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 Randomized Controlled Trial of Tocilizumab -

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Running head: Anti-IL-6R antibody therapy in RA
ABSTRACT

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

Methods. In the multi-center, X-ray reader-blinded, randomized, 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 forefeet were scored by the van der Heijde modified Sharp method. This trial was registered in clinical trials.gov (NCT00144508).

Results. Patients had a mean disease duration of 2.3 years and DAS28 score of 6.5 at baseline. Mean total modified Sharp score (TSS) was 29.4, which was very high despite 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, 3.2) than DMARDs group (mean 6.1; 95%CI 4.2, 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 DMARDs groups, respectively.

Conclusion. Tocilizumab monotherapy was generally well tolerated and provided radiographic benefit in patients with RA.

Key words: Rheumatoid Arthritis, Clinical Trial, Interleukin-6, Tocilizumab, Radiography
Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by persistent synovitis and destruction of bone and cartilage in multiple joints.[1] Although etiological causes are still obscure, constitutive overproduction of interleukin-6 (IL-6), a pleiotropic cytokine that regulates the immune response, inflammation, hematopoiesis, and bone metabolism, is thought to play a pathological role in RA.[2] Overproduction of IL-6 augments autoimmune reaction and causes systemic inflammatory manifestations. IL-6, synergistically with IL-1β or TNFα, induces the production of vascular endothelial growth factor, a potent inducer of angiogenesis necessary to oxygenate the hyperplastic synovial tissues in the affected joints.[3] IL-6, in the presence of soluble IL-6 receptor, induces osteoclast differentiation and may be responsible for joint destruction and osteoporosis associated with RA.[4, 5] In fact, elevated IL-6 levels are observed in both serum and synovial fluid in RA patients [6-10] and correlate with disease activity and radiological joint damage.[5,11-14] IL-6 levels also correlate with matrix metalloproteinase 3,[15] which degrades the proteoglycan of cartilage and also predicts radiological progression.[15-17]

Tocilizumab, a humanized anti-IL-6 receptor (IL-6R) monoclonal antibody,[18] has been demonstrated to improve the signs and symptoms of RA in the previous clinical trials;[19-22] however, there is no study to investigate the potential of tocilizumab in inhibiting joint damage and improving disability, which are also important therapeutic endpoints.

To investigate whether tocilizumab monotherapy provides radiographic and clinical benefits to active RA patients, we conducted a multi-center, X-ray reader-blinded, randomized, controlled study.

**METHODS**

**Patients.** Eligible patients were age > 20 years, fulfilled the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) 1987 revised criteria for the classification of RA,[23] with a disease duration of ≥ 6 months and < 5 years. In addition, they had ≥ 6 tender joints (of 49 evaluated), ≥ 6 swollen joints (of 46 evaluated), an erythrocyte sedimentation rate (ESR) of ≥ 30 mm/hour and C-reactive protein (CRP) of ≥ 20 mg/L. All candidates had an inadequate response to at least one disease modifying antirheumatic drug (DMARD) or immunosuppressant. Use of anti-TNF agents and leflunomide were not allowed within 3 months before the first dose. Change in dose and type of DMARDs and/or immunosuppressants, plasma exchange therapies and surgical treatments were not allowed within 4 weeks. Oral corticosteroids (prednisolone, ≤ 10 mg per day) were allowed if the dosage had not been changed within 2 weeks. Eligible patients had white blood cell counts of at least 3.5 x 10⁹/L, lymphocyte counts of at least 0.5 x 10⁹/L and platelet counts of at least 100 x 10⁹/L at enrollment. Patients were excluded if they had a medical history of a serious allergic reaction, significant concomitant diseases, or an active intercurrent infection requiring medication within 4 weeks before the first dose. Sexually active premenopausal women were required to have a negative urine pregnancy test at the entry and to use effective contraception during the study.
Study protocol. This study was conducted at 28 sites in Japan. The study protocol was approved by the Ministry of Health, Labor and Welfare of Japan, and by the local ethical committee, and patients gave their written informed consent. This trial was registered in clinical trials.gov (NCT00144508).

Patients were randomly assigned to receive either tocilizumab monotherapy at 8 mg/kg intravenously every 4 weeks or conventional DMARDs 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 randomization was done by registering the patients to the patient registration center utilizing a centralized allocation method. For the tocilizumab group, DMARDs and/or immunosuppressants were discontinued from the study start. Oral corticosteroids (≤ 10 mg prednisolone per day) were allowed but the dosage could not be increased during the study. Intraarticular corticosteroid injections were not allowed. Use of one nonsteroidal anti-inflammatory drug (NSAID), including switching to another NSAID, was allowed. For the conventional DMARDs 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 intraarticular corticosteroid injections were also allowed. Surgical treatment and use of bisphosphonates were not allowed in both groups. Safety was assessed through recording adverse events, physical examinations, and standard laboratory tests in 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 imputed by linear extrapolation using data at baseline, week 28 and the early termination visit. Radiographs were scored using the van der Heijde modified Sharp method [24, 25] independently by 2 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.

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 DMARDs 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 analyzed by the
chi-square test.

All statistical analyses were 2-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 (Figure 1). Four patients were withdrawn before dosing due to their ineligibility or patients’ requests. A total of 302 patients received study drugs. One hundred thirty-four 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).

Table 1. Patient demographics and clinical characteristics at baseline*

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Conventional DMARDs (n = 145)</th>
<th>8 mg/kg Tocilizumab (n = 157)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>53.1 ± 12.5</td>
<td>52.9 ± 11.6</td>
</tr>
<tr>
<td>No. of men / No. of women</td>
<td>26:119</td>
<td>32:125</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA duration, years</td>
<td>2.4 ± 1.3</td>
<td>2.2 ± 1.4</td>
</tr>
<tr>
<td>No. of failed DMARDs, mean (range)</td>
<td>2.8 (1-7)</td>
<td>2.7 (1-7)</td>
</tr>
<tr>
<td>Functional Class†, I/II/III/IV</td>
<td>11:14:20:0</td>
<td>12:12:6:19:0</td>
</tr>
<tr>
<td>RA Stage†, I/II/III/IV</td>
<td>18:57:51:19</td>
<td>14:77:46:20</td>
</tr>
<tr>
<td>Tender joint count, 0-49 scale</td>
<td>14.4 ± 7.2</td>
<td>15.3 ± 7.3</td>
</tr>
<tr>
<td>Swollen joint count, 0-46 scale</td>
<td>11.9 ± 5.5</td>
<td>12.5 ± 6.4</td>
</tr>
<tr>
<td>ESR, mm/hour</td>
<td>71.0 ± 25.2</td>
<td>70.8 ± 27.9</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>49 ± 29</td>
<td>47 ± 29</td>
</tr>
<tr>
<td>DAS28</td>
<td>6.4 ± 0.9</td>
<td>6.5 ± 0.8</td>
</tr>
<tr>
<td>Radiographic findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified TSS, 0-448 scale</td>
<td>30.6 ± 42.0</td>
<td>28.3 ± 43.9</td>
</tr>
<tr>
<td>Erosion score, 0-280 scale</td>
<td>13.9 ± 21.7</td>
<td>13.8 ± 24.6</td>
</tr>
<tr>
<td>Joint space narrowing score, 0-168 scale</td>
<td>16.7 ± 21.8</td>
<td>14.5 ± 20.8</td>
</tr>
<tr>
<td>Estimated annual TSS progression</td>
<td>12.3 ± 16.2</td>
<td>14.1 ± 26.9</td>
</tr>
<tr>
<td>Treatment Classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX+ at least one DMARDs (patient No (%))</td>
<td>53(37)</td>
<td>43(27)</td>
</tr>
<tr>
<td>MTX monotherapy (patient No (%))</td>
<td>44(30)</td>
<td>73(46)</td>
</tr>
<tr>
<td>DMARDs/immunosuppressants (patient No (%))</td>
<td>32(22)</td>
<td>30(19)</td>
</tr>
<tr>
<td>MTX dose, mg/week</td>
<td>7.1 ± 1.9</td>
<td>6.9 ± 2.0</td>
</tr>
<tr>
<td>Prednisolone equivalent corticosteroid dose, mg/day</td>
<td>5.4 ± 3.2</td>
<td>5.4 ± 3.1</td>
</tr>
</tbody>
</table>

* Except where indicated otherwise, values are the mean ± SD.
DMARDs = disease-modifying antirheumatic drugs; Tocilizumab = humanized anti-interleukin-6 receptor antibody; RA = rheumatoid arthritis; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; DAS28 = Disease Activity Score in 28 joints; TSS = total Sharp score

† RA functional status determined by American College of Rheumatology criteria. RA stage determined by Steinbrocker’s criteria.

Mean disease duration was 2.3 years. Patients had active disease, indicated by a DAS28 score of 6.5 and CRP of 48 mg/L at baseline. Moreover, TSS at baseline was 29.4, which was very high despite 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 DMARDs 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 frequently used in more than 5% of the patients.

**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 depicts 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 favor of the tocilizumab monotherapy group. The plots representing the TSS changes in the tocilizumab group clearly shifted to the right compared with those in the conventional DMARDs, indicating that fewer patients in the tocilizumab group showed radiographic progression and also a smaller amount of progression than those in the DMARDs group. At week 52, 56% of patients receiving tocilizumab had no radiographic progression (i.e., change from baseline in the TSS ≤ 0.5) compared with 39% of patients receiving conventional DMARDs (p < 0.01). Moreover, more patients receiving tocilizumab monotherapy had negative TSS scores than those receiving conventional DMARDs (24 patients and 18 patients at week 52, respectively).

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).

Table 2. Change in radiographic scores

<table>
<thead>
<tr>
<th></th>
<th>Conventional DMARDs (n=143)</th>
<th>8 mg/kg Tocilizumab (n=157)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WEEK28</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Sharp score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>4.5 (3.1, 6.0)</td>
<td>1.9 (1.2, 2.6) *</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>1.0 (0.0, 5.0)</td>
<td>0.5 (0.0, 2.0)</td>
</tr>
<tr>
<td>Erosion score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>2.4 (1.6, 3.2)</td>
<td>0.8 (0.4, 1.2) †</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>0.5 (0.0, 2.5)</td>
<td>0.0 (0.0, 1.0)</td>
</tr>
<tr>
<td>Joint space narrowing score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>2.2 (1.4, 2.9)</td>
<td>1.1 (0.7, 1.6)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>0.0 (0.0, 2.0)</td>
<td>0.0 (0.0, 1.0)</td>
</tr>
<tr>
<td><strong>WEEK52</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Sharp score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>6.1 (4.2, 8.0)</td>
<td>2.3 (1.5, 3.2) †</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>2.5 (0.0, 7.0)</td>
<td>0.5 (0.0, 3.0)</td>
</tr>
<tr>
<td>Erosion score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>3.2 (2.1, 4.3)</td>
<td>0.9 (0.3, 1.4) ‡</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>1.0 (0.0, 3.5)</td>
<td>0.0 (0.0, 1.0)</td>
</tr>
<tr>
<td>Joint space narrowing score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td>2.9 (2.0, 3.8)</td>
<td>1.5 (0.9, 2.1) *</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>1.0 (0.0, 4.0)</td>
<td>0.0 (0.0, 1.7)</td>
</tr>
</tbody>
</table>

* p < 0.05, † p < 0.01, ‡ p < 0.001

P values were analyzed 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 = humanized anti-interleukin-6 receptor antibody; 95% CI = 95% confidence interval; IQR = interquartile range

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, 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, 3.6).

**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 DMARDs group, respectively, indicating the superiority of tocilizumab monotherapy to conventional DMARDs 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) [28] was achieved in 59% of patients receiving tocilizumab while it was in only 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). More than a 0.22-unit decrease in HAQ scores represents significant clinical improvements and the minimum clinically important difference.[29] Such improvement was seen in 40% of the patients treated with tocilizumab as early as week 4, the first scheduled study visit, and 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 DMARDs groups, respectively. Most of adverse events were mild or moderate. Table 3 shows frequent adverse events observed in at least 5% of the patients.

<table>
<thead>
<tr>
<th></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>Diarrhea</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 = humanized anti-interleukin-6 receptor antibody

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

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

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

Laboratory test abnormalities were reported in 61% and 31% of patients in the tocilizumab and DMARDs 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 increased high-density lipoprotein cholesterol (HDLC) above normal range in 24% of the patients. 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, randomized, 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 of tocilizumab significantly retarded the radiological progression. It is of interest whether tocilizumab in combination with MTX provides more benefit, which 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 may inhibit the osteoclast activation in RA. Additionally,
tocilizumab therapy reduced MMP-3 levels (data not shown), which may also contribute to the radiographic benefit.

In addition to the radiographic benefits, tocilizumab monotherapy improved signs and symptoms as well as functional evaluation with MHAQ. Although this was an open-label study for clinical efficacy endpoints, the results of previous phase II studies [21, 22] were confirmed. Moreover, significant improvement in MHAQ scores indicates that tocilizumab improves patients’ activity of daily living.

There was no decrease in the efficacy of tocilizumab during the one year treatment. The benefit of a humanized antibody was again emphasized in the repetitive treatment, because anti-tocilizumab antibodies were detected in only 4 patients (2.5%) without requiring the use of immunosuppressive agents such as MTX. It may be also the advantage of tocilizumab which blocks IL-6 action to induce B cell differentiation into antibody producing cells.

Tocilizumab monotherapy was generally well tolerated. There was no specific infection related to tocilizumab therapy including tuberculosis, which was often a problem in anti-TNF therapy [30], although patients had neither prophylactic medication nor screening in this study.

Three malignancies occurred in patients treated with tocilizumab in this study. There are many reports describing relationship between IL-6 and malignant diseases, where IL-6 is often a culprit.[31] To know the carcinogenesis risk or the benefit of IL-6 inhibition, further analysis will be required to compare the incidence with an epidemiology surveillance data base regarding malignancies in Japanese patients with RA.

The increase in TC is also observed in anti-TNF therapy [32] and therefore it may be secondary to the improvement in inflammation. We have reported that tocilizumab treatment improves wasting in Castleman’s disease, an atypical lymphoproliferative disease with overproduction of IL-6 but not TNFα, where tocilizumab monotherapy normalizes hypocholesterolemia but seldom causes hypercholesterolemia.[33] Therefore, IL-6 plays a role in regulating serum cholesterol levels.

Since increase in serum IL-6 levels has been reported as a cardiovascular risk [34, 35] and since IL-6 may contribute to the atherosclerosis,[35] it is of interest whether tocilizumab therapy reduces the incidence of cardiovascular events. This issue will be also proven in a future epidemiological surveillance of patients treated long-term with tocilizumab.

In conclusion, this study clearly demonstrates the superiority of tocilizumab monotherapy in preventing joint damage to conventional DMARDs in Japanese RA patients. The result needs to be confirmed in the trials in western RA patients.

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COMPETING INTERESTS STATEMENT

Dr. Nishimoto has served as consultants to and/or received honoraria from Chugai Pharmaceutical, the manufacture of tocilizumab. Dr. Kishimoto holds a patent for tocilizumab. Other authors have no competing interests.

FIGURE LEGENDS

Figure 1. Randomization, reasons for withdrawal, and numbers of patients who completed the trial.
DMARDs = disease-modifying antirheumatic drugs; Tocilizumab = humanized anti-interleukin-6 receptor antibody

Figure 2. Cumulative probability distribution of radiographic changes in total Sharp/van der Heijde scores from baseline to week 52 for patients treated with tocilizumab or with conventional DMARDs.
The space between the curves indicates the different treatment effects with a considerable difference in favor of the tocilizumab group.

Figure 3. Percentage of responders according to the American College of Rheumatology (ACR) improvement criteria and the Disease Activity Score in 28 joints (DAS28) as well as mean change in Modified Health Assessment Questionnaire (MHAQ) scores.
Percentage of responders according to the ACR improvement criteria (A) and the DAS28 (B) according to the ITT analysis over 52 weeks. Mean change in MHAQ scores from baseline to week 52 (C). ‡ = p < 0.001 versus DMARDs by paired t-test
REFERENCES


Enrolled 306

Randomization

DMARDs group 148
- Completed 131 (90%)
- Withdrawn 14 (10%)
  - Not treated 3

Tocilizumab group 158
- Completed 134 (85%)
- Withdrawn 23 (15%)
  - Not treated 1

AE: 5
- Exacerbation of disease: 3
- Refused treatment: 4
- Protocol violation: 2

Nishimoto et al., Fig. 1
Nishimoto et al., Fig. 2

- **DMARDs**
- **Tocilizumab**

Change from Baseline vs. Cumulative Probability
Disease Activity Score

[Graph showing the effect of Tocilizumab on Disease Activity Score over weeks.]

DMARDs

Nishimoto et al., Fig. 3
DMARDs

Tocilizumab

C

Nishimoto et al., Fig. 3

MHAQ

DMARDs

Tocilizumab

Weeks

0 4 8 12 24 36 48 52

0.0 0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6
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 Randomized Controlled Trial of Tocilizumab

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