The efficacy of biologic agents in patients with rheumatoid arthritis and an inadequate response to tumour necrosis factor inhibitors: a systematic review

Robert J. Moots¹ and Barbara Naisbett-Groet²

Abstract

Objective. To assess the relative efficacy of subsequent biologic therapies in patients with RA who have had an inadequate response to prior therapy with a TNF-α inhibitor.

Methods. A systematic review was conducted using the MEDLINE, Embase and Cochrane Library databases and abstract lists from the European League Against Rheumatism, American College of Rheumatology and British Society of Rheumatology congresses. Searches covered the period from May 2009 (August 2009 for MEDLINE) to January 2011. Therapies considered were abatacept, adalimumab, etanercept, infliximab and rituximab, used at European licensed standard dose regimens.

Results. Four full publications and 41 congress abstracts met the criteria for inclusion. Significant improvements in RA signs and symptoms were reported for TNF inhibitors (individual agents or groups of agents, depending on the study) and for abatacept and rituximab. Rituximab was also associated with significantly improved radiographic outcomes. No head-to-head randomized controlled trials directly comparing different agents were published during the search period. Comparative data from registries and other observational studies suggest that rituximab is at least as effective as an alternative TNF inhibitor, and in some studies significantly more effective, in TNF inadequate responders.

Conclusions. RA patients with an inadequate response to one or more TNF inhibitors derive significant clinical benefit from subsequent therapy with an alternative TNF inhibitor or with rituximab or abatacept. Prospective randomized controlled trials are needed to help physicians in the best choice of further therapy for their patients.

Key words: abatacept, adalimumab, B cells, etanercept, infliximab, rituximab, T cells.

Introduction

RA is a chronic inflammatory disease characterized by synovitis, joint damage, functional disability and significantly increased mortality. Early intervention using DMARDs is now recognized as being critical to preventing structural joint damage and progressive loss of function [1]. For patients who either fail to respond to DMARD therapy or who develop an inadequate response to these drugs over time, biologic DMARDs are an effective add-on treatment option [1]. The first choice of biologic therapy is usually a TNF-α inhibitor.

Approximately 30–40% of patients who start TNF inhibitor treatment subsequently develop an inadequate response to these drugs [2–7]. Options for continuation of treatment in TNF inadequate responder (TNF-IR) patients include the use of a second biologic agent. However, within this overall strategy there is ongoing debate as to the relative effectiveness of using an alternative TNF inhibitor (cycling) or a biologic agent with a different mode of action (switching) [8–11].

Options available for switching include the monoclonal antibody rituximab, which selectively targets and depletes...
Biologic therapies after TNF inhibitors in RA

Methods

Objective

The aim of the review was to identify all studies that reported on the efficacy or effectiveness of biologic DMARD therapies in the treatment of patients with RA who had an inadequate response to at least one TNF inhibitor.

Search strategy

The following databases were searched: MEDLINE and MEDLINE-in progress, Embase and the Cochrane Library. Abstracts lists from the European League Against Rheumatism (EULAR), American College of Rheumatology (ACR) and British Society of Rheumatology (BSR) annual meetings were also searched. Searches covered the period from May 2009 to January 2011 (except MEDLINE, which covered the period from August 2009 to January 2011) and used the following search terms: (rituximab OR abatacept OR adalimumab OR etanercept OR infliximab OR TNF OR TNF inhibitor OR anti-TNF OR biologics OR biological agent) AND (rheumatoid arthritis OR RA) AND (switch* OR cycl* OR sequent*). The search was limited to English-language articles involving humans in clinical trials and observational studies.

Selection of studies

Articles were considered for further analysis if they reported results from clinical trials or observational studies involving patients with RA who had an inadequate response to at least one TNF inhibitor and subsequently switched to a different biologic therapy. The alternative biologic therapies considered were rituximab, abatacept, adalimumab, etanercept and infliximab, used at European standard dose regimens with or without concomitant methotrexate. To be included, studies had to report at least one outcome measure that reflected the signs, symptoms and impact on physical function of RA, such as ACR20 (or ACR50/70), EULAR response, Health Assessment Questionnaire–Disease Index, Disease Activity Score (DAS) or radiographic outcomes.

Initial screening of articles was based on an appraisal of the title and abstract. Selected articles were then analysed in detail. Screening and selection were carried out independently by two researchers, with any disagreements resolved by consensus or by involvement of a third researcher. A summary of the inclusion and exclusion criteria is shown in Table 1.

Data extraction

Key findings from each eligible study were extracted by recording the results on a data extraction form. Extracted data included information on study design, trial comparison selection criteria, study population and patient characteristics, interventions, outcome measures, duration of follow-up, results and author’s conclusions. Data extraction was carried out by one researcher and reviewed by a second researcher; any discrepancies were resolved by consensus.

Results

A flow diagram summarizing the screening and selection of articles is shown in Fig. 1. Searching the publications databases identified 294 articles, of which 9 were eligible for inclusion based on information provided in the title and/or abstract. Five of these articles were subsequently excluded, as either the intervention or outcomes were out of scope, leaving four articles for data extraction. A total of 2125 abstracts were identified from the three congresses. Of these, 109 abstracts were retrieved. Forty-one met the inclusion criteria for data extraction. A number of the abstracts involved updated analyses of results presented in previous abstracts.

The majority of the trials were non-comparator studies that evaluated the efficacy of TNF inhibitors (either individually or as a class) abatacept and rituximab in patients with a previous inadequate response, intolerance or contraindication to TNF inhibitors. These studies are summarized in Table 2.

Six studies evaluated TNF inhibitors [17–22, 41]. Each of these studies reported clinical responses to the alternative TNF inhibitor(s) under evaluation. Fleischmann et al. [17, 41] reported that 51% of 197 evaluable patients who had previously had an inadequate response to either etanercept or adalimumab achieved a EULAR response at 26 weeks after treatment with infliximab. Improvements in other disease activity measures were also reported in this study. Adalimumab treatment after an inadequate response to infliximab or etanercept was shown in two studies to be effective in terms of ACR20/50 and Disease Activity Score (28 joints) responses [19, 22]. In the Feuchtenberger et al. study [19], patients who had received three prior biologic therapies responded less well to adalimumab than those who had received one or two biologics. In a small single-cohort study, patients who had developed antibodies to their previous TNF inhibitor treatment achieved clinical responses to etanercept that were better than in patients who had not developed antibodies and equivalent to those achieved by TNF inhibitor-naïve patients [21]. In a registry study, better clinical responses were achieved when switching from a monoclonal anti-body TNF inhibitor (adalimumab or infliximab) to etanercept rather than to an alternative monoclonal antibody TNF inhibitor [18]. In contrast, another study found that...
### Table 1: Inclusion and exclusion criteria for selection of studies

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient population</strong></td>
<td>Abstract selection: RA patients; RA patients receiving a TNF inhibitor</td>
<td>Patients without RA; patients with other conditions such as juvenile arthritis, Crohn’s disease, PsA or other forms of SpA excluded unless RA patients could be distinguished in the results; RA patients receiving first-line TNF inhibitor treatment; RA patients receiving treatments other than the specified biologics</td>
</tr>
<tr>
<td></td>
<td>Full-text selection: Studies that included only patients with RA who failed on ( \geq 1 ) TNF inhibitor and were subsequently treated with another biologic (rituximab, abatacept, adalimumab, etanercept or infliximab) (i.e. patients on second- or third-line TNF inhibitor after failure of ( \geq 1 ) TNF inhibitor for RA)</td>
<td>Patients without RA; patients with other conditions such as juvenile arthritis, Crohn’s disease, PsA or other forms of SpA excluded unless RA patients could be distinguished in the results; RA patients receiving first-line TNF inhibitor treatment; RA patients receiving treatments other than the specified biologics</td>
</tr>
<tr>
<td><strong>Treatments and comparators</strong></td>
<td>Abstract selection: Rituximab, abatacept, adalimumab, etanercept or infliximab</td>
<td>Patients without RA; patients with other conditions such as juvenile arthritis, Crohn’s disease, PsA or other forms of SpA excluded unless RA patients could be distinguished in the results; RA patients receiving first-line TNF inhibitor treatment; RA patients receiving treatments other than the specified biologics</td>
</tr>
<tr>
<td></td>
<td>Full-text selection: Rituximab, abatacept, adalimumab, etanercept or infliximab on European standard doses and as second- or third-line treatment for RA</td>
<td>Patients without RA; patients with other conditions such as juvenile arthritis, Crohn’s disease, PsA or other forms of SpA excluded unless RA patients could be distinguished in the results; RA patients receiving first-line TNF inhibitor treatment; RA patients receiving treatments other than the specified biologics</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Abstract selection and full-text selection: Studies that reported efficacy outcome measures; studies that reported radiographic outcome measures</td>
<td>Studies that reported safety outcome measures only; studies that reported quality-of-life outcomes only</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td>Abstract selection and full-text selection: Clinical trials including randomized or non-randomized controlled trials; observational studies</td>
<td>Post hoc or retrospective analyses; economic evaluations; cost studies; reviews or meta-analyses; comments or letters; methodology studies or protocols; sample size &lt;20 patients in one treatment arm; study duration &lt;2 weeks</td>
</tr>
</tbody>
</table>

---

**Fig. 1** Results of search.

- **Search strategy:** MEDLINE, Embase, Cochrane Library
- **294 titles/abstracts identified**
- **Embase/MEDLINE:** 285
  - **Cochrane Library:** 9
- **9 full publications retrieved**
- **References excluded:** 285
  - Patient population out of scope: 93
  - Intervention out of scope: 40
  - Comparison out of scope: 3
  - Outcomes out of scope: 45
  - Study design out of scope: 100
  - Repeat abstracts: 3
  - Not English language: 1

- **2125 titles/abstracts identified**
- **Embase/MEDLINE:** 285
- **Cochrane Library:** 9
- **109 conference abstracts retrieved**
  - **ACR:** 36
  - **BSR:** 7
  - **EULAR:** 66
- **41 abstracts included and data extracted**
  - **ACR:** 14
  - **EULAR:** 25
  - **BSR:** 2
- **References excluded:** 68
  - Patient population out of scope: 6
  - Intervention out of scope: 11
  - Comparison out of scope: 1
  - Outcomes out of scope: 45
  - Study design out of scope: 5
<table>
<thead>
<tr>
<th>Authors (reference)</th>
<th>Study type</th>
<th>No. of patients</th>
<th>Previous treatment</th>
<th>Study treatments</th>
<th>Main outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fleischmann et al. [17]</td>
<td>Open-label</td>
<td>203</td>
<td>Inadequate response to previous ADA or ETA</td>
<td>INF [all received same initial dose; non-responders (EULAR) at week 14 or 22 received dose escalation] Alternative TNFi</td>
<td>Efficacy responses at week 26: ACR20/50/70 36%/18%/7%, EULAR response 52%</td>
</tr>
<tr>
<td>Chatzidionysiou et al. [18]</td>
<td>Registry</td>
<td>679</td>
<td>Inadequate response to previous TNFi</td>
<td>INF (or anakinra)</td>
<td>DAS28 change vs baseline (6 months) −1.24 to −1.57 (depending on previous and alternative TNFi received)</td>
</tr>
<tr>
<td>Feuchtenberger et al. [19]</td>
<td>Prospective observational study</td>
<td>1815</td>
<td>Inadequate response to ETA, INF</td>
<td>ADA</td>
<td>DAS28 change vs baseline (12 months): 1 prior biologic (n = 1395): −1.7 2 prior biologics (n = 371): −1.7 3 prior biologics (n = 49): −1.2</td>
</tr>
<tr>
<td>Lequerre et al. [20]</td>
<td>Single-centre study</td>
<td>72</td>
<td>Prior TNFi</td>
<td>INF (or anakinra)</td>
<td>Response to first TNFi vs second TNFi: EULAR response at 6 months: ETA to ADA/INF: 23% vs 50%; INF to ADA/ETA: 16% vs 58%</td>
</tr>
<tr>
<td>Jamnitski et al. [21]</td>
<td>Cohort study</td>
<td>292</td>
<td>Mixed population: inadequate response to INF or ADA</td>
<td>ETA</td>
<td>DAS28 change vs baseline at 28 weeks: TFN-IR: −2.0 (pts with anti-INF or anti-ADA antibodies) and −1.20 (pts without anti-INF or anti-ADA antibodies)</td>
</tr>
<tr>
<td>Burmester et al. [22]</td>
<td>Observational study</td>
<td>484</td>
<td>Mixed response to TNFi (n = 76); TNFi naïve (n = 408)</td>
<td>ADA</td>
<td>Clinical efficacy at 3 years: DAS28 change vs baseline; TNF naïve: 5.9 to 3.0; TNF-IR: 6.3 to 3.5; ACR20/50 TNF naïve: 84%/67%; TNF-IR: 77%/53%</td>
</tr>
<tr>
<td>Schiff et al. [23]</td>
<td>Open-label 2-arm (ARRIVE)</td>
<td>1046</td>
<td>Inadequate response to previous/current TNFi (ADA, ETA, ADA)</td>
<td>Washout ABA (pts discontinued TNFi for ≥2 months before screening) (n = 449); direct switch ABA (pts received TNFi within 2 months of screening) (n = 597)</td>
<td>Signs and symptoms: mean change in DAS28-CRP at 6 months: ABA washout: −2.0; ABA direct switch: −2.0 LDAS/remission (DAS28): ABA washout: 22.5%/12.0%; ABA direct switch: 22.3%/13.7%</td>
</tr>
<tr>
<td>Schiff et al. [24]</td>
<td>Subanalysis of RCT (ATTEST)</td>
<td>136</td>
<td>INF + MTX (12 months)</td>
<td>ABA + MTX</td>
<td>Improvement in DAS 82%, 61% and 64% in DAS, MDAS and LDAS, respectively, at year 1; improved disease state at year 2, 71% in DAS remission at year 1; maintained disease state at year 2</td>
</tr>
<tr>
<td>Genovese et al. [25]</td>
<td>Open-label long-term extension of RCT (ATTAIN)</td>
<td>317</td>
<td>Inadequate response to previous/current TNFi (ADA, ETA, ADA)</td>
<td>Open-label long-term extension (4 years) ABA + MTX (n = 317)</td>
<td>ACR and DAS response ACR20/50/70 (4 years): 81%/45%/23% LDAS/DAS remission (4 years): 37%/26%</td>
</tr>
<tr>
<td>Genovese et al. [26]</td>
<td>Open-label long-term extension of RCT (ATTAIN)</td>
<td>317</td>
<td>Inadequate response to previous/current TNFi (ADA, ETA, ADA)</td>
<td>ABA + MTX</td>
<td>Efficacy (4 years); DAS28 change vs baseline: −2.90; HAQ-DI reduction: −0.6</td>
</tr>
<tr>
<td>Massafra et al. [27]</td>
<td>Single-centre cohort study</td>
<td>20</td>
<td>Inadequate response to TNF inhibitor</td>
<td>ABA</td>
<td>EULAR response at 28 weeks: stopped TNFi for inefficacy (n = 12): 66%; stopped TNFi for intolerance (n ≥ 8): 63%</td>
</tr>
<tr>
<td>Rituuximab Keystone et al. [28]</td>
<td>RCT (REFLEX)</td>
<td>517</td>
<td>Inadequate response to previous/current TNFi (ADA, ETA, ADA)</td>
<td>Placebo + MTX (n = 209); RTX + MTX (n = 308)</td>
<td>Radiographic mean change mTSS at week 56: placebo (n = 186): 2.31; RTX (n = 277): 1.00 (P = 0.005)</td>
</tr>
<tr>
<td>Authors (reference)</td>
<td>Study type</td>
<td>No. of patients</td>
<td>Previous treatment</td>
<td>Study treatments</td>
<td>Main outcomes reported</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------</td>
<td>----------------</td>
<td>-------------------</td>
<td>-----------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Cohen et al. [29]</td>
<td>RCT (REFLEX)</td>
<td>517</td>
<td>Inadequate response to previous/current TNFi (ADA, ETA, ADA)</td>
<td>Placebo + MTX ($n = 209$); RTX + MTX ($n = 308$)</td>
<td>Radiographic mean change mTSS at week 104; placebo ($n = 187$): 2.81; RTX ($n = 281$): 1.14 ($P &lt; 0.0001$)</td>
</tr>
<tr>
<td>Mease et al. [30]</td>
<td>RCT (SUNRISE)</td>
<td>559</td>
<td>Inadequate response to previous/current TNFi (ADA, ETA, ADA)</td>
<td>All pts: open-label RTX (1 course) + MTX; from 24 weeks, randomization (double-blind) to placebo + MTX ($n = 157$); RTX + MTX ($n = 318$)</td>
<td>Signs and symptoms: ACR20 at week 48; placebo: 45%; RTX: 54% ($P = 0.02$); mean change in DAS28 at week 48; placebo: $-1.5$; RTX: $-1.9$ ($P = 0.006$)</td>
</tr>
<tr>
<td>Keystone et al. [31]</td>
<td>Long-term extension of RCTs</td>
<td>500</td>
<td>Inadequate response to previous/current TNFi</td>
<td>RTX repeat treatment</td>
<td>ACR response by course (C1/C2/C3/C4): ACR20: 61%/70%/71%/64%; ACR50: 30%/41%/47%/42%; ACR70: 12%/19%/25%/21%</td>
</tr>
<tr>
<td>van Vollenhoven et al. [32]</td>
<td>Registry pooled analysis</td>
<td>1372</td>
<td>Mixed population including TNF-IR (63%) and TNFi naïve (37%) pts</td>
<td>RTX</td>
<td>DAS28 change vs baseline (6 months): TNF naïve: 6.2 to 4.1; 1 prior TNFi: 6.1 to 4.1; &gt;1 prior TNFi: 5.6 to 4.3</td>
</tr>
<tr>
<td>Vander Cruyssen et al. [33]</td>
<td>Registry</td>
<td>497</td>
<td>Inadequate response to &gt;1 previous TNFi</td>
<td>RTX</td>
<td>DAS28 change vs baseline: 16 weeks: $-1.8$; 1 year: $-1.9$; 2 years: $-2.2$</td>
</tr>
<tr>
<td>Harauyi et al. [34]</td>
<td>Open-label single-arm study (RESET)</td>
<td>120</td>
<td>Inadequate response to 1 TNF inhibitor</td>
<td>RTX</td>
<td>Clinical efficacy at 24 weeks: ACR20: 58%; ACR50: 27%; ACR70: 7%; DAS28 change vs baseline: $-2.0$ EULAR response: 73%</td>
</tr>
<tr>
<td>Gossec et al. [35, 36]</td>
<td>Open-label study</td>
<td>224</td>
<td>Inadequate response to TNF inhibitor</td>
<td>RTX</td>
<td>Clinical efficacy at 24 weeks: DAS28-28 vs baseline: $-1.6$ EULAR response: 71%</td>
</tr>
<tr>
<td>Khan et al. [37]</td>
<td>Single-centre study</td>
<td>139</td>
<td>Inadequate response to previous TNFi</td>
<td>RTX</td>
<td>DAS28 change vs baseline: seronegative pts: $-0.6$; seropositive pts: $-2.2$</td>
</tr>
<tr>
<td>Pruchomme et al. [38]</td>
<td>Prospective observational study</td>
<td>95</td>
<td>Inadequate response to TNFi ($n = 81$)</td>
<td>RTX</td>
<td>EULAR response: good/moderate/no: 63%/11%/26%</td>
</tr>
<tr>
<td>Yoo et al. [39]</td>
<td>Prospective study</td>
<td>40</td>
<td>Inadequate response to &gt;1 TNF inhibitor</td>
<td>RTX</td>
<td>Clinical efficacy at 24 weeks/48 weeks: ACR20: 48%/83%; ACR50: 8%/38%; EULAR response: 70%/85%</td>
</tr>
<tr>
<td>Nallasivan et al. [40]</td>
<td>Single-centre study</td>
<td>25</td>
<td>Inadequate response or contra-indication to TNF inhibitor</td>
<td>RTX</td>
<td>DAS28 change vs baseline at 3 months $-3.3$</td>
</tr>
</tbody>
</table>

ABA: abatacept; ADA: adalimumab; C: course; DBPC: double-blind placebo-controlled; ETA: etanercept; HDAS: high disease activity score; INF: infliximab; LDAS: low disease activity score; MDAS: medium disease activity score; mTSS: modified Total Sharp Score; pts: patients; RCT: randomized controlled trial; RTX: rituximab; TNF: TNF inhibitor; TNF-IR: TNF inadequate responder.
clinical response to the second TNF inhibitor was not influenced by the previous TNF inhibitor used [20].

The vast majority of data concerning switching to abatacept after TNF inhibitor therapy came from long-term follow-up or subanalyses of three abatacept Phase III clinical trials [23–26, 42–44]. Improvements in clinical signs and symptoms were reported with abatacept treatment in the ARRIVE and ATTAIN trials (TNF-IR patients) [23, 26] and in the ATTEST trial (prior exposure to infliximab) [24]. In one subanalysis of the ARRIVE trial it was shown that clinical responsiveness to abatacept was comparable regardless of whether patients underwent a 2-month washout after stopping their prior infliximab treatment [42]. A subanalysis of the ATTEST trial showed that the level of response to infliximab had little effect on subsequent response to abatacept; patients who had a poor response to infliximab achieved responses to subsequent abatacept therapy that were comparable to those achieved by patients with a good response to infliximab [43]. Apart from publications from the abatacept clinical trial programme, the only other study identified was a small single-centre cohort study that reported clinical efficacy after abatacept treatment in patients (n = 20) who had discontinued TNF inhibitors because of inefficacy or safety reasons [27].

Several publications reported results from studies evaluating rituximab in TNF-IR patients. Long-term follow-up data from the Phase III REFLEX randomized controlled trial, which involved patients with an inadequate response to one or more TNF inhibitors, showed that rituximab provided radiographic benefit for up to 2 years [28, 29]. Patients initially randomized to rituximab in REFLEX had improved radiographic outcomes (inhibition of joint damage progression as measured by Total Sharp Score, erosion score and joint-space narrowing) compared with those initially randomized to placebo. Results from another Phase III trial in TNF-IR patients (SUNRISE) showed that rituximab was superior to placebo [in terms of clinical response: ACR response and change in DAS (28 joints; DAS28)] as repeat treatment after an initial single course of rituximab [30]. A pooled analysis of TNF-IR patients involved in the rituximab global clinical trial programme indicated that multiple courses of rituximab led to sustained efficacy over time [45, 47].

Data from European registries indicated that rituximab was effective in patients with an inadequate response to at least one TNF inhibitor [32, 33, 46, 47]. In a pooled analysis of data from 10 European registries [32], responsiveness to rituximab was better in patients who were either TNF inhibitor naive [change in DAS28 at 6 months (ΔDAS286mo) −2.1] or had been treated with a single TNF inhibitor (ΔDAS286mo −2.0) than in patients treated with two or more previous TNF inhibitors (ΔDAS286mo −1.3), although no statistical evidence was provided. Results from several other small single-centre studies add to the body of evidence that rituximab is effective in patients with an inadequate response to TNF inhibitors [34–40].

The search failed to identify any randomized controlled studies directly comparing the effectiveness of different biologic therapies in TNF-IR patients. However, a number of registries and other observational studies provide information regarding the relative effectiveness of rituximab and alternative TNF inhibitors in this patient group (Table 3). Results from two large European registries—MIRAR conducted in Sweden [48] and STURE conducted in Spain [49, 55]—suggested that rituximab may be a more effective treatment for TNF-IR patients than an alternative TNF inhibitor. In the Swedish registry [48], mean ΔDAS286mo was significantly greater (P = 0.002) with rituximab than with monoclonal antibody TNF inhibitors (adalimumab or infliximab). However, although there was a trend towards greater improvement in DAS28 with rituximab vs etanercept, this was not statistically significant. In the MIRAR study [49, 55], rituximab treatment was significantly more effective than an alternative TNF inhibitor (individual agent not specified) in terms of DAS28 change from baseline at 9–12 months (P = 0.016) and EULAR response (P = 0.04). Two other studies reported results of statistical tests. In a single-centre cohort study [50], rituximab was significantly more effective than alternative TNF inhibitor treatment in terms of DAS28 improvement over 6 months (−1.64 vs −1.19; P = 0.013); in addition, more rituximab-treated patients than TNF inhibitor-treated patients achieved a EULAR good/moderate response (82% vs 72%). The second study reported experience at a single centre and found no significant difference in DAS28 reductions or EULAR response rates between patients treated with rituximab and those who received a TNF inhibitor [51]. In both of these studies, the individual TNF inhibitor was not specified. In the other comparative studies, rituximab treatment was associated with numerically greater improvements in measures of RA signs and symptoms than treatment with an alternative TNF inhibitor, but statistical analyses were not reported [52, 53]. Finally, a prospective study of a cohort of 644 patients from a Swiss registry reported that rituximab was as effective as an alternative TNF inhibitor in preventing radiographic damage in patients in whom a previous TNF inhibitor had failed [54]. After adjusting for prognostic factors, the annualized rates of radiographic progression (erosion score) were +0.17% in the TNF inhibitor group and −0.01% in the rituximab group (P = 0.52).

Discussion

The results of this systematic review indicate that patients with RA who have an inadequate response to one or more TNF inhibitors benefit from subsequent therapy with another biologic agent. Significant improvements in RA disease symptoms (including ACR, EULAR and DAS28 responses) were reported for both alternative TNF inhibitors and for biologic therapies with a different mechanism of action. Rituximab was the only biologic therapy for which radiographic outcomes were reported for a TNF-IR population. Consistent with the improvements in RA clinical signs and symptoms reported in

www.rheumatology.oxfordjournals.org
### TABLE 3 Summary of active comparator studies

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Study type</th>
<th>No. patients</th>
<th>Previous treatment</th>
<th>Study treatments</th>
<th>Main outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chatzidionysiou et al. [48]</td>
<td>Registry</td>
<td>850</td>
<td>Inadequate response to $\geq 1$ previous TNFi</td>
<td>Alternative TNFi ($n = 679$) or RTX ($n = 171$)</td>
<td>DAS28 change vs baseline (6 months) All TNFs: -1.37 ADA/INF: -1.15 ETA: -1.58 RTX: -1.79 ($P = 0.002$ vs ADA/INF; $P = 0.32$ vs ETA)</td>
</tr>
<tr>
<td>Gomez-Reino et al. [49]</td>
<td>Observational prospective study</td>
<td>1626</td>
<td>Inadequate response to $\geq 1$ previous TNFi</td>
<td>Alternative TNFi ($n = 1201$) or RTX ($n = 425$)</td>
<td>DAS28 change vs baseline (9–12 months) TNFi: -1.34 RTX: -1.84 ($P = 0.016$) EULAR good/moderate response TNFi: 71% RTX: 83% ($P = 0.04$)</td>
</tr>
<tr>
<td>Kekow et al. [50]</td>
<td>Single-cohort study</td>
<td>196</td>
<td>Inadequate response to previous TNFi (ADA, ETA or INF)</td>
<td>Alternative TNFi ($n = 106$) or RTX ($n = 90$)</td>
<td>DAS28 change vs baseline (6.6 months) TNFi: -1.19 RTX: -1.64 ($P = 0.013$)</td>
</tr>
<tr>
<td>Buch et al. [51]</td>
<td>Prospective single-centre study</td>
<td>202</td>
<td>Inadequate response to $\geq 1$ previous TNFi</td>
<td>Alternative TNFi ($n = 101$) or RTX ($n = 101$)</td>
<td>Efficacy endpoints (week 24) DAS28 change vs baseline Alternative TNFi: 1.68 RTX: 1.42 EULAR response Alternative TNFi: 60% RTX: 59%</td>
</tr>
<tr>
<td>Ancuta et al. [52]</td>
<td>Analysis of national insurance database (Romania)</td>
<td>200</td>
<td>Previous treatment with TNFi</td>
<td>Alternative TNFi ($n = 98$) or RTX ($n = 102$)</td>
<td>DAS28 change vs baseline TNFi: +0.96 RTX: -2.39</td>
</tr>
<tr>
<td>Venkatachalam et al. [53]</td>
<td>Observational study</td>
<td>75</td>
<td>Inadequate response to 1 TNF inhibitor</td>
<td>Alternative TNFi ($n = 24$) or RTX ($n = 51$)</td>
<td>DAS28 change vs baseline at 3 months Alternative TNFi: -1.5 RTX: -3.2</td>
</tr>
<tr>
<td>Finckh et al. [54]</td>
<td>Prospective cohort study</td>
<td>644</td>
<td>Inadequate response to $\geq 1$ previous TNFi</td>
<td>Alternative TNFi ($n = 389$) or RTX ($n = 255$)</td>
<td>Radiographic annualized rate of joint erosion progression Alternative TNFi: +0.17% RTX: +0.01% ($P = 0.52$)</td>
</tr>
</tbody>
</table>

ADA: adalimumab; ETA: etanercept; INF: infliximab; RTX: rituximab; TNFi: TNF inhibitor.
various studies of rituximab treatment, rituximab was also associated with significantly improved radiographic outcomes over 2 years relative to placebo treatment.

As to the relative effectiveness of different biologic therapies in TNF-IR patients, the current literature is limited to results from various registries and other observational studies. No head-to-head randomized controlled trials have been published that directly compare different agents or classes of agents. The only comparative studies published during the period covered by the search involved rituximab and an alternative TNF inhibitor. Within these reports there is a relatively consistent finding that rituximab is at least as effective as an alternative TNF inhibitor, and some studies found it significantly more effective.

Although there is some guidance regarding the most appropriate order of therapy for patients with RA [1, 8], there remains a need to identify strong predictive biomarkers to help optimize therapy for individual patients. For example, seropositivity might guide the rheumatologist to choose rituximab over an alternative TNF inhibitor, whereas seronegative patients might be better treated with a second TNF inhibitor [56]. Indeed, as the TNF inhibitors do not have identical mechanisms of action and have different pharmacokinetic profiles and affinity and binding to TNF, failure of one TNF inhibitor does not necessarily preclude the use of another [57]. The cost burden of these expensive biological therapies may also be reduced if predictive biomarkers could be assessed before therapy to identify patients with a greater chance of response. Assessment of potential biomarkers should be included in any future head-to-head randomized controlled studies.

This analysis is limited by the terms of the primary search. Only reports in English and those published from May 2009 to January 2011 were included. In addition, the search was restricted to the three established TNF inhibitors plus rituximab and abatacept. Additional biological therapies, including two new TNF inhibitors (certolizumab pegol and golimumab) and the interleukin-6 inhibitor tocilizumab, have recently been licensed for the treatment of patients with RA. Tocilizumab and golimumab have both been shown in Phase III randomized controlled trials to significantly reduce the signs and symptoms of RA compared with placebo in TNF-IR patients [58, 59].

The optimal management of RA currently involves inducing and then maintaining the lowest possible disease activity—ideally remission. The results of this systematic review indicate that patients with RA who have an inadequate response to one or more TNF inhibitors derive significant clinical benefit from subsequent therapy with an alternative TNF inhibitor or with rituximab or abatacept. There is clearly a need for prospective randomized controlled trials comparing different treatments after failure of a first biologic agent and for the identification of strong predictive biomarkers. The results of such studies will help physicians in the best choice of further therapy for their patients.

---

**Rheumatology key messages**

- Not all patients with RA respond to TNF inhibitors.
- TNF inhibitor failure in RA is managed by swapping the TNF inhibitor or using a drug targeting a different pathway.
- Switching mode of action, particularly to rituximab, is effective after TNF inhibitor failure in RA patients.

**Acknowledgements**

We gratefully acknowledge the contributions of Yunni Yi, Melinda Goodall and Claire Snowball, who screened and selected the search results and carried out the data extraction.

**Funding:** Support for third-party writing assistance, furnished by Neil Anderson, PhD, was provided by F. Hoffman-La Roche.

**Disclosure statement:** R.J.M., or members of his group, have received research and/or educational grant funding from Abbott, MSD, Pfizer, Roche and UCB Pharma. B.N.-G. is an employee of Roche Products Ltd.

**References**

7. St Clair EW, van der Heijde DM, Smolen JS et al. for the Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset.


31 Keystone E, Fleischmann RM, Emery P et al. Sustained efficacy is achieved with repeat courses of rituximab in patients with rheumatoid arthritis with an inadequate response to one or more TNF inhibitors. Rheumatology 2010;49(Suppl 1):i89–111.

32 van Vollenhoven R, Chatzidionysiou K, Nasonov E et al. Six-month results from the collaborative European registries for rituximab in rheumatoid arthritis (CERERRA). Efficacy of rituximab is highest in RF-positive patients and in those who failed at most one prior anti-TNF. Arthritis rheum 2009;60(Suppl):S624–5.


43 Schiff M, Keiserman MW, Moniz Reed D et al. An increasing proportion of patients achieve a low disease activity state or remission when switched from infliximab to abatacept regardless of initial infliximab treatment response: results from the ATTEST trial. Arthritis Rheum 2009;60(Suppl):S619.


51 Buch M, Vital EM, Dass S et al. Switching to rituximab and an alternative TNF inhibitor in patients with rheumatoid arthritis that have failed previous TNF inhibitor(s) are both effective treatment options with good maintenance rates. Ann Rheum Dis 2010;69(Suppl 3):379.


