Continued inhibition of structural damage over 2 years in patients with rheumatoid arthritis treated with rituximab in combination with methotrexate

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Published in: Annals of the Rheumatic Diseases

DOI: 10.1136/ard.2009.119222

Citation for published version (APA):
Continued inhibition of structural damage over 2 years in patients with rheumatoid arthritis treated with rituximab in combination with methotrexate

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ABSTRACT

BACKGROUND Rituximab inhibited structural damage at 1 year in patients with rheumatoid arthritis (RA) who had had a previous inadequate response to tumour necrosis factor (TNF) inhibitors.

Objective To assess structural damage progression through 2 years.

Methods Intention-to-treat patients with one post-baseline radiograph (rituximab n=281; placebo n=187) received background methotrexate (MTX) and were randomised to rituximab (2×1000 mg infusions, 2 weeks apart) or placebo; patients were eligible for rituximab re-treatment every 6 months. By week 104, 82% of the placebo population had received ≥1 dose of rituximab. Radiographic end points included the change in total Sharp score (TSS), erosion and joint space narrowing scores at week 104.

Results At week 104, significantly lower changes in TSS (1.14 vs 2.81; p<0.0001), erosion score (0.72 vs 1.80; p<0.0001) and joint space narrowing scores (0.42 vs 1.00; p<0.0009) were observed with rituximab plus MTX vs placebo plus MTX. Within the rituximab group, 87% who had no progression of joint damage at 1 year remained non-progressive at 2 years.

Conclusions Rituximab plus MTX demonstrated significant and sustained effects on joint damage progression in patients with RA and a previously inadequate response to TNF inhibitors. REFLEX have been described previously. Briefly, patients were included if they had active RA despite treatment with methotrexate (MTX) ≥10 mg/week and had experienced an inadequate response (lack of efficacy or intolerance) to at least one TNF inhibitor.

The study was performed in accordance with the Declaration of Helsinki. All participating sites received approval from their governing institutional review board (or equivalent) and all patients provided written informed consent.

Study protocol REFLEX was a randomised, double-blind, placebo-controlled, phase III study with an option for further treatment courses under a separate extension study. Patients continued background MTX and were randomly assigned to placebo or rituximab (MabThera, Roche, Welwyn Garden City, UK; Rituxan, Genentech, South San Francisco, California, USA and Biogen Idec, San Diego, California, USA). Rituximab 1000 mg was administered by intravenous infusion on days 1 and 15. All patients received corticosteroid treatment, consisting of intravenous methylprednisolone 100 mg before each infusion and oral prednisone during the 2-week treatment period (60 mg on days 2−7, 30 mg on days 8−14).

From weeks 16 to 24, patients who failed to respond to treatment could receive rescue therapy. Patients randomised to placebo could receive rituximab and patients randomised to rituximab could receive standard care. Patients completing week 24 were eligible to receive further courses of rituximab within an open-label extension study. Further courses of rituximab were also available for placebo patients who had responded to rescue treatment.

Radiographs of hands, wrists (posterior/anterior) and feet (anterior/posterior) were performed at screening (baseline) and at weeks 24, 56 and 104, relative to randomisation. Radiographs were read at a central reading facility by two independent expert radiologists and scored using the Genant-modified Sharp scoring system.11 Radiologists were blinded to the treatment group assignment, chronological order of the radiographs and patients' clinical response.

Radiographic outcome measures Radiographic assessments included the mean change in total Genant-modified Sharp score (mTSS), the erosion score, the joint space narrowing score and the proportion of patients with no further joint damage progression (defined as a change in mTSS ≤0). All assessments compared
baseline and week 104. Radiographic changes were also determined during discrete time intervals of baseline to 24 weeks, 24–56 weeks and 56–104 weeks. The annualised progression rate (APR) was calculated to provide a measure of the rate of change in progression standardised to a common time interval. The APR for each patient was calculated as follows:

\[
\text{APR} = 364 \times \frac{\text{Score}_{\text{time2}} - \text{Score}_{\text{time1}}}{\text{StudyDay}_{\text{time2}} - \text{StudyDay}_{\text{time1}}}
\]

**Statistical analysis**

The primary population for the radiographic analysis was defined as all patients (including those withdrawing or receiving rescue) included in the REFLEX intension-to-treat (ITT) population who had at least one post-baseline radiograph (either 24, 56 or 104 weeks). All missing data were imputed using linear extrapolation of the progression observed from baseline to the week 24/week 56 radiographs. Analyses were conducted using a non-parametric analysis (Van Elteren test), stratified by region (USA vs non-USA) and baseline rheumatoid factor (positive vs negative). In addition, sensitivity analyses were conducted using observed data only.

**RESULTS**

**Patient characteristics and disposition**

A total of 517 patients were randomised: 308 to rituximab plus MTX and 209 to placebo plus MTX. Of these, 468 patients (281 rituximab patients and 187 placebo patients) were included in the REFLEX ITT population, and had a baseline film at screening and at least one post-baseline radiographic. A total of 197 rituximab and 135 placebo patients had radiographs at both baseline and week 104. The baseline characteristics and measures of disease activity were similar in both treatment groups and were similar to those of the original ITT population (table 1).

By week 104, 165/281 patients (59%) in the rituximab group who had received two or more courses of rituximab. Of the 187 patients randomised to placebo, 154 (82%) had received at least one dose of rituximab before their last observed radiograph, compared with 94 (50%) having received two or more courses. Only 33 patients (18%) initially randomised to placebo did not receive rituximab treatment.

**Radiographic efficacy**

The mean change in the mTSS from baseline to 104 weeks was significantly lower in the rituximab group than in the placebo group (1.14 vs 2.81, respectively; p<0.0001). Significant differences in the mean change in erosion and joint space narrowing scores were also observed (figure 1).

The proportion of patients with no progression in joint damage over 2 years was significantly higher in the rituximab group compared with the placebo group—most of whom had by then received rituximab—showed slower rates of change during their second year (figure 2C). Similarly, whereas in the rituximab group the APR remained consistent, in the placebo group it gradually declined from 1.60 points/year during the initial 24-week period to 0.95 points/year in the second year (figure 2D).

The proportion of patients with no change in their mTSS (figure 2A) and with no new erosions increased during each time period in each treatment group (figure 2B). Of those patients randomised to rituximab who did not progress during the first year, 87% did not progress during the second year either.

**DISCUSSION**

Inhibition of structural joint damage by rituximab in patients with RA and a previous inadequate response to TNF inhibitors was first described over a 1-year period. Here we have demonstrated that the initial effects of rituximab are maintained over an extended interval of 2 years, with all measures of joint damage significantly improved compared with placebo plus MTX.

Treatment with rituximab was associated with a significantly higher proportion of patients with no progression of joint damage over the 2 years compared with placebo plus MTX. The proportion of patients with no progression (57%) achieved with rituximab treatment compares well with that seen with other

**Table 1** Baseline demographic characteristics of the patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo plus MTX (n=187)</th>
<th>Rituximab plus MTX (n=281)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male (n (%))</td>
<td>150 (80)/37 (20)</td>
<td>228 (81)/53 (19)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52.9 (12.1)</td>
<td>52.5 (12.2)</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>11.7 (7.7)</td>
<td>11.9 (8.2)</td>
</tr>
<tr>
<td>Swollen joint count</td>
<td>23.1 (12.8)</td>
<td>23.2 (11.9)</td>
</tr>
<tr>
<td>Tender joint count</td>
<td>33.2 (15.7)</td>
<td>33.2 (15.1)</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>3.7 (3.8)</td>
<td>3.7 (3.9)</td>
</tr>
<tr>
<td>Anti-CCP positive (n (%))</td>
<td>82 (44)</td>
<td>130 (46)</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>48.7 (26.5)</td>
<td>47.8 (25.6)</td>
</tr>
<tr>
<td>HAQ-DI score</td>
<td>1.9 (0.54)</td>
<td>1.8 (0.57)</td>
</tr>
<tr>
<td>Total Genant–modified Sharp score</td>
<td>32.5 (31.5)</td>
<td>30.6 (26.7)</td>
</tr>
</tbody>
</table>

*Except where indicated otherwise values are the mean (SD). CCP, cyclic citrullinated peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; MTX, methotrexate.

**Figure 1** Changes from baseline to 2 years in total Genant–modified Sharp, erosion and joint space narrowing (JSN) scores in patients treated with rituximab (2 x 1000 mg) plus methotrexate (MTX) or placebo plus MTX *p<0.005; **p<0.0001 versus placebo plus MTX.
treatments with biological agents, albeit in less treatment-refractory patient populations. Importantly, of those rituximab patients with no progression in the first year, 87% maintained a non-progressive status during the second year.

Although patients were initially randomised to either rituximab or placebo, 82% of placebo patients had switched to rituximab by 2 years. The impact of this switch on the progression of joint damage in this placebo–rituximab group is evident by the reduced changes in scores between time periods and the gradual slowing in their APR. The consequence of this switch to active treatment is that the degree of progression observed in the ‘placebo’ group is less than would have been observed had those patients been maintained solely on MTX, thereby underestimating the relative treatment effect. The extent of this discrepancy can be estimated using the method devised by Strand and Sharp for estimating APRs. By dividing the baseline mean mTSS (32.5) by the mean disease duration (11.7), the predicted progression for the placebo group over 2 years was 5.55. However, the observed progression was much lower (2.81), suggesting that the switch to rituximab had a large influence on the progression of joint damage in this control group. Consequently, the relative treatment effect size cannot be accurately measured. Nevertheless, using the predicted and observed progression in the placebo group a reduction in joint damage of 59–79% for rituximab plus MTX compared with placebo plus MTX could be estimated. Given the estimated nature of this effect, together with the lack of available radiographic data in similar patient populations, comparisons of this effect size with other biological agents used for RA would not be appropriate.

In conclusion, this 2-year analysis demonstrates that rituximab plus MTX has significant and sustained effects on the inhibition of joint damage in a population of patients with active RA who had previously experienced an inadequate response to TNF inhibitors.

Acknowledgements Writing assistance was provided by Claire Snowball (Adelphi Communications Ltd) in consultation with the authors, Roche Products Ltd and Genentech.

Funding This study was sponsored by F Hoffmann-La Roche Ltd, Genentech, Inc and Biogen Idec, Inc. A portion of this work (Stanford University) was supported in part by a grant from the National Institutes of Health National Center for Research Resources (5 M01 RR000070).

Competing interests SC has received consulting and speaker fees and research grants from Genentech and Biogen Idec. PE and PPT have received consulting and speaker fees and research grants from Roche. EK has received consulting and speaker fees from Roche and Genentech and research grants from Roche. MCG has received speaker fees and research grant support from Roche and has served as a consultant for Roche, Biogen Idec and Genentech. DH and MWC are employees of Biogen Idec. TS is an employee and owns shares in Roche Products Ltd. CP has received
consulting and speaker fees from Genentech and Biogen Idec and is an employee of
Syncarc.

Ethics approval This study was conducted with the approval of the protocol for this
study and any accompanying material provided to the patient (eg, patient information
sheets and descriptions of the study used to obtain informed consent) were
submitted by the investigator to the associated independent ethics committee (IEC)
or institutional review board (IRB). Approval from the committee was obtained before
starting the study, and was documented in a letter to the investigator specifying the
date on which the committee met and granted the approval. Any modifications made
to the protocol after receipt of the IEC/IRB approval were also to be submitted by the
investigator to the committee in accordance with local procedures and regulatory
requirements.

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