EXTENDED REPORT

Sustained inhibition of progressive joint damage with rituximab plus methotrexate in early active rheumatoid arthritis: 2-year results from the randomised controlled trial IMAGE

Paul P Tak,1 William Rigby,2 Andrea Rubbert-Roth,3 Charles Peterfy,4 Ronald F van Vollenhoven,5 William Stohl,6 Emma Healy,7 Eva Hessey,7 Mark Reynard,7 Tim Shaw7

ABSTRACT

Background In the IMAGE study, rituximab plus methotrexate (MTX) inhibited joint damage and improved clinical outcomes at 1 year in MTX-naive patients with early active rheumatoid arthritis.

Objective The aim of this study was to assess joint damage progression and clinical outcomes over 2 years.

Methods Patients (n=755) were randomised to receive rituximab 2×500 mg+MTX, 2×1000 mg+MTX or placebo+MTX. The placebo-controlled period continued to week 104. Two-year end points were defined as secondary or exploratory and included change in total Genant-modified Sharp score (mTSS), total erosion score and joint space narrowing score from baseline to week 104. Clinical efficacy and physical function end points were also assessed.

Results At 2 years, rituximab 2×1000 mg+MTX maintained inhibition of progressive joint damage versus MTX alone (mTSS change 0.41 vs 1.95; p<0.0001 (79% inhibition)), and a higher proportion of patients receiving rituximab 2×1000 mg+MTX had no radiographic progression over 2 years compared with those receiving MTX alone (57% vs 37%; p=0.0001). Contrary to 1-year results, exploratory analysis of rituximab 2×500 mg+MTX at 2 years showed that progressive joint damage was slowed by ~61% versus placebo+MTX (mTSS, exploratory p=0.0041). Improvements in clinical signs and symptoms and physical function seen after 1 year in rituximab-treated patients versus those receiving placebo were maintained at year 2. Safety profiles were similar between groups.

Conclusions Treatment with rituximab 2×1000 mg+MTX was associated with sustained improvements in radiographic, clinical and functional outcomes over 2 years. Clinical trials.gov identifier NCT00299104.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease in which joint damage and physical disability adversely affect quality of life and increase morbidity and premature mortality.1 2 Recent recommendations suggest that early treatment should be targeted towards the goal of clinical remission or low disease activity (LDA) and that this can lead to better structural and functional outcomes for patients. Furthermore, remission or LDA should be maintained throughout the course of the disease.3 4 In addition to clinical targets, maintaining inhibition of joint damage is important for the patient, given the association between structural damage and long-term loss of function.5

B cell depletion with rituximab 2×1000 mg is an established and effective treatment for RA. In combination with methotrexate (MTX), rituximab has been shown to significantly reduce clinical signs and symptoms of RA in patients with an inadequate response (IR) to either conventional disease-modifying antirheumatic drugs or tumour necrosis factor (TNF) inhibitors6–8 and to inhibit radiographic progression in TNF-IR patients.9–11 In the IMAGE study—a randomised placebo-controlled trial of rituximab plus MTX in MTX-naive patients with early active RA—rituximab 2×1000 mg+MTX significantly inhibited progression of joint damage and improved clinical outcomes and physical function compared with MTX alone after 1 year.12 13 Here, we present clinical and radiographic outcomes from the 2-year analysis of this study.

METHODS

Full eligibility criteria have been previously reported.12 In brief, patients were required to have a disease duration of ≥8 weeks but ≤4 years, no prior MTX treatment and active disease (swollen joint count ≥8 at screening and baseline, and Creactive protein level ≥1.0 mg/dl). Patients seronegative for rheumatoid factor (RF) were only eligible if they had radiographic evidence of erosive damage attributable to RA. This study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional review board or the ethics committee at each study site. All patients gave written informed consent.

In October 2009, following a spontaneous report outside of clinical trials of a case of progressive multifocal leucoencephalopathy (PML) in a rituximab-treated patient not previously treated with biologics, rituximab treatment was discontinued in the IMAGE trial and patients were subjected instead to safety follow-up. By this time, all patients had completed their 104-week follow-up.
and, consequently, the discontinuation does not impact the data presented here.

Patients were randomised (1:1:1) to receive rituximab 2×500 mg+MTX, 2×1000 mg+MTX or placebo+MTX. Rituximab or placebo was administered by intravenous infusion on days 1 and 15. Patients received intravenous methylprednisolone 100 mg premedication before all infusions. Oral MTX was commenced in all patients at 7.5 mg/week and escalated to 20 mg/week by week 8, as tolerated. Repeat courses of rituximab or placebo were permitted from week 24. To be eligible for re-treatment, patients had to have a Disease Activity Score in 28 joints (DAS28-erythrocyte sedimentation rate (ESR)) ≥2.6, with further re-treatment permitted 24 weeks after each course based on the same criteria. The placebo-controlled period continued to week 104. At week 52, the sponsor was unblinded to all treatment assignments for the purposes of data analysis, but investigators, sites, patients and radiographic readers remained blinded. Radiographs (hands, wrists and feet) were performed at screening and weeks 24, 52 and 104 and were read by two independent expert radiologists using the Genant-modified Sharp scoring system.14 15

The primary end point was the change in total Genant-modified Sharp score (mTSS) at week 52 from baseline.12 At week 104, radiographic end points included the change in mTSS, total erosion score and joint space narrowing from baseline to week 104. Proportions of patients with no progression in mTSS and erosion scores were also assessed. Clinical end points included the proportion of patients achieving American College of Rheumatology (ACR)20/50/70/90 criteria responses, European League Against Rheumatism (EULAR) responses and change in DAS28-ESR. ACR index of improvement in RA (ACRn) was calculated as described previously.16 Physical function was assessed using the Health Assessment Questionnaire-Disability Index (HAQ-DI). Radiographic outcomes and ACR50 responses were also analysed by serological status (RF and/or anticitrullinated peptide antibody (ACPA) presence). Adverse events (AEs) were recorded throughout the study and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3).

STATISTICAL ANALYSIS
Radiographic end points were analysed using a modified intention-to-treat population (all randomised and treated patients with a screening and at least one postbaseline radiographic evaluation). The intention-to-treat population (all patients randomised and treated) was used for all other efficacy and all safety end points.

Efficacy end points were grouped and ranked according to three objectives (prevention of joint damage, improvement in clinical signs and symptoms and improvement in physical function). All clinical signs and symptoms end points at week 104 were defined as exploratory in the protocol. Within the other two categories, all end points were secondary or exploratory at week 104, using a hierarchical approach to significance testing to control for multiplicity. When an end point did not reach significance at week 52, that end point and all end points lower in the hierarchy were treated as exploratory at week 104. When a secondary end point did not reach significance at week 104, all end points lower in the hierarchy were treated as exploratory. The primary end point (change in mTSS vs placebo at week 52) was achieved for rituximab 2×1000 mg+MTX; however, the change in mTSS with rituximab 2×500 mg+MTX was not statistically significant. Therefore, all p-values associated with radiographic outcomes at week 104 for this lower dose are exploratory and should be interpreted with caution. Exploratory p-values are denoted by ‘ex-p’.

Changes in radiographic scores were assessed with pairwise comparisons using a non-parametric test (Van Elteren) adjusted for baseline stratification factors (RF and region). Missing values were imputed by linear extrapolation. Percentage of inhibition of radiographic progression was calculated as (mean mTSS change in placebo group–mean mTSS change in a rituximab group)×100/(mean mTSS change in placebo group). Differences in the proportions of patients without radiographic progression were assessed using the Cochran–Mantel–Haenszel test, adjusting for baseline stratification factors. Patients were deemed to have progressed if their progression status could not be determined. Clinical signs and symptoms and physical efficacy differences were assessed using the Cochran–Mantel–Haenszel test and analysis of variance for categorical and continuous end points, respectively, adjusting for baseline stratification factors. Endpoint baseline values were included in analysis-of-variance models, if applicable. Non-responder imputations were used for categorical end points, and last observation carried forward was used for continuous end points.

RESULTS
A total of 755 patients were randomised, with 748 included in the intention-to-treat and safety population and 716 in the modified intention-to-treat population analysed for radiographic outcomes. Overall, 606 patients (80%) completed week 104; lack of efficacy and refusal of treatment were the most common reasons for withdrawal, with 4%, 3% and 5% of patients in the rituximab 2×500 mg+MTX, 2×1000 mg+MTX and placebo+MTX groups, respectively, withdrawing due to safety reasons. The proportion of randomised patients completing week 104 was higher in the rituximab 2×500 mg+MTX and 2×1000 mg+MTX groups compared with the placebo+MTX group (85% and 85% vs 71%, respectively). At 2 years, 67–68% of patients had received a third course of treatment, with some patients receiving up to five courses. The number of courses received was balanced between the placebo and rituximab treatment groups; overall, 249, 250 and 249 patients in the rituximab 2×500 mg+MTX, 2×1000 mg+MTX and placebo+MTX groups, respectively, received ≥1 course; 215, 219 and 212 received ≥2 courses; 169, 172 and 169 received ≥3 courses; 106, 107 and 122 received ≥4 courses; and 24, 26 and 31 received ≥5 courses. Baseline characteristics were similar across all treatment groups and have been reported previously.12 As at 1 year, MTX doses were similar across groups at 2 years.

Radiographic end points
At week 104, rituximab 2×1000 mg+MTX continued to inhibit progressive joint damage (PJD) in patients. The change in mTSS from baseline was 0.41 for patients treated with rituximab 2×1000 mg+MTX compared with 1.95 in the placebo+MTX group (p=0.0001), equating to 79% inhibition in mTSS (figure 1). Change from baseline in total erosion score also continued to be significantly lower with rituximab 2×1000 mg+MTX versus placebo+MTX at this time point (mean change 0.23 vs 1.32; p<0.0001) (figure 1). Furthermore, a positive effect on joint space narrowing scores was observed with rituximab 2×1000 mg+MTX versus placebo+MTX (0.18 vs 0.63; ex-p=0.0183), an effect that was not seen at week 52 (figure 1). Also, contrary to the results observed at week 52, exploratory analysis showed that PJD was reduced in patients receiving rituximab 2×500 mg+MTX over the 2-year time period: change in mTSS was reduced by approximately 61% compared with...
placebo+MTX (ex-p=0.0041), and erosive progression was slowed (mean change 0.50; ex-p=0.0019) (figure 1).

As observed at 1 year, a significantly higher proportion of patients receiving rituximab 2×1000 mg+MTX showed no radiographic progression (defined as change in mTSS ≤0) over 2 years compared with those receiving placebo+MTX (57% vs 37%; p<0.0001). In an exploratory analysis, a higher proportion of patients in the rituximab 2×500 mg+MTX group also showed no progression compared with the placebo+MTX group (49% vs 37%; ex-p=0.0059). Across both rituximab groups, 82% of patients with no radiographic progression at week 52 maintained this status to week 104 compared with 64% in the placebo group. A higher proportion of patients in the rituximab 2×500 mg and 2×1000 mg+MTX groups had no increase in erosion score at week 104 compared with the placebo+MTX group (55%, 59% and 38%, respectively; ex-p<0.001 and p<0.0001).

As previously reported, the majority of joint damage observed in rituximab-treated patients occurred between baseline and 24 weeks. Thereafter, minimal further change occurred in both rituximab groups, whereas joint damage progression continued in a near-linear fashion in the placebo group (figure 2A). Annualised rates of progression of mTSS further demonstrated the markedly slowed disease progression from week 24 into the second year of treatment in both rituximab groups compared with the placebo group (figure 2B). From week 24 to week 104, rituximab 2×1000 mg+MTX demonstrated near-complete inhibition (97%) of PJD compared with placebo+MTX (0.02 vs 0.72, respectively) and rituximab 2×500 mg+MTX induced 90% inhibition of PJD versus placebo+MTX (0.07 vs 0.72, respectively).

This study was not powered to compare outcomes between rituximab doses; however, in an exploratory analysis, all radiographic end points assessed from screening to week 104 for rituximab 2×1000 mg+MTX were numerically superior to rituximab 2×500 mg+MTX (online supplementary table S1).

**Clinical signs and symptoms**

Exploratory analyses showed that the improved clinical outcomes observed after 52 weeks were maintained at 104 weeks in both rituximab groups compared with the placebo group. ACR20/50/70/90 responses were achieved by higher proportions of patients in each rituximab group compared with the placebo group over the 2 years (figure 3A–D). In addition, mean ACn was higher at week 104 in the rituximab groups, and a larger proportion of patients achieved a major clinical response (ACR70 maintained for at least six consecutive months) in each rituximab group compared with the placebo group (table 1).

Greater improvements in disease activity (as measured by mean change in EULAR response and DAS28-ESR) were also observed to week 104 in both rituximab+MTX groups compared with the placebo+MTX group (figure 3E,F). Almost two times more patients achieved a EULAR good response or DAS28-ESR clinical remission with rituximab+MTX compared with placebo+MTX (table 1). The proportions of patients with LDA and remission continued to increase over time in all treatment groups, but the increases were greatest in the rituximab+MTX groups.

**Physical function**

Improvements in physical function were also sustained throughout the second year of treatment with both rituximab+MTX doses resulting in significantly greater mean decreases in HAQ-DI score compared with placebo+MTX (p<0.0001 at week 104) (figure 4). At week 104, exploratory analysis indicated that the proportion of patients with at least a minimal clinically important difference in HAQ-DI (decrease ≥0.22) was greater in the rituximab 2×1000 mg+MTX group than in the placebo+MTX group (table 1); proportions of patients achieving more marked improvements (ie, decreases of ≥0.3 or ≥0.5) were also greater in the rituximab 2×1000 mg+MTX group (data not shown). While the proportion of patients in the rituximab 2×500 mg+MTX group achieving the minimal clinically important difference in
Safety data over 104 weeks were consistent with those observed at 52 weeks with no new safety signals observed. The overall safety profile of rituximab+MTX was similar to that observed in the placebo+MTX group (table 2).

Withdrawals due to AEs were low: 3% in both rituximab groups compared with 7% in the placebo group. There was no predominant AE that led to withdrawal. Six deaths occurred during the 104-week study: three in the placebo+MTX group (two due to pneumonia and one due to cerebral infarction), two in the rituximab 2×500 mg+MTX group (one due to pneumonia; primary cause of death was unknown/unobtainable in the other—the patient had breathing difficulties and subsequently died in the hospital) and one in the rituximab 2×1000 mg+MTX group (due to duodenal ulcer). The incidence of all/serious AEs and rates of all/serious infections were similar across all treatment groups (table 2). Proportions of patients experiencing HAQ-DI was numerically higher than in the placebo group, this did not reach statistical significance.

Efficacy in subgroups

Subgroup analysis was performed on data from patients seropositive or seronegative for RF and/or ACPA. At week 104, RF and/or ACPA seropositive patients treated with rituximab+MTX had a greater probability of having no radiographic progression, and a greater proportion achieved an ACR50 response, compared with patients receiving MTX alone. In seronegative patients, rituximab treatment had a less pronounced effect on radiographic responses and no effect on clinical responses. Comparisons between treatment groups should be interpreted with caution due to small numbers of seronegative patients and overlapping CI. Results are presented in online supplementary table S2.

Figure 3  Efficacy over 2 years. (A) ACR20, (B) ACR50, (C) ACR70 and (D) ACR90 responses. LOCF used for tender and swollen joint counts, HAQ score, CRP, ESR and VAS assessments. ACRn was set to ‘non-responder’ when the score was missing. Patients were classified as non-responders from the point of withdrawal or rescue use. (E) EULAR good response. LOCF used for tender and swollen joint counts, ESR and patient’s Global Assessment of Disease Activity VAS. EULAR response was set to ‘non-responder’ when the DAS28 score was missing. Patients were classified as non-responders from the point of withdrawal or rescue use. (F) Mean change in DAS28. LOCF used for tender and swollen joint counts, ESR and patient’s Global Assessment of Disease Activity VAS. Error bars show ±1.96×standard error. ACR, American College of Rheumatology; CRP, C reactive protein; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; HAQ, Health Assessment Questionnaire; LOCF, last observation carried forward; MTX, methotrexate; VAS, visual analogue scale.
The proportion of patients showing no progression of joint damage after 2 years was significantly higher in the rituximab dose groups compared with the placebo+MTX group. The figure of 57% observed for the 2×1000 mg dose was almost identical (56.8%) to that seen at 2 years in a similar population treated with abatacept+MTX. The majority of joint damage progression in the current study was observed within the first 6 months, with further damage almost entirely prevented thereafter; the reasons for this are unknown.

Over 2 years, both doses of rituximab continued to demonstrate significant improvements over placebo in relieving the signs and symptoms of RA, as exemplified by significantly higher proportions of patients achieving ‘high hurdle’ end points, such as ACR70 and ACR90, major clinical response, EULAR good response and DAS28 remission. In addition, improvements in physical function were maintained, with significantly greater mean changes in HAQ-DI observed in both rituximab groups than in the placebo group throughout the observation period.

This study was not powered to compare rituximab doses, but exploratory results generally show that numerically greater responses for radiographic outcomes were achieved with the higher dose, while clinical outcome responses were generally numerically similar for both doses. In addition, the disconnect between radiographic and clinical responses with rituximab 2×500 mg+MTX previously observed at 1 year was reduced at 2 years—an effect attributed to a slower onset of radiographic inhibition during the initial 6 months of treatment with the 500-mg dose. A recent consensus statement discussed the optimal dose of rituximab in patients with RA. The authors proposed that the 500-mg dose may provide equivalent clinical and radiographic benefits to 1000 mg; however, the 500-mg dose is not approved and has not been studied in the licensed TNF-IR patient population. Consequently, further analysis would be required to confirm any equivalence of doses. In the present study, while both rituximab doses provided benefit in improving clinical signs and symptoms, data suggest that the higher dose slows PJD sooner, an observation that is relevant to an early population with RA (data presented in online supplementary table S1).

As at 1 year, and consistent with observations made in other patient populations, patients in the small subgroup who were seronegative for both RF and ACPA showed limited evidence of radiographic or clinical improvement with rituximab+MTX or
placebo+MTX treatment. Conversely, radiographic and clinical responses among patients seropositive for RF and/or ACPA were significantly improved for rituximab compared with MTX alone.

The 2-year safety profile is consistent with that observed at 1 year and with previously reported data in TNF-IR patients and pooled data from long-term rituximab studies. The incidence of serious infections remained low and consistent with previously reported rates, and no further opportunistic infections were reported beyond those observed up to week 52. Infusion-related reactions remained the most common safety event overall; however, their incidence generally declined following the first infusion of the first course.

Table 2  Summary of safety profile over 104 weeks (safety population)

<table>
<thead>
<tr>
<th>Patient-years of observation</th>
<th>Placebo+MTX (n=249)</th>
<th>Rituximab ×500 mg+MTX (n=249)</th>
<th>Rituximab ×1000 mg+MTX (n=250)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE incidence, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any AE</td>
<td>215 (66)</td>
<td>206 (83)</td>
<td>217 (87)</td>
</tr>
<tr>
<td>First course*</td>
<td>183 (73)</td>
<td>167 (67)</td>
<td>188 (75)</td>
</tr>
<tr>
<td>Second course*</td>
<td>135 (64)</td>
<td>128 (60)</td>
<td>140 (64)</td>
</tr>
<tr>
<td>Third course*</td>
<td>107 (63)</td>
<td>96 (57)</td>
<td>111 (65)</td>
</tr>
<tr>
<td>Fourth course*</td>
<td>52 (43)</td>
<td>55 (52)</td>
<td>55 (51)</td>
</tr>
<tr>
<td>Fifth course*</td>
<td>5 (16)</td>
<td>7 (29)</td>
<td>6 (31)</td>
</tr>
<tr>
<td>Any serious AE (all courses)</td>
<td>42 (17)</td>
<td>37 (15)</td>
<td>33 (13)</td>
</tr>
<tr>
<td>AE leading to withdrawal (all courses)</td>
<td>17 (7)</td>
<td>8 (3)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>All deaths†</td>
<td>3 (1)</td>
<td>2 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

Infusion-related reaction, n (%)  
First course* 31 (12)  35 (14)  46 (18)  
Second course* 21 (10)  20 (9)  21 (10)  
Third course* 10 (6)  11 (7)  12 (7)  
Fourth course* 10 (8)  10 (9)  8 (7)  
Fifth course* 2 (6)  1 (4)  3 (12)  
Infection, n (%)  
Any 146 (59)  162 (65)  160 (64)  
Serious§ 19 (8)  13 (5)  12 (5)  
Malignancy, n (%)  
Any 7 (3)  6 (2)  3 (1)  
Serious 6 (2)  5 (2)  2 (<1)  
AE rates per 100 patient-years (95% CI)  
Overall infection rate 99.50 (90.42 to 109.49)  92.37 (83.98 to 101.61)  109.50 (100.36 to 119.47)  
Serious infection§ rate 4.97 (3.24 to 7.63)  4.15 (2.85 to 6.50)  3.25 (1.96 to 5.38)

*Percentage of incidence based on number receiving each treatment course (as described in the Results section).  
†Includes patients who died during the safety follow-up period.  
‡Percentage of incidence based on number receiving each treatment course (as described in the Results section).  
§Reported as serious and/or treated with intravenous antibiotics.  
AE, adverse event; MTX, methotrexate.

Consequently, the positive results presented here for the IMAGE trial, in which patients were treated on average 1 year after RA disease onset, may be relevant to a TNF-IR patient who initiates treatment with rituximab.

In conclusion, this 2-year analysis of the IMAGE study demonstrates that rituximab ×1000 mg+MTX led to sustained and significant inhibition of joint damage progression and significant improvements in clinical signs and symptoms of RA and functional ability compared with MTX alone in an early population of patients with RA.

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Mark Reynard and Tim Shaw

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