Rituximab versus tocilizumab and B-cell status in TNF-alpha inadequate-responder rheumatoid arthritis patients: the R4-RA RCT

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Scientific summary

The R4-RA RCT

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Scientific summary

Background

Although biological therapies have transformed the outlook for those with rheumatoid arthritis, the lack of any meaningful response in approximately 40% of patients, the potential side effects and the high cost of these drugs have highlighted the need to define predictive biomarkers of response and to stratify patients according to therapeutic outcome. The importance of B cells in rheumatoid arthritis pathogenesis is supported by the efficacy of the B-cell-depleting agent rituximab (MabThera, F. Hoffman La-Roche Ltd, Basel, Switzerland). Rituximab is licensed for use with rheumatoid arthritis following the failure of conventional synthetic disease-modifying antirheumatic drugs and tumour necrosis factor inhibitor biologicals. In this increasing therapeutically resistant cohort, only 30% of patients achieve a major treatment response at 6 months. However, over 50% of patients show low/absent synovial B-cell infiltration, suggesting that synovial inflammation is driven by alternative cell types. This prompted us to test the hypothesis that, in synovial-biopsy B-cell-poor patients, tocilizumab (RoActemra, F. Hoffman La-Roche Ltd, Basel, Switzerland) (targeting interleukin 6) is superior to rituximab (targeting $CD20^+$/B cells).

Objectives

The main aim of this study was to test the hypothesis that the presence or absence of specific synovial cellular and molecular signatures (B cells and B-cell-associated signatures), assessed following a synovial tissue biopsy, will enrich for response/non-response to the B-cell-depleting anti-CD20 monoclonal antibody, rituximab.

Methods

Design

We conducted a Phase IV, open-label, multicentre, randomised controlled trial. Patients were randomised to receive rituximab or tocilizumab and were stratified according to histological classification of baseline synovial biopsy (B-cell poor, B-cell rich, germinal centre positive or unknown) and by site (Queen Mary University of London vs. all other sites).

Patients were followed up at 4-weekly intervals throughout the 48-week trial treatment period, at which times the rheumatoid arthritis disease activity measurements and safety data were collected. An optional repeat synovial biopsy of the same joint sampled at baseline was performed at 16 weeks.

Setting

Rheumatology outpatient clinics in 19 European centres.

Participants

Patients aged $\geq$ 18 years fulfilling the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis, and who were eligible for treatment with rituximab therapy in accordance with UK National Institute for Health and Care Excellence guidelines [i.e. failing on or intolerant to conventional synthetic disease-modifying antirheumatic drug therapy and at least one biological therapy (excluding trial investigational medicinal products)], were eligible for recruitment to the study and identified through rheumatology outpatient clinics at each study site.

Sample size

A sample size of 82 B-cell-poor patients was planned to provide 90% power to detect a 35% difference (assuming 55% response in tocilizumab and 20% response in rituximab) in the proportion of patients who had a response. The assumed proportions of B-cell-poor, B-cell-rich and germinal centre-positive recruited patients were 60%, 35% and 5%, respectively. After accounting for 10% ungradable biopsy samples and a 5% dropout rate, we estimated that a total of 160 patients was required to achieve 90% power for the study. No power calculation was conducted for the B-cell-rich population.

Interventions

Patients underwent a synovial biopsy of a clinically active joint at trial entry. Synovial tissue was retained for both histological analysis and ribonucleic acid extraction. Histological classification of synovial tissue was performed following immunohistochemical staining for $CD20^+$ B cells according to a predefined algorithm to stratify patients into B-cell-rich and B-cell-poor categories. Following synovial biopsy and subsequent randomisation, rituximab was administered at baseline as two 1000-mg infusions 2 weeks apart, or tocilizumab was administered at baseline as an 8-mg/kg infusion at 4-weekly intervals.

Outcome measures

The study was powered to test in the B-cell-poor population superiority of tocilizumab over rituximab at 16 weeks. The primary end point was defined as an improvement in the Clinical Disease Activity Index (CDAI) score of $\geq 50\%$ from baseline. In addition, patients were considered to be non-responders if they did not reach an improvement in CDAI score of $\geq 50\%$ and a CDAI score of < 10.1, defined for simplicity as CDAI major treatment response (CDAI-MTR).

Patients who were deemed to be responders at 16 weeks continued on their allocated treatment, with rituximab infusions being repeated at 24 weeks. Non-responders were switched to the alternative biological therapy (switch patients) and treatment response was determined at 16 weeks post switch.

Secondary outcomes included assessment of CDAI response (as defined for primary outcome analysis) at 16 weeks in the B-cell-rich cohort. Additional secondary efficacy analyses were performed in both the B-cell-rich and the B-cell-poor populations with and without week 16 switch patients based on the following parameters at week 16: mean improvement in Disease Activity Score in 28 joints (DAS28) C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR); number of patients in remission, defined as DAS28 of ≤ 2.6, or with low disease activity, defined as DAS28 of ≤ 3.2; and percentage of patients with low disease activity, defined as a CDAI score of < 10.1. Additional key secondary end points included the rates of low disease activity and remission as measured by DAS28(ESR) and DAS28(CRP) and patient-reported outcomes such as fatigue up to week 48. The incidence and severity of all adverse events were recorded.

Exploratory end points included the evaluation of change in synovial molecular signatures and therapeutic response to tocilizumab or rituximab.

Analysis

The primary end point and other binary end points were analysed using a two-sided alpha of 0.05 significance level by chi-squared test or Fisher's exact test, as appropriate. For continuous secondary outcomes, an analysis of covariance was performed with treatment as the factor and baseline score as the covariate. Changes from baseline within groups were analysed using paired Wilcoxon signed-rank tests. All statistical analyses were carried out using R version 3.5.1 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients and demographics

Of the 212 patients screened, 190 consented and 164 were randomised. The trial ended because the recruitment targets were reached. Eighty-three patients were randomised to receive rituximab and 81 patients were randomised to receive tocilizumab. A total of 161 patients received the investigational medicinal product. Baseline characteristics, disease activity and histological groups were balanced across the treatment groups. Most patients were female (80%) and the majority were seropositive for rheumatoid factor (67%) or anticitrullinated peptide antibodies (77%). The median disease duration was 9 years (interquartile range 4–19 years). Disease activity was high [mean DAS28(ESR) of 5.8 (standard deviation 1.2)] and a total of 49% of patients were classified as B-cell poor compared with 40% of patients being classified as B-cell rich.

Treatment response in the B-cell-poor population

Seventy-nine (49%) patients who received the investigational medicinal product were classified as B-cell poor histologically, 38 (48%) of whom were randomised to rituximab and 41 (52%) to tocilizumab. At 16 weeks, there was no significant difference between groups in the primary outcome, an improvement in CDAI score of $\geq$ 50% response rate (risk ratio 1.25, 95% confidence interval 0.8 to 1.96). However, a supplementary analysis of CDAI-MTR did reach statistical significance (risk ratio 1.96, 95% confidence interval 1.01 to 3.78). When B-cell-poor classification was determined by ribonucleic acid sequencing, 67 (50%) patients were classified as B-cell poor, of whom 33 (49%) were randomised to rituximab and 34 (51%) to tocilizumab. In this case, the primary end point and CDAI-MTR were both met (risk ratio 1.72, 95% confidence interval 1.02 to 2.91, and risk ratio 4.12, 95% confidence interval 1.55 to 11.01, respectively). Similar results were obtained for other secondary end points, with significantly more patients in the tocilizumab group than in the rituximab group achieving DAS28(ESR) remission and DAS28 (ESR) moderate/good European League Against Rheumatism response and tocilizumab-treated patients achieving significantly greater decreases in DAS28(ESR), DAS28(CRP) and Functional Assessment of Chronic Illness Therapy (FACIT) fatigue score between baseline and week 16 than those in the rituximab group. The area under the curve of mean change in DAS28(ESR/CRP) between baseline and 16 weeks was also significantly greater in patients treated with tocilizumab than in those treated with rituximab. We performed further analyses including patients who responded to first-line investigational medicinal product and those who were switched to alternative investigational medicinal product after failing to achieve the primary end point (improvement in CDAI score of $\geq$ 50%) or CDAI-MTR (improvement in CDAI score of $\geq$ 50% and CDAI score of $<$ 10.1) at 16 weeks. Treatment responses at 16 weeks following treatment initiation again demonstrated significantly higher response rates to tocilizumab through the majority of outcome measures evaluated. Per-protocol analyses showed results consistent with the intention-to-treat analysis.

Treatment response in the B-cell-rich population

Although the study was not powered for the analysis of the B-cell-rich group, 64 (40%) patients who received investigational medicinal product were classified as B-cell rich. Of these, 33 (52%) were randomised to the rituximab group and 31 (48%) to the tocilizumab group. At week 16, there were no significant differences in the number or proportion of patients achieving the primary end point (improvement in CDAI score of $\geq$ 50%: risk ratio 1.31, 95% confidence interval 0.76 to 2.26) or the CDAI-MTR (an improvement in CDAI score of $\geq$ 50% and CDAI score of $<$ 10.1: risk ratio 2.34, 95% confidence interval 0.92 to 5.97) when patients were classified histologically or molecularly. Likewise, there were no significant differences between treatment groups in secondary end points, except that the number of patients achieving DAS28(ESR) remission was significantly larger in the tocilizumab group than in the rituximab group, and that the mean decrease in DAS28(ESR) was significantly greater in the tocilizumab group. Analyses included patients who switched to the alternative investigational medicinal product at week 16 (following treatment failure to the primary drug) and per-protocol analyses, which showed consistent results.

Interaction between the treatment response and the B-cell status

The likelihood ratio test that was performed through logistic regression showed no evidence of an interaction between the investigational medicinal product and the histologically defined B-cell subgroups for the primary end point ($p = 0.95$) or CDAI-MTR ($p = 0.82$). When testing the interaction between the ribonucleic acid sequencing-defined B-cell subgroup and the investigational medicinal product, no significant interaction was observed when using the primary end point ($p = 0.096$), but a significant interaction was observed when using the CDAI-MTR ($p = 0.049$). The study was not powered for this analysis because this would require a larger number of patients.

Treatment response and immune histological parameters

There were no differences in the baseline histological parameters that were evaluated between the rituximab-treated and tocilizumab-treated groups. A paired week 16 synovial biopsy was available in 41 patients who were treated with rituximab and 24 patients who were treated with tocilizumab. In the rituximab group, we saw a significant decrease in $CD20^+$ and $CD79a^+$ B-cell scores, synovitis scores, $CD138^+$ plasma cell scores and $CD68^+$ sublining macrophage scores at 16 weeks. In the rituximab-treated group, when patients were stratified into week 16 responder and non-responder (improvement in CDAI score of $\geq$ 50%) groups, $CD20^+$ and $CD79a^+$ B-cells decreased significantly between baseline and 16 weeks in both groups, although the percentage decrease was larger in the responder group. For rituximab-treated patients, the $CD138^+$ plasma cell score was the only histological parameter that demonstrated a significant decrease in the responder group only. In patients treated with tocilizumab in whom a paired biopsy was available, the only significant change at week 16 was a decrease in $CD68^+$ sublining macrophages. Changes in histological parameters when tocilizumab-treated patients were stratified into responder and non-responder groups were less notable than in the rituximab-treated group, with only $CD68^+$ sublining macrophages showing a significant change from baseline.

Ribonucleic acid sequencing analysis

Ribonucleic acid sequencing analysis was carried out in patients for whom high-quality data could be obtained following quality control of library preparation and principal components analysis evaluation. We analysed patients who were treated with rituximab ($n = 101$) and tocilizumab ($n = 82$) separately to assess the change in gene expression between the baseline and the primary end point in responders and non-responders to treatment (European League Against Rheumatism good/moderate vs. none). As well as analysing the change in responders and non-responders individually, the difference in the change between these two groups was also investigated.

In the gene-level analysis, the expression of *MS4A1* (the gene encoding CD20) decreased significantly ($p < 0.05$) in the rituximab-treated group in both responders and non-responders, but the reduction in *MS4A1* expression over time was more significant in responders, which may suggest that individuals responded better because of improved B-cell depletion in synovial tissue. The expression of the interleukin-6 gene in the tocilizumab-treated group decreased in responders ($p < 0.05$), but there was no significant change in non-responders.

Next, we examined the change in module or pathway expression between groups and found a significant decrease in B-cell module expression in the responders ($p < 0.05$), but not in the non-responders in the rituximab-treated group. There were no significant changes in the degree of interleukin-6 pathway expression in the tocilizumab-treated group in either the responders or the non-responders.

Safety and adverse events

There were more adverse events in patients treated with tocilizumab than in those treated with rituximab (327 vs. 284), and also more serious adverse events (18 vs. 8, respectively). One patient in the rituximab-treated group and three patients in the tocilizumab-treated group discontinued the investigational medicinal product because of serious adverse events. The serious adverse events included six infections, three in each group, and five ischaemic cardiac events, four in the tocilizumab group and one in the rituximab group. One death because of suicide was reported in the rituximab group. No malignancies were reported. Importantly, no serious adverse events related to synovial biopsy were reported.

Conclusions

To our knowledge, this is the first biopsy-based, multicentre, randomised controlled trial for rheumatoid arthritis, and we were unable to demonstrate that tocilizumab is more effective than rituximab in patients with a B-cell-poor pathotype in our primary analysis. However, superiority was shown in some supplementary and secondary analyses. The supplementary and secondary analyses overcame possible unavoidable weaknesses in our original study plan, in which the histological method of determining B-cell status may have misclassified some participants, and our chosen primary outcome that was insufficiently sensitive. In more detail, when synovial B-cell-poor status was defined histologically, no significant difference was observed in the primary outcome. However, superiority was found in the supplementary analyses that examined the proportion of patients treated with tocilizumab or rituximab who achieved CDAI-MTR. In addition, when B-cell-poor classification was determined molecularly, both the primary end point and the CDAI-MTR were met. Other secondary end points showed similar findings, with statistically more tocilizumab-treated patients than rituximab-treated patients achieving favourable outcomes.

Although the study was not powered to detect differences in a B-cell-rich rheumatoid arthritis population, the results of the analyses, whether patients were classified histologically or molecularly, suggested that clinical outcomes were similar when patients were treated with rituximab or tocilizumab. Importantly, our results were consistent in both the intention-to-treat and the per-protocol cohort analyses, and similar outcome results were demonstrated through to week 24.

Analysis of the synovial histological response to rituximab is in line with previously published data from observational cohorts, which report significant decreases in synovial B cells following treatment with rituximab, although no significant associations between the degree of synovial B-cell depletion and the clinical response were observed. This result may have been influenced by a skewed population of participants who agreed to have a second biopsy and which included a larger number of non-responder patients. Importantly, in line with previous reports, our data identified $CD138^+$ plasma cell depletion as a significant marker of response to rituximab. In addition, the significant decrease in expression of genes associated with B cells, at both module and single-gene level (*MS4A1*, the gene encoding CD20, which is the target of rituximab) in responders but not in non-responders, suggests that modulation of specific target expression levels measured by ribonucleic acid sequencing may be a more sensitive method than analysing the number of B cells histologically to determine the mechanisms of treatment response.

The safety analysis showed a larger number of serious adverse events and adverse events in patients treated with tocilizumab than in those treated with rituximab; these adverse events were largely unrelated to the study drug but may suggest, in this first head-to-head trial of rituximab and tocilizumab, that tocilizumab is less well tolerated than rituximab. Importantly, there were no serious adverse events related to synovial biopsy.

The study does have limitations, including uncertainty about the optimal B-cell-poor/-rich classification (cellular vs. molecular) and the inclusion of an active comparator (tocilizumab), which, similar to rituximab, modulates B-cell function and survival. The selection of tocilizumab was a pragmatic choice based largely on the accessibility of NHS trusts participating in the trial to this biological treatment. An additional limitation is the lack of double blinding for the investigational medicinal product. Finally, the adoption of the CDAI as a primary outcome measure rather than the DAS28/European League Against Rheumatism response has significantly influenced the clinical response rates to investigational medicinal products.

In conclusion, the trial failed to demonstrate superiority of tocilizumab over rituximab when the biopsy was analysed histologically, suggesting that this method cannot be used for drug selection. However, the molecular classification showed stronger correlations with clinical responses indicating that in B-cell-poor rheumatoid arthritis patients tocilizumab is significantly more likely to induce a clinical response than

rituximab. Future studies will be required to establish whether or not molecular pathology analysis of synovial tissue has clinical utility in accurately identifying patients with low B-cell infiltrate and in guiding biological choice (e.g. rituximab) in rheumatoid arthritis.

Trial registration

This trial is registered as ISRCTN97443826.

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