Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x-ray reader-blinded randomised controlled trial of tocilizumab

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Objective: To evaluate the ability of tocilizumab (a humanised anti-IL-6 receptor antibody) monotherapy to inhibit progression of structural joint damage in patients with RA.

Methods: In a multi-centre, x-ray reader-blinded, randomised, controlled trial, 306 patients with active RA of <5 years’ duration were allocated to receive either tocilizumab monotherapy at 8 mg/kg intravenously every 4 weeks or conventional disease-modifying antirheumatic drugs (DMARDs) for 52 weeks. Radiographs of hands and forefoot were scored by the van der Heijde modified Sharp method.

Results: Patients had a mean disease duration of 2.3 years and a disease activity score in 28 joints of 6.5 at baseline. Mean total modified Sharp score (TSS) was 29.4, which was very high despite the relatively short disease duration. At week 52, the tocilizumab group showed statistically significantly less radiographic change in TSS (mean 2.3; 95% CI 1.5 to 3.2) than the DMARD group (mean 6.1; 95% CI 4.2 to 8.0; p<0.01). Tocilizumab monotherapy also improved signs and symptoms. The overall incidences of AEs were 89% and 82% (serious AEs: 18% and 13%; serious infections: 7.6% and 4.1%) in the tocilizumab and DMARD groups, respectively.

Conclusion: Tocilizumab monotherapy was generally well tolerated and provided radiographic benefit in patients with RA.
Patients were randomly assigned to receive either tocilizumab monotherapy at 8 mg/kg intravenously every 4 weeks or conventional DMARD therapy for 52 weeks. A long-term placebo-controlled study in RA patients with highly active disease was not acceptable from an ethical point of view, and therefore DMARDs were used for the controls. The randomisation was performed by registering of patients at the patient registration centre with a centralised allocation method. For the tocilizumab group, DMARDs and/or immunosuppressants were discontinued from the start of the study. Oral corticosteroids (< 10 mg prednisolone per day) were allowed, but the dosage could not be increased during the study. Intra-articular corticosteroid injections were not allowed. Use of one non-steroidal anti-inflammatory drug (NSAID), including switching to another NSAID, was allowed. For the conventional DMARD group, the dose, type and combination of DMARDs and/or immunosuppressants, except for anti-TNF agents and leflunomide, could be varied according to disease activity at the discretion of the treating physician. Variations of NSAIDs and/or corticosteroids including intra-articular corticosteroid injections were also allowed. Surgical treatment and use of bisphosphonates was not allowed in either group. Safety was assessed through recording of adverse events, physical examinations, and standard laboratory tests for both groups.

Radiographic and clinical assessment
Posteroanterior radiographs of hands and anteroposterior radiographs of feet were performed at baseline, week 28 and week 52 or at the last visit for patients who withdrew from the study prior to week 52. For patients who dropped out before week 52, missing radiograph values at week 52 were estimated by linear extrapolation using data at baseline, week 28 and the early termination visit. Radiographs were scored using van der Heijde's modified Sharp method 24 25 independently by two readers who were well trained and competent to score radiographs. The readers were blinded to the treatment group, chronologic order of the films and clinical response of each patient. Ten percent of the patients’ films were re-read for the analysis of intra-reader variability.

ACR20, 50 and 70 responses, and disease activity score in 28 joints (DAS28) were assessed for clinical improvement of RA using an intent-to-treat (ITT) analysis.

Clinical assessment
Joints in both hands and both feet were assessed at baseline, week 28 and week 52 for assessment of joint tenderness, swelling, and numbers of joints with a dolorimetre. The American College of Rheumatology 20, 50 and 70 responder criteria were applied.

Statistical analysis
A sample size of 120 patients per treatment group was estimated to provide 80% power for detecting a significant (p < 0.05) difference in mean change score of radiographic findings between the tocilizumab and DMARD groups. We decided to recruit 150 patients per treatment group to allow for anticipated withdrawals. Radiographic endpoints, such as TSS, erosion score and joint space narrowing score, were assessed with a rank transformed analysis of covariance (ANCOVA) on the change scores that included factors for baseline score and baseline disease duration. The incidences of clinical improvements were analysed by the chi-square test.

All statistical analyses were two-sided and p values less than 0.05 were considered significant. All patients receiving at least one dose of study drug were included in the efficacy and safety analysis.

RESULTS
Characteristics of the patients
This study enrolled 306 patients in total (Figure 1). Four patients were withdrawn before treatment either due to their ineligibility or at the patients’ request. A total of 302 patients received study drugs. A total of 134 patients in the tocilizumab group and 131 patients in the DMARDs group completed 52 weeks treatment. Discontinuation occurred in 23 patients in the tocilizumab group and 14 patients in the DMARDs group. The reported reasons for withdrawal are shown in Figure 1.

Demographics and baseline disease characteristics did not differ between the two groups (Table 1).

Mean disease duration was 2.3 years. Patients had active disease, indicated by a DAS28 score of 6.6 and CRP of 48 mg/L at baseline. Moreover, TSS at baseline was 29.4, which was very high despite the relatively short disease duration. The mean estimated yearly progression rate, calculated from the baseline TSS divided by disease duration for each patient, was 13.3 Sharp units.

Treatment in the conventional DMARD group
At baseline, 67% of the patients in the DMARDs group received methotrexate (MTX): 37% received a combination of MTX and DMARDs, 30% received MTX monotherapy, and 22% received DMARDs and/or immunosuppressants other than MTX, besides corticosteroids. The dose of MTX was 7.1 ± 1.9 mg/week (mean ± SD) in patients treated with MTX. During the study, 123 patients (85%) received MTX: 81 (56%) received a
combination of MTX and DMARDs, 42 (29%) received MTX monotherapy, and 20 (14%) received DMARDs and/or immunosuppressants other than MTX, besides corticosteroids. The dose of MTX was 8.0 ± 2.1 mg/week in patients treated with MTX (Japanese government recommends 6–8 mg/week of MTX based on the evidence from the Japanese clinical trial of MTX for RA).26–27 Besides MTX, salazosulfapyridine (41%), bucillamine (23%), mizoribine (8%) and D-penicillamine (8%) were used.

Reliability of radiographic scoring
Intra-reader intraclass correlation coefficients for erosion, joint space narrowing and TSS were all 0.99 for both readers. Inter-reader intraclass correlation coefficients for erosion, joint space narrowing and TSS were 0.98, 0.96 and 0.98, respectively.

Radiographic evaluation of joint damage
Figure 2 shows the cumulative probability plots of the change from baseline to week 52 in the TSS. The space between the curves indicates different treatment effects with a considerable difference in favour of the tocilizumab group. tocilizumab monotherapy had negative TSS scores than those receiving conventional DMARDs. The space between the curves indicates the different treatment effects with a considerable difference in favour of the tocilizumab group.

The mean changes in the TSS as well as erosion scores at week 28 were statistically significantly less in the tocilizumab group than in the DMARDs group with an ANCOVA model (Table 2).

The efficacy was more evident at week 52. In addition to the TSS and erosion score, joint space narrowing scores also showed significantly less change in the tocilizumab group than in the DMARDs group. In the tocilizumab group, patients who achieved a higher ACR response showed less radiological progression at week 52 (in the patients with ACR70 response (n = 73), mean TSS 1.6; 95% CI 0.3 to 2.8). A similar effect was observed in the DMARDs group (in the patients with ACR70 response (n = 8), mean TSS 1.5; 95% CI −0.6 to 3.6).

Table 2 Change in radiographic scores

<table>
<thead>
<tr>
<th>Week 28</th>
<th>Conventional DMARDs (n = 143)</th>
<th>8 mg/kg Tocilizumab (n = 157)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Sharp score</td>
<td>Mean (95% CI)</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>4.5 (3.1 to 6.0)</td>
<td>1.9 (1.2 to 2.6)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>1.0 (0.0 to 5.0)</td>
<td>0.5 (0.0 to 2.0)</td>
</tr>
<tr>
<td>Erosion score</td>
<td>Mean (95% CI)</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>2.4 (1.6 to 3.2)</td>
<td>0.8 (0.4 to 1.2)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>0.5 (0.0 to 2.5)</td>
<td>0.0 (0.0 to 1.0)</td>
</tr>
<tr>
<td>Joint space narrowing score</td>
<td>Mean (95% CI)</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>2.2 (1.4 to 2.9)</td>
<td>1.1 (0.7 to 1.6)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>0.0 (0.0 to 2.0)</td>
<td>0.0 (0.0 to 1.0)</td>
</tr>
<tr>
<td>Week 52</td>
<td>Total Sharp score</td>
<td>Mean (95% CI)</td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>6.1 (4.2 to 8.0)</td>
<td>2.3 (1.5 to 3.2)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>2.5 (0.0 to 7.0)</td>
<td>0.5 (0.0 to 3.0)</td>
</tr>
<tr>
<td>Erosion score</td>
<td>Mean (95% CI)</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>3.2 (2.1 to 4.3)</td>
<td>0.9 (0.3 to 1.4)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>1.0 (0.0 to 3.5)</td>
<td>0.0 (0.0 to 1.0)</td>
</tr>
<tr>
<td>Joint space narrowing score</td>
<td>Mean (95% CI)</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>2.9 (2.0 to 3.8)</td>
<td>1.5 (0.9 to 2.1)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>1.0 (0.0 to 4.0)</td>
<td>0.0 (0.0 to 1.7)</td>
</tr>
</tbody>
</table>

*p < 0.05, †p < 0.01, ‡p < 0.001.

P values were analysed with a rank transformed analysis of covariance (ANCOVA) on the change scores that included factors for baseline score and baseline disease duration. DMARDs, disease-modifying antirheumatic drugs; Tocilizumab, humanised anti-interleukin-6 receptor antibody; 95% CI, 95% confidence interval; IQR, interquartile range.
Clinical efficacy
At week 52, proportions of the patients achieving ACR20, ACR50, and ACR70 response were 78%, 64%, and 44% in the tocilizumab group and 34%, 13%, and 6% in the DMARD group, respectively, indicating the superiority of tocilizumab monotherapy to conventional DMARD therapy ($p < 0.001$, for each comparison) although clinical efficacy was assessed unblinded (Figure 3A).

Greater reduction in DAS28 scores and higher remission rates were also observed in the tocilizumab group than in the DMARDs group (Figure 3B). At week 52, clinical remission (defined as DAS28 $< 2.6$) was achieved in 59% of patients receiving tocilizumab, but only in 3% of patients receiving DMARDs ($p < 0.001$). Major clinical response (ACR70 response for 6 consecutive months) was achieved in 24% of patients receiving tocilizumab compared with only 2% of patients receiving DMARDs during the study period of 52 weeks.

Physical function and health-related quality of life
Tocilizumab monotherapy significantly improved MHAQ scores compared to conventional DMARDs (Figure 3C). A decrease of $> 0.22$ units in HAQ scores represents significant clinical improvement and the minimum clinically important difference. Such improvement was seen in 40% of the patients treated with tocilizumab as early as week 4, the first scheduled study visit, and was even more evident at week 52 (68% in the tocilizumab group and 40% in the DMARDs group, $p < 0.001$).

Safety
The percentages of patients with adverse events were 89% and 82% in the tocilizumab and DMARD groups, respectively. Most of adverse events were mild or moderate. Table 3 shows frequent adverse events observed in at least 5% of the patients.

Nasopharyngitis was the most common adverse event, but the incidences were similar in both groups.

Serious adverse events were reported in 18% and 13% in the tocilizumab group and DMARDs group, respectively. In the tocilizumab group, 12 serious infections were reported: 3 (1.9%) patients with pneumonia, 2 (1.3%) with upper respiratory tract infection, 2 (1.3%) with cellulitis, 1 (0.6%) each with gastroenteritis, herpes zoster, herpes simplex, perianal abscess and an unidentified infection. In the DMARD group, 8 serious infections were reported: 3 (2.1%) patients with gastroenteritis, 2 (1.4%) with pneumonia, and 1 (0.7%) each with upper respiratory tract infection, herpes zoster and sepsis. All the serious adverse events improved with appropriate treatment. There was no significant prolongation of infection by the tocilizumab treatment. Tuberculosis was not observed in this 1-year study without required screening or prophylactic use of any antituberculous drug.

Three malignancies were reported in the tocilizumab group: 2 patients with breast cancer (including 1 lobular carcinoma in situ) and 1 with colon cancer, which were improved or resolved by appropriate treatment (including surgery). No malignancies were reported in the DMARD group.

Drug-related infusion reactions were reported 14 times in 11 (7.0%) patients of the tocilizumab group: 3 with transient increase in blood pressure, 2 with injection site redness, 2 with headache, 2 with nausea, 2 with skin eruption, and 1 each with vomiting, pruritus, and malaise. All the infusion reactions were mild, and no patient withdrew from the study as a consequence.

Laboratory test abnormalities were reported in 61% and 31% of patients in the tocilizumab and DMARD groups, respectively. In the tocilizumab group, lipid metabolism-related reactions were common. Anomalous increases in total cholesterol (TC), triglycerides, and low-density lipoprotein cholesterol were reported in 38%, 17%, and 26% of the patients, respectively, and most of them were grade 1 according to the National Cancer Institute Common Toxicity Criteria. Twenty-seven patients were treated (HMG-CoA reductase inhibitor, 26 cases; fenofibrate, 1 case) and their cholesterol levels improved during the study. Tocilizumab monotherapy also raised high-density lipoprotein cholesterol (HDLC) levels to above the normal range...
in 24% of patients. The atherogenic index, calculated by (TC-HDLc)/HDLc, did not change during the study period of 52 weeks. No cardiovascular complications were observed in association with abnormal lipid profile.

Anti-tocilizumab antibodies were detected in 4 patients (2.5%). Only one patient showed a skin eruption at the third injection, while the other three were asymptomatic. They were all withdrawn according to the study protocol.

DISCUSSION

This 52-week, x-ray reader-blinded, randomised, controlled trial demonstrated that tocilizumab monotherapy in patients with active RA significantly inhibited the progression of structural joint damage compared with conventional DMARDs therapy. Note that even monotherapy with tocilizumab significantly retarded the radiological progression. It is of interest whether tocilizumab in combination with MTX would provide greater benefit; this is being investigated in the European studies.

The results of this study confirmed that IL-6 plays a pathological role in the joint destruction in RA. IL-6 blockade can inhibit the osteoclast activation in RA. Additionally, tocilizumab therapy reduced MMP-3 levels (data not shown), which could also contribute to the radiographic benefit.

In addition to the radiographic benefits, tocilizumab monotherapy improved signs and symptoms as well as functional endpoints, the results of previous phase II studies were confirmed. Moreover, significant improvement for clinical efficacy endpoints, the results of previous phase II studies were confirmed. These results need to be confirmed in the trials in western RA patients.

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Competing interests: NN has served as a consultant to and/or received honoraria from Chugai Pharmaceutical, the manufacturer of tocilizumab. TK holds a patent for tocilizumab. The other authors have no competing interests.

REFERENCES


Table 3 Adverse events observed in at least 5% of patients

<table>
<thead>
<tr>
<th>Disease</th>
<th>Conventional DMARDs (n = 145)</th>
<th>8 mg/kg Tocilizumab (n = 157)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>47 (32.4)</td>
<td>56 (35.7)</td>
</tr>
<tr>
<td>Rash</td>
<td>6 (4.1)</td>
<td>17 (10.8)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>13 (9.0)</td>
<td>13 (8.3)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (2.1)</td>
<td>11 (7.0)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>13 (9.0)</td>
<td>9 (5.7)</td>
</tr>
<tr>
<td>Eczema</td>
<td>6 (4.1)</td>
<td>9 (5.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (1.4)</td>
<td>9 (5.7)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (1.4)</td>
<td>9 (5.7)</td>
</tr>
<tr>
<td>Paronychia</td>
<td>1 (0.7)</td>
<td>9 (5.7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (3.4)</td>
<td>8 (5.1)</td>
</tr>
<tr>
<td>Vertebral compression fracture</td>
<td>8 (5.5)</td>
<td>3 (1.9)</td>
</tr>
</tbody>
</table>

*Values are the number (%) of patients.

DMARDs, disease-modifying antirheumatic drugs; Tocilizumab, humanised anti-interleukin-6 receptor antibody.
Anti-IL-6R antibody therapy in RA 1167


