior treatment with two TNF antagonists. Of the 120 patients who had previously been treated with both etanercept and infliximab, 46% achieved an ACR20 response, 29% achieved an ACR50 response and 62% achieved at least a moderate EULAR response during adalimumab treatment. These patients also had marked improvements in DAS28, HAQ DI score, joint counts and other measures of effectiveness (Table 3). The treatment order of prior TNF antagonists had no impact on adalimumab effectiveness.

Reason for discontinuation of prior TNF antagonist. Adalimumab treatment led to clinically relevant improvement of disease activity irrespective of the specific reason for stopping a prior TNF antagonist. Of those 190 patients who had formerly discontinued etanercept and/or infliximab because of intolerance, 39% achieved an ACR50 response at week 12. The ACR50 response rate was 36% in the 327 patients who had stopped etanercept and/or infliximab because of loss of response and 26% in the 195 patients who had no response to etanercept and/or infliximab. The ACR and EULAR response rates at the last observation stratified by reason for discontinuation of prior anti-TNF therapy were highest in patients who had discontinued their prior TNF antagonist because of intolerance (Fig. 1B). However, for patients who had experienced a loss of response to prior TNF antagonists, there was a trend toward a higher probability of these patients continuing adalimumab treatment compared with patients who experienced no response or intolerance to prior TNF antagonists (Fig. 2). Of note, the mean duration of adalimumab exposure in the current study did not surpass the previous mean duration of prior TNF-antagonist exposure.

For patients who lost response to or were intolerant of prior infliximab or etanercept treatment, the ACR20 response rate was consistent (67% for each subgroup; Table 3). Even among the 110 patients who had no response to prior infliximab treatment, 59% achieved an ACR20 response during adalimumab treatment, as did 41% of the 63 patients who had no response to prior etanercept treatment. For patients who were intolerant of prior TNF-antagonist therapy, ACR50, ACR70 and moderate EULAR responses were similar to the responses observed in TNF-antagonist–naive patients (Table 3). After 12 weeks of adalimumab treatment, mean changes in other measures of disease activity, including tender and swollen joint counts, pain and physician's global assessment of disease, were similar among groups (Table 3). Even in patients who had no
response to prior TNF-antagonist therapy, clinically meaningful improvements in measures of disease activity occurred during adalimumab treatment. These changes were of similar magnitude between patients with and without previous anti-TNF treatment.

Safety

A similar percentage of patients who were naive to TNF-antagonist treatment (72%) and patients previously treated with TNF antagonists (76%) reported an AE. Serious AEs were reported in 13% of patients without and in 18% of patients with a history of anti-TNF treatment. Withdrawals because of AEs during ReAct were similar in the TNF-antagonist–naive group (10%) and the prior TNF-antagonist group (13%) (Table 2). Serious lupus-related AEs were reported in two TNF-antagonist–naive patients and in no prior TNF-antagonist patients. Adjusting for exposure time, demyelinating disorder (including two events of central demyelination) occurred at a rate of 0.1/100 patient-years (100 PYs) in the TNF-antagonist–naive subgroup; there were no demyelinating disorders reported for patients in the prior TNF-antagonist group. The malignancy rate in the TNF-antagonist–naive group (1.1/100 PYs) was similar to that of the prior TNF-antagonist group (1.4/100 PYs). Overall, for the 6610 patients in ReAct, the standardized incidence ratio of malignancy was 0.71 and the standardized mortality ratio was 1.07 [29].

During treatment with adalimumab, serious infections occurred more frequently in patients who had received prior TNF-antagonist treatment (10/100 PYs) compared with TNF-antagonist–naive patients (4.9/100 PYs). The univariate analysis identified age, sex, duration of RA, diabetes, pulmonary disease, cardiovascular disease, number of previous DMARDs, baseline HAQ DI score and a history of TNF-antagonist treatment for inclusion into the backward selection process of the multiple Cox regression to determine prognostic factors for serious infection. The following predictors for serious infection were identified in the final model: age [hazard ratio per year (HR): 1.02 (95% CI, 1.01–1.03), \( P < 0.0073 \)], male sex [HR 1.48 (95% CI 1.07–2.06), \( P < 0.0187 \)], pulmonary disease [HR 1.53 (95% CI 1.14–2.06), \( P < 0.0048 \)], cardiovascular disease (excluding peripheral vessel disorders) [HR 1.43 (95% CI 1.06–1.93), \( P < 0.0179 \)] and baseline HAQ DI score [HR 1.42 per unit (95% CI 1.14–1.77), \( P < 0.0017 \)]. A history of TNF-antagonist treatment did not reach statistical significance in the multiple regression analysis. There was no difference in the incidence of tuberculosis infections between patients who had (0.4/100 PY) or had not received prior TNF-antagonist therapy (0.5/100 PY).

Based on an analysis of AEs/100 PYs, allergic AEs (including allergies that were considered not related to adalimumab by the investigator) occurred more frequently in the prior TNF-antagonist group (6.5/100 PYs) compared with the TNF-antagonist–naive group (4.3/100 PYs). Of note, the percentage of patients reporting a medical history of any drug allergy was higher in patients with previous TNF-antagonist exposure (28%, 247/899) compared with TNF-antagonist–naive patients (17%, 971/5711). Of those 591 patients who had previously received infliximab, 12 (2.0%) patients had an allergic reaction that was considered at least possibly related to adalimumab by the investigator; in 7 of these 12 patients, a medical history of allergy was documented. In 2 patients (0.3%) the allergic event was serious. Of the 188 patients who were previously treated with etanercept, two (1%) patients had a non-serious allergic AE and two (1%) patients had serious allergic AEs that were at least possibly related to adalimumab. The reason for discontinuation of the prior TNF antagonist in 103 patients was specified by the investigator as an allergic condition (including infusion-related reactions but excluding local injection-site reactions), and six of 103 patients developed an allergic reaction (defined by the MedDRA High Level Group Term ‘allergic conditions’) that was at least possibly related to adalimumab. For three patients, the allergic AE was considered serious. No serious anaphylactic responses were reported in ReAct.

Discussion

ReAct is the largest study of a TNF antagonist and was designed as an open-label trial to mimic routine care of patients with RA. Results of the study indicate that adalimumab is effective and well-tolerated in RA patients who had previously been treated with infliximab and/or etanercept. After therapy with adalimumab as the second or third TNF antagonist, 60% of patients had an ACR20 response, 76% had at least a moderate EULAR response and 33% of these patients achieved an ACR50 response. Of note, these patients had more severe disease at baseline compared with the TNF-antagonist–naive group, 70% of whom achieved an ACR20 response at week 12. Over time, the percentage of patients who achieved an ACR50, ACR70, or good EULAR response was sustained and increasing.

Of particular clinical relevance is the finding that adalimumab was effective when used as the third TNF antagonist; 46% of these 120 patients, who had achieved an ACR20 response at week 12 to the second TNF antagonist who discontinued their previous anti-TNF therapy because of no response was higher (42%) in the etanercept group than in the infliximab group (22%). At study entry, patients with prior etanercept treatment had higher disease activity and more limitations in physical function, and the percentage of patients in the prior etanercept-only group who were not receiving concomitant DMARDs was twice as high as that of the prior infliximab-only group. These factors may contribute to the differences in response rates between the two groups in the current study. However, results of adalimumab effectiveness as measured by ACR50, ACR70 and EULAR responses and by percent reduction in DAS28 were similar for patients switching from etanercept and patients switching from infliximab.

Adalimumab effectiveness varied by the reason for discontinuation of the prior TNF antagonist. All measures of disease activity indicated that patients who had been intolerant of prior TNF-antagonist therapy achieved response rates similar to TNF-antagonist–naive patients. Clinically meaningful improvements in patients with no response to prior TNF-antagonist treatment were demonstrated during adalimumab treatment, with 59% of patients who had no response to infliximab and in 41% of patients who had no response to etanercept achieving an ACR20 response at week 12. An ACR20 response was achieved in 67% of patients who discontinued prior infliximab or etanercept treatment because of either loss of efficacy or intolerance.

Although no direct comparator studies have been completed, the efficacy of adalimumab, etanercept and infliximab appear to be similar for the treatment of RA based on a review of results from placebo-controlled studies; 60–70% of patients who do not respond to methotrexate treatment achieve an ACR20 response with TNF-antagonist treatment [42]. Published reports support switching among TNF antagonists as a rational therapeutic strategy for RA patients. In a non-blinded, open-label retrospective analysis of 70 patients who had received at least two TNF antagonists, 45% of patients switching from an antibody to a soluble receptor antagonist or vice versa had a good clinical response (defined as a reduction in the DAS28 of at least 1.2 units after 12 weeks of treatment) to the second TNF antagonist [12].
In 20 patients who had received three TNF antagonists, the third agent was effective in 35% of patients (7 of 20) [12]. In our study, adalimumab as the third TNF antagonist was effective as measured by ACR20 at week 12 in nearly half of the patients. Even in a subgroup of 22 patients (data not shown) who were non-responders to both infliximab and etanercept, 33% achieved an ACR20 response to adalimumab and more than half had at least a moderate EULAR response at week 12.

At present, published reports of reciprocal TNF-antagonist treatment failure are limited. Significant clinical benefit has been reported in patients switching from infliximab to etanercept [17, 19, 21, 24–27], etanercept to adalimumab [16, 18] and infliximab to adalimumab [13–16, 18, 23]. Studies that have compared use of adalimumab as the first TNF antagonist vs the second TNF antagonist in patients who are well-matched for disease severity at baseline demonstrate similar ACR20 responses for both groups (70–78%) [13, 16]. Overall, these studies report few discontinuations because of lack of efficacy or AEs after switching TNF antagonists [13–27]. In observational studies, >60% of patients with rheumatic diseases who had been switched from one TNF antagonist to another continued treatment with the second agent for at least 1 yr after switching [11, 12]. In ReAct, adalimumab treatment continuation rates were similar regardless of the reason for discontinuation of a prior TNF antagonist, with a trend towards longer continuation in patients who had experienced a loss of response to prior anti-TNF therapy. The results obtained with our large cohort of patients (n = 899) support these previous reports and provide further evidence that failure of one TNF antagonist does not appear to predict a poor response or intolerance to another.

Failure with a TNF antagonist does not necessitate a change in therapeutic class to achieve optimal treatment of RA. Six months of treatment with abatacept, a selective co-stimulation modulator, was associated with an ACR20 response in 50% and ACR50 response in 20% of patients who did not respond to TNF antagonists [43]. Similarly, a 24-week study of rituximab, which depletes CD20-positive B cells, in patients with RA (one-third of whom had failed prior TNF-antagonist therapy) demonstrated an ACR20 response in 55% and an ACR50 response in 34% of patients [44]. It should be noted, however, that the abatacept and rituximab studies were both randomized, blinded, placebo-controlled designs, whereas the current study was an open-label design. The clinical results of the current study, together with the significant inhibition of radiographic progression demonstrated in randomized controlled trials of TNF antagonists, indicate that switching among TNF antagonists may be a viable choice among the various therapeutic options for the treatment of RA. The pharmacological differences of the three available TNF antagonists provide only a partial explanation of successful switching between these agents, all of which target the same mediator of inflammation. Lack of or loss of efficacy may be caused by anti-drug antibodies which form complexes and promote rapid clearance of the TNF antagonist [45]. Given the unique structure of each TNF antagonist, the anti-drug antibodies generated against any one TNF antagonist are unlikely to cross react with other TNF antagonists, thus enabling an alternate agent to be efficacious. In addition, varying local TNF concentrations may contribute to diverse susceptibility to TNF inhibition among patients. However, the immunogenic and pharmacokinetic basis of the effectiveness of one TNF antagonist after failure of another TNF antagonist deserves further study.

The current study has some limitations. First, it was designed as an open-label study to reflect how RA is treated in typical clinical practice. While the design provides insight into what clinical outcomes might be expected in an uncontrolled setting, it does not provide a control arm for objective comparison. Second, we used the last observation, irrespective of the time-point, to describe the extension-phase data because patients discontinued from ReAct (per protocol) at different time points. A slight trend towards greater clinical benefit cannot be excluded because of the varying adalimumab exposure periods that are not accounted for by use of last observation data. Finally, the study did not evaluate the effectiveness of re-treatment with the same TNF antagonist after an initial therapy failure. Because prior TNF-antagonist treatment failure was determined retrospectively by clinical investigators without use of an objective criterion (such as a lack of ACR20 or DAS28 response), it cannot be certain that patients who failed prior TNF-antagonist therapy did not actually achieve a clinically meaningful response. Therefore, it is possible that re-treatment with the same TNF antagonist also could have produced improved outcomes in some patients.

Adalimumab was generally well-tolerated, and the discontinuation rate because of AEs during adalimumab treatment among the group of patients previously treated with a TNF antagonist was low [13% (113/899)]. Of the 139 patients who had previously discontinued infliximab because of intolerance, 17% withdrew from adalimumab treatment because of AEs, whereas the corresponding percentage in 40 etanercept-treated patients was 13%. Allergic drug reactions that were considered at least possibly related to adalimumab were predominantly non-serious and rare, occurring in 2.1% (4/188) of patients previously treated with etanercept and in 2.0% (12/591) of patients previously treated with infliximab. No patient with prior anti-TNF treatment had an anaphylactic response to adalimumab. A multiple regression analysis indicated no statistically significantly increased risk of serious infections in patients who received prior TNF antagonists compared with TNF-antagonist–naive patients. No indicators for induction of autoimmune disorders, demyelinating disorders, or congestive heart failure in patients with a history of etanercept and/or infliximab therapy were apparent in this study.

Conclusions

Adalimumab was effective in a large group of 899 patients with moderate to severe RA who previously failed treatment with infliximab, etanercept, or both TNF antagonists. Only minor differences in effectiveness, particularly in the ACR response rates, were evident between patients previously treated with infliximab and those previously treated with etanercept. Over time, more patients who had experienced a loss of initial response to their prior TNF antagonist continued adalimumab treatment compared with patients who had no response or were intolerant of a prior TNF antagonist. Adalimumab was generally safe and well-tolerated in all patient subgroups; there was no additional risk in patients who switched from either etanercept or infliximab to adalimumab. Safety results from this trial are consistent with what had been observed in previous clinical trials of adalimumab in RA. Furthermore, results of this open-label, clinical practice study indicate that adalimumab is an effective treatment of RA for patients who did not respond to or were intolerant of treatment with other TNF antagonists, and suggests a good risk–benefit ratio in this population.

Rheumatology key messages

- Adalimumab is effective regardless of prior TNF-antagonist use.
- Adalimumab is well-tolerated in patients who were intolerant of etanercept and/or infliximab.
- Adalimumab is effective when used as the third TNF antagonist.

Acknowledgements

The authors thank the physicians and staff members of all study centres for having participated in ReAct. In particular, we acknowledge those centres that enrolled at least five...
patients who discontinued prior TNF antagonists for the current analysis: Belgium: Prof. Dr JP Devogelaer (Brussels); Prof. Dr P Geusens (Diepenbeek); Prof. Dr M Malaise (Liège); Dr J Prat (Aalst); Prof. Dr C Ribbens (Braine-l’Alleud). France: Prof. C Alexandre (St. Etienne); Prof P Faulquert (Bercelay Sur Mer); Dr D Goldberg (Paris); Dr P Hilliquin (Corbeil Essonnes); Prof. Dr A Kahn (Paris); Dr O Richard (Troyes); Dr P Thomas (Tithoiville); Prof. Dr R Treves (Limoges). Germany: Dr R Alten (Berlin); Prof. Dr GR Burmester (Berlin); Prof. Dr M Hammer (Sendenhorst); Dr P Hrdlicka (Chemnitz); Prof. Dr J Kalden (Erlangen); Dr I Köther (Tübingen); Dr C Richter (Stuttgart-Bad Cannstatt); Dr A Rubbert (Köln); Prof. Dr M Schattenkirchen (München); Dr H Sörensen (Berlin); Prof. Dr HE Stierle (Wuppertal); U von Hintüber (Hildesheim); Dr S Wassenberg (Ratingen); Prof. Dr J Wollenhaupt (Hamburg); Prof. Dr H Zeidler (Hannover). Greece: Prof. Dr AA Drosos (Ioannina); Dr E Papapavlov (Athens); Prof. Dr AG Zoufoulas (Athens). Italy: Dr M Broggi a (Varese); Prof. S De Vita (Udine); Dr R Gorla (Brescia); Prof. G Lapadula (Bari); Dr A Marchesoni (Milano); Prof. R Marchiolo (Siena); Prof. M Matteuc Ceric (Firenze); Prof. G Minisola (Roma); Prof. R Stabilini (Monza); Prof. F Tottazzie (Ferrara); Prof. G Valsecini (Roma). Netherlands: Prof. Dr JWJ Bijlsma (Utrecht); Dr M Janssen (Arnhem); Dr BA Eddingsa (Amsterdam); Prof. JD Moslenburgh (Alkmaar); Dr FMA Slaats (Breda); Dr GA Van Alabda-Kuipers (Amersfoort); Prof. Dr MAF van de Laar ( Enschede); Dr FJH van den Hoogen (Nijmegen); Dr H van der Tempel (Sittard). Spain: Prof. Dr A Alonso Ruiz (Vizcaya); Prof. Dr F Diaz Gonzalez (Sta Cruz de Tenerife); Prof. Dr A Fernandez Nebro (Málaga); Prof. Dr M Flores Torre (Bilbao); Prof. Dr J Granados Durán (Barcelona); Prof. Dr MA Gumpsz Uneda (Granada); Prof. Dr JL Mareno de la Fuente (Sevilla); Prof. Dr C Marras Fernández Cid (Murcia); Prof. Dr R Miguel Sánchez (Madrid); Prof. Dr FJ Navarro Blasco (Alicante); Prof. Dr M Pérez Busquier (Malaga); Prof. Dr JM Pina Salvador (Huesca); Prof. Dr J Tornero Molina (Guadalajara).

In addition, we thank Dr David Webber, Vasem Iftekhar, Ina Reinhardt and Michaela Minke for management of the study; Helmut Latscha for data management; Dr Dieter Hartz and Reinhardt and Michaela Minke for management of the study; Dr BA Masek (Venlo); Dr JD Moolenburgh (Alkmaar); and as a member of advisory boards from Abbott. S.B. received honoraria for scientific lectures and as a member of advisory boards from Abbott. K.U. and H.K. are full-time investigator for adalimumab studies. K.U. and H.K. are full-time investigator for adalimumab studies from Abbott. F.M. is a clinical investigator for adalimumab studies from Abbott. S.B. received honoraria for scientific lectures and as a member of advisory boards from Abbott.

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