were harvested. A BD Cytometric Bead Array (BD Biosciences) and a DuoSet enzyme-linked immunosorbent assay (R&D Systems) were used to measure cytokine concentrations. To analyze cell proliferation, cells were pulsed with $^3$H-thymidine for the last 16 hours of culture. Cell apoptosis was evaluated by staining with fluorescein isothiocyanate–conjugated annexin V and propidium iodide (PI) (BD PharMingen). RASFs were plated at a density of $5 \times 10^3$ cells/200 $\mu$l and stimulated with LPS from *Escherichia coli* 055:B5 (10 ng/ml; Sigma-Aldrich), IL-1$\beta$ (10 pg/ml; Relia Tech), or IL-17 (10 ng/ml; R&D Systems) for 48 hours. CD14+ cells were plated at $1 \times 10^5$ cells/200 $\mu$l and cultured for 24 hours.

**TaqMan polymerase chain reaction analysis.** Total RNA was isolated using an RNeasy Mini Kit (Qiagen), and complementary DNA was synthesized. TaqMan Gene Expression Assays for human IL-17A (Hs99999082_m1), IFN$\gamma$ (Hs99999041_m1), and GAPDH (Hs99999905_m1) (Applied Biosystems) were used to evaluate gene expression. The relative quantities were obtained using the comparative threshold ($C_t$) method and were normalized to GAPDH. Stimulation-dependent fold induction was calculated relative to the $C_t$ value obtained in the unstimulated cells. All experiments were performed in triplicate.

**SCID-HuRAg mice.** Male SCID mice (CB17/Icr; CLEA Japan), 6–8 weeks of age, were housed in specific pathogen–free conditions at our university animal center. Synovial tissue, articular cartilage, and bone obtained as a mass from 2 patients with RA at the time of joint replacement surgery were used. Synovium was cut into pieces 5–10 mm in diameter, and cartilage was cut into 2-mm$^3$ pieces. Mice were anesthetized according to the guidelines established by our animal ethics committee, and synovium and cartilage were transplanted onto the backs of 9 SCID mice (day 0). One week after implantation, the 9 mice were randomly divided into 3 groups, and tofacitinib dissolved in polyethylene glycol 300 (Sigma-Aldrich) was administered continuously at dosages of 0 mg/kg/day (n = 3), 1.5 mg/kg/day (n = 3), or 15 mg/kg/day (n = 3) via Alzet osmotic minipumps (DURECT Corporation) (5,15) implanted subcutaneously on the backs. Blood samples were collected, and the sera were stored at −80°C until measurement of IL-6 and IL-8.

**Histologic evaluation of SCID-HuRAg mice.** Implanted tissues were removed from the SCID-HuRAg mice 5 weeks after implantation, paraffin embedded, and stained with hematoxylin and eosin. Immunostaining was performed with anti–IL-6 antibodies (R&D Systems) and anti–IL-8 antibodies (R&D Systems). Invasion of synovial tissue into the cartilage was quantified according to a semiquantitative score ranging from 0 to 4, based on the number of invading cell layers and the number of affected cartilage sites. Erosion was classified as previously described (16), as follows: 0 = no or minimal invasion, 0.5 = invasion of 1–2 cell layers, 1 = invasion of 3–5 cell layers, 1.5 = invasion of 3–5 cell layers at 3 independent sites of the cartilage, 2 = invasion of 6–10 cell layers, 2.5 = invasion of 6–10 cell layers at 3 independent sites, 3 = invasion of >10 cell layers, 3.5 = invasion of >10 cell layers at 2 independent sites, and 4 = invasion of >10 cell layers at ≥3 independent sites. The invasion scores were determined by counting cells at 400× magnification in 7 high-power fields in each specimen. Histologic assessments were made under double-blind conditions. Three animal researchers recorded the data on separate case record forms without exchanging any information.

**Statistical analysis.** All data were evaluated by one-way analysis of variance with Dunnett's post hoc test. *P* values less than 0.05 were considered significant.

## RESULTS

**Tofacitinib-induced inhibition of proliferation of CD4+ T cells from synovium and peripheral blood.** We first analyzed the effect of tofacitinib on the proliferation of CD4+ T cells isolated from the synovium and peripheral blood of patients with active RA. When CD4+ T cells were stimulated with anti-CD3 and anti-CD28 antibodies, marked proliferation was induced. However, the addition of tofacitinib to the culture inhibited the proliferation in a dose-dependent manner, with a statistically significant difference starting at 10 n*M*) (Figures 1A and B). Similar inhibitory effects were observed in CD4+ T cells from healthy subjects (data

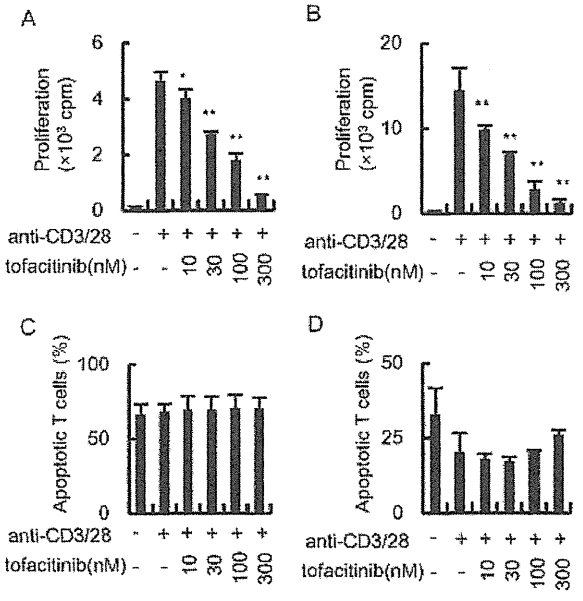


**Figure 1.** Tofacitinib inhibits proliferation of CD4+ T cells derived from the synovium and peripheral blood of patients with rheumatoid arthritis (RA), without cell toxicity. Synovial (**A** and **C**) and peripheral blood (**B** and **D**) CD4+ T cells were stimulated with anti-CD3/anti-CD28 antibodies in the presence of increasing doses of tofacitinib. **A** and **B**, To analyze cell proliferation, cells were pulsed with $^3$H-thymidine for the last 16 hours of culture. Values are the mean ± SD of triplicate cultures. The experiments were repeated in 3 RA patients, and the results were similar; representative data are shown. * = $P <$ 0.05; ** = $P < 0.01$ versus stimulated untreated cells. **C** and **D**, Cell apoptosis was evaluated by staining with fluorescein isothiocyanate–conjugated annexin V and propidium iodide. Values are the mean ± SD results of all experiments.

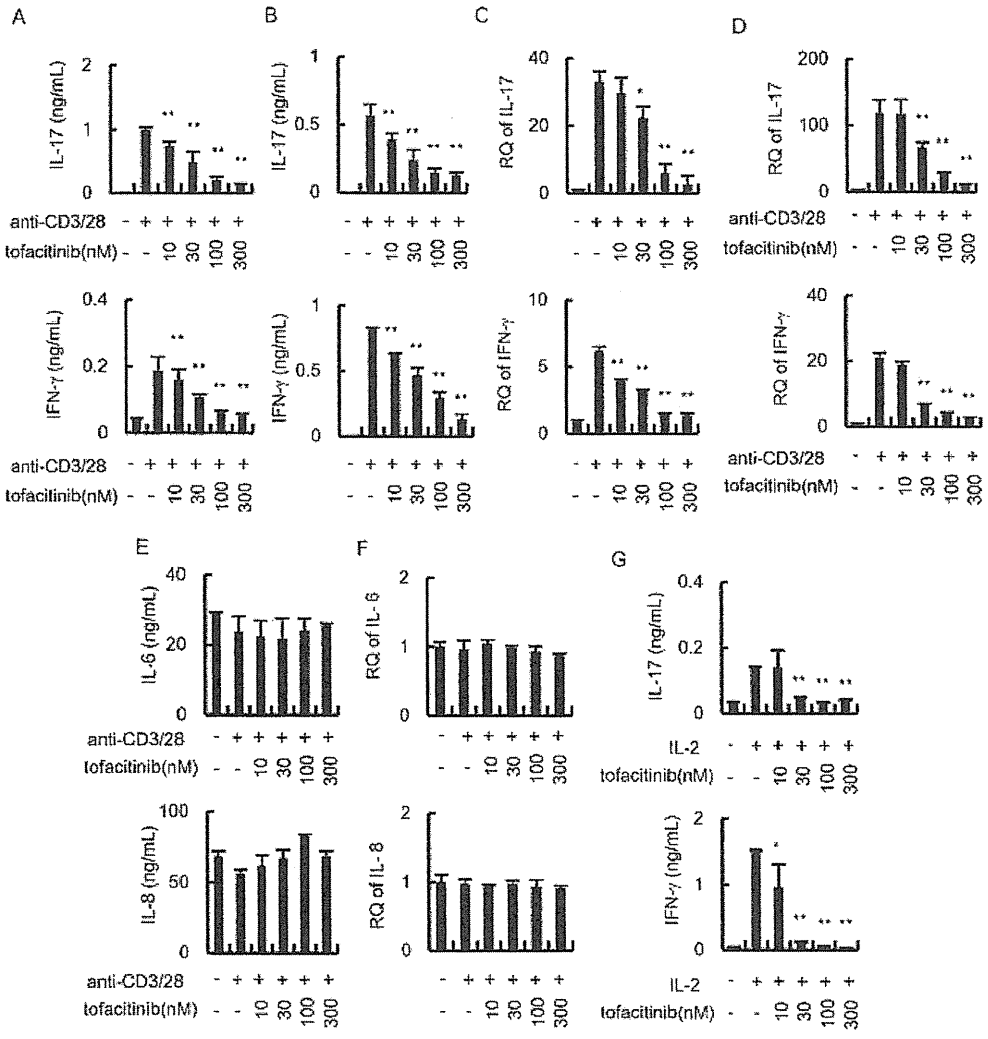


**Figure 2.** Inhibitory effect of tofacitinib on interleukin-17 (IL-17) and interferon-γ (IFNγ) production, but not IL-6 and IL-8 production, by CD4+ T cells derived from the synovium and peripheral blood of patients with rheumatoid arthritis (RA). Synovial (**A, C, E,** and **F**) and peripheral blood (**B** and **D**) CD4+ T cells were stimulated with anti-CD3/anti-CD28 antibodies for 72 hours in the presence of increasing concentrations of tofacitinib. **A, B,** and **E,** Culture supernatants were collected for analysis of cytokine production. **C, D,** and **F,** Messenger RNA expression (fold induction versus unstimulated cells) was determined by TaqMan polymerase chain reaction. **G,** After prestimulation with anti-CD3/anti-CD28 antibodies for 72 hours, peripheral blood CD4+ T cells were restimulated with IL-2 (100 ng/ml) for 72 hours, and supernatants were harvested. Values are the mean ± SD of triplicate cultures. The experiments were repeated in 3 RA patients, and the results were similar; representative data are shown. * = $P < 0.05$; ** = $P < 0.01$ versus stimulated untreated cells. RQ = relative quantity.

not shown). Next, in order to evaluate whether these inhibitory effects were mediated by the cytotoxicity of tofacitinib, synovial and peripheral blood CD4+ T cells were stained with annexin V and PI. The addition of tofacitinib did not significantly affect the percentage of apoptotic cells (annexin V–positive/PI-negative and annexin V–positive/PI-positive) even at the highest concentration of tofacitinib (300 n*M*) (Figures 1C and D), indicating that the effects of tofacitinib were not mediated by apoptosis.

**Tofacitinib-induced inhibition of IL-17 and IFNγ production by CD4+ T cells.** We next assessed the effects of tofacitinib on cytokine production by CD4+ T cells obtained from patients with RA. Although stimulation of CD4+ T cells derived from both the synovium and peripheral blood with anti-CD3/anti-CD28 anti-

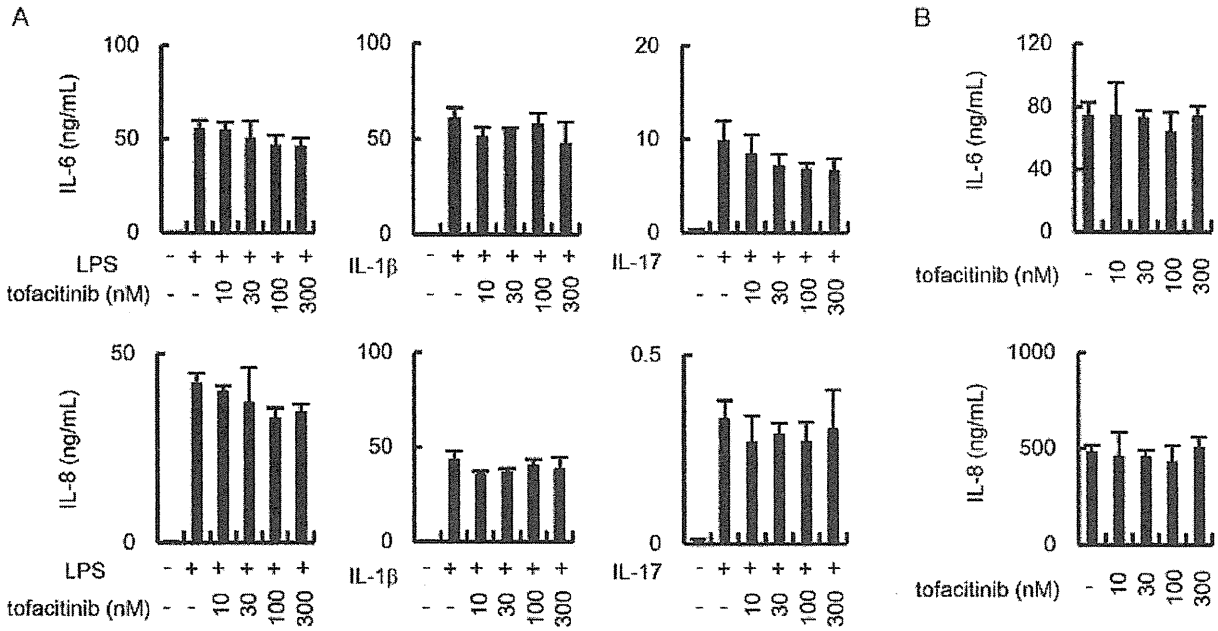


**Figure 3.** Tofacitinib does not affect interleukin-6 (IL-6) and IL-8 production by rheumatoid arthritis synovial fibroblasts (RASFs) and CD14+ monocytes originating from RA synovium. **A,** RASFs were stimulated with 10 ng/ml of lipopolysaccharide (LPS), 10 pg/ml of IL-1β, or 10 ng/ml of IL-17 for 48 hours, alone or with tofacitinib in increasing concentrations. **B,** CD14+ monocytes were cultured for 24 hours with increasing concentrations of tofacitinib, and supernatant was collected for analysis of IL-6 and IL-8 production. Values are the mean ± SD of triplicate cultures. The experiments were repeated in 3 RA patients, and the results were similar; representative data are shown.

bodies strongly induced the production of IL-17 and IFNγ, the addition of tofacitinib to the culture inhibited production of these cytokines in a dose-dependent manner, starting at the minimum concentration of 10 n*M* (Figures 2A and B). Furthermore, tofacitinib decreased messenger RNA (mRNA) levels of IL-17 and IFNγ in a dose-dependent manner, indicating inhibitory effects on gene transcription (Figures 2C and D). In contrast to its effect on IL-17 and IFNγ, tofacitinib did not affect IL-6 and IL-8 production by synovial and peripheral blood CD4+ T cells, at both the protein and mRNA levels (Figures 2E and F, and data not shown). Furthermore, when peripheral blood CD4+ T cells were restimulated with IL-2 (100 ng/ml) for 72 hours in the presence or absence of tofacitinib after prestimulation with anti-CD3/anti-CD28 antibodies, production of IL-17 and IFNγ by peripheral blood CD4+ T cells was inhibited by tofacitinib in a dose-dependent manner (Figure 2G). These results suggest that inhibition of IL-17 and IFNγ production could be associated with inhibition of the IL-2–mediated JAK-1/3/STAT-5 pathway by tofacitinib.

**Lack of effect of tofacitinib on IL-6 and IL-8 production by RASFs and CD14+ monocytes.** We next investigated the effect of tofacitinib on RASFs and CD14+ monocytes, which together are the major source of cytokines in RA synovium. Because RASFs expressed JAK-1 and JAK-2 abundantly but did not express JAK-3 (data not shown), we expected off-target effects of tofacitinib on RASFs. Both LPS and IL-1β, which are not implicated in JAK/STAT signaling, strongly induced the production of IL-6 and IL-8 by RASFs. The production of these cytokines was not, however, affected by the addition to the culture of tofacitinib at any concentration (Figure 3A). Furthermore, although CD14+ monocytes isolated from RA synovium produced large amounts of IL-6 and IL-8 without any stimulation, the addition of tofacitinib did not affect production of these cytokines (Figure 3B). Based on our previous studies of JAK-3–deficient DCs, we expected tofacitinib to increase IL-10 production by CD14+ monocytes. However, we did not observe the parallel phenotype in vitro (data not shown). These results indicate that the mode of action of tofacitinib appeared to be restricted to

proliferation and particular cytokine production by CD4+ T cells rather than CD14+ monocytes and RASFs in patients with RA.

**Indirect effect of tofacitinib on IL-6 production by RASFs and IL-8 production by CD14+ monocytes.** Because direct inhibitory effects of tofacitinib on IL-6 and IL-8 production by RASFs and CD14+ monocytes were not observed, we next investigated the possibility of an indirect effect of tofacitinib through CD4+ T cells. We collected the culture supernatants from purified CD4+ T cells that were stimulated with anti-CD3/anti-CD28 antibodies in the presence of tofacitinib, added the obtained conditioned medium to RASFs or CD14+ monocytes from RA synovium, and assessed IL-6 and IL-8 levels in the supernatants of RASFs and CD14+ monocytes after further incubation. When RASFs were cultured with supernatant from CD4+ T cells treated with tofacitinib, IL-6 production was reduced significantly at doses of 30 n*M* and higher, while IL-8 production was not affected (Figure 4A). When CD14+ monocytes were cultured with the supernatant, IL-8 production decreased significantly at doses of 30 n*M* and higher, whereas IL-6 production was not affected (Figure 4B). Thus, tofacitinib-induced inhibition of cytokine production by CD4+ T cells appeared to result in reduced production of IL-6 and IL-8 from RASFs and CD14+ monocytes in a cell-trophic manner.

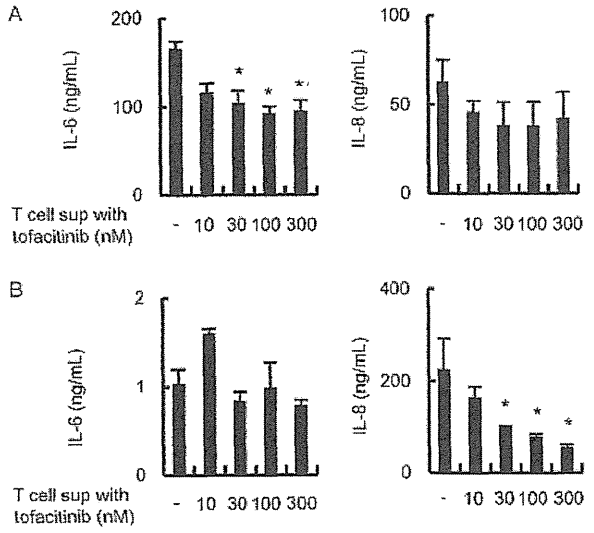


**Figure 4.** Tofacitinib indirectly suppresses IL-6 production by RASFs and IL-8 production by CD14+ monocytes. Peripheral blood CD4+ T cells were stimulated with anti-CD3/anti-CD28 antibodies for 72 hours in the presence of increasing concentrations of tofacitinib. Culture supernatants (sup) were harvested and cultured with RASFs or peripheral blood CD14+ cells. RASFs (A) and CD14+ monocytes (B) were cultured for 48 hours and 24 hours, respectively, and the supernatants were collected to measure cytokine concentration. Values are the mean ± SD of 3 individual experiments. The experiments were repeated in 3 RA patients, and the results were similar. * = $P < 0.05$; ** = $P < 0.01$ versus stimulated untreated cells. See Figure 3 for other definitions.

**Effect of tofacitinib on production of human IL-6 and IL-8 and invasion of synovial cells into cartilage in SCID-HuRAg mice.** In order to clarify the mode and mechanism of action of tofacitinib, we assessed the in vivo effects of tofacitinib in SCID-HuRAg mice. Tofacitinib was continuously administered to these mice by osmotic minipump. We observed increased production of human IL-6 and IL-8 in serum from the SCID-HuRAg mice, which peaked 7–14 days after implantation and then gradually decreased and became undetectable within 21 to 28 days (data not shown). Human TNF and IL-10 were not detected in the serum. Because of the variable levels of cytokine production depending on the condition of synovium samples, IL-6 and IL-8 levels on day 14 were compared with those on day 7 to evaluate the effect of tofacitinib in vivo (Figure 5A). In the groups receiving tofacitinib at dosages of 1.5 mg/kg/day and 15 mg/kg/day, the serum level of human IL-8 was significantly lower compared with that in the control group. Human IL-6 was also inhibited by tofacitinib, although there was no significant difference compared with control.

To further investigate the effect of tofacitinib on cytokine expression and cartilage destruction, we removed the implanted specimens on day 35 and performed histologic evaluation. Immunohistochemical analysis demonstrated that IL-6 was highly expressed in the RA synovium grafts in mice treated with vehicle, but that the number of IL-6–positive cells was markedly reduced in the tofacitinib-treated group (Figure 5C). Tofacitinib also decreased the expression of IL-8 (Figure 5C) and IL-17 (data not shown) in the implanted RA synovium graft. Furthermore, the mice treated with vehicle alone showed prominent invasion of synovial tissue into the implanted cartilage. However, treatment with tofacitinib markedly inhibited this invasion (Figure 5D). Histologic evaluation according to the erosion score also showed a dose response, with significant differences between mice treated with high-dose tofacitinib (15 mg/kg/day) and placebo-treated controls (Figure 5B).

## DISCUSSION

The JAK/STAT pathway is a common signaling pathway activated by inflammatory cytokines, which has recently received attention as a new potential molecular target for the treatment of RA. In this study, we used

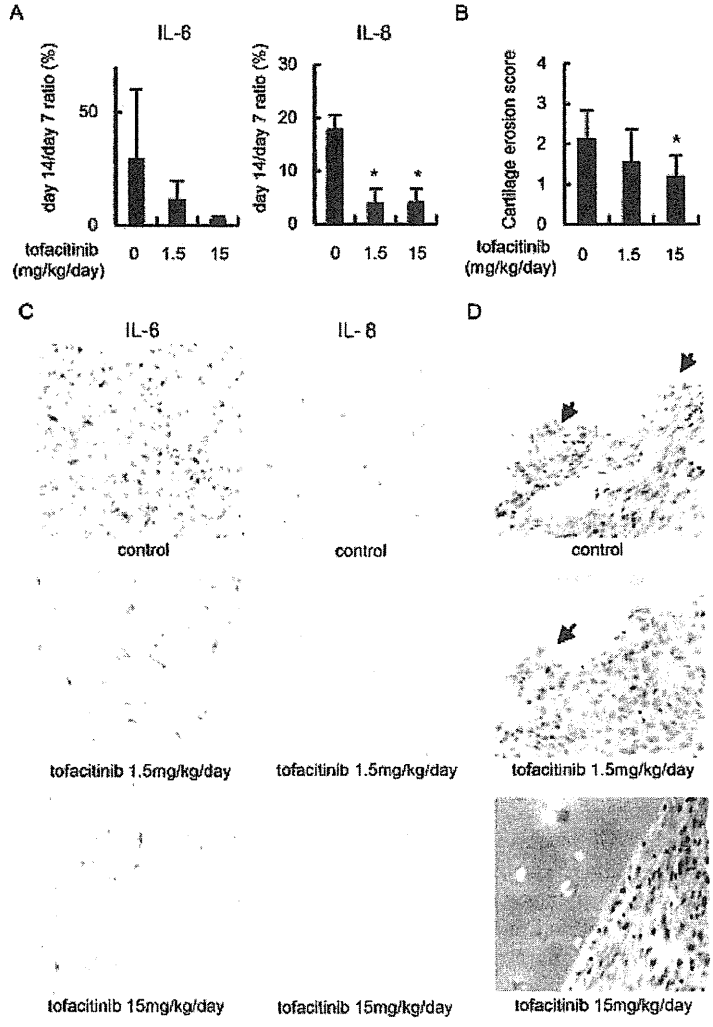


**Figure 5.** Tofacitinib suppresses human interleukin-6 (IL-6) and IL-8 production and cartilage destruction in SCID-HuRAg mice. Rheumatoid arthritis (RA) synovium and articular cartilage were co-implanted onto the backs of SCID mice. Treatment with vehicle or tofacitinib (1.5 or 15 mg/kg/day) was initiated on day 7, and thereafter serum was collected weekly. The co-implants were removed on day 35 and stained for histologic evaluation. **A,** Markedly decreased production of human IL-6 and IL-8 in the tofacitinib-treated groups compared with the vehicle-treated group. **B,** Cartilage erosion score in each treatment group. The experiments were repeated in 2 RA patients, and the results were similar. Bars show the mean ± SEM of 3 individual experiments. * = $P < 0.05$ versus control. **C** and **D,** Immunohistochemical evaluation of human IL-6– and IL-8–positive cells (**C**), and light microscopic features of cartilage erosion in the engrafted specimens (**D**). **Arrows** show the invasive front of the synovial tissue. Original magnification × 400.

CD4+ T cells, RASFs, and CD14+ monocytes purified from the synovium and peripheral blood of patients with RA to clarify the mechanism of the JAK inhibitor tofacitinib, which has shown clinical benefit in trials involving patients with active RA (6–8). Although the high specificity of tofacitinib for JAK-3 was shown in earlier studies (9), recent in vitro evidence (10,12) and the emergence of anemia and neutropenia in clinical trials (6,8) have indicated that tofacitinib also exerts an inhibitory effect on other JAKs. The present study showed that the therapeutic potency of tofacitinib in patients with RA could occur via the inhibition of CD4+ T cells, especially proliferation and cytokine production for which JAK plays a critical role in physiologic processes.

IL-6 plays a pivotal role in the pathologic pro-

cesses in RA, and anti–IL-6 receptor antibody is therapeutically useful in RA (17,18). Although previous studies have shown that tofacitinib decreased the serum IL-6 level in a rodent model of arthritis (5,11), this study is the first to show that tofacitinib inhibited both human IL-6 and IL-8 derived from RA synovium implanted in SCID mice. However, we observed that tofacitinib did not directly affect IL-6 and IL-8 production by RASFs, CD14+ monocytes, and CD4+ T cells in vitro, whereas IL-17 and IFNγ production by CD4+ T cells was markedly decreased by tofacitinib in vitro. In contrast, we also observed that production of IL-6 and IL-8 by RASFs and CD14+ monocytes was significantly reduced in a concentration-dependent manner when these cells were cultured with supernatant from CD4+ T cells treated with tofacitinib. This suggests that tofacitinib inhibited IL-6 production by RASFs and IL-8 production by CD14+ monocytes in an indirect manner through the inhibition of CD4+ T cells. Moreover, the numbers of IL-6– and IL-8–positive cells were significantly reduced, with decreased cartilage destruction in SCID-HuRAg mice treated with tofacitinib. Thus, it appears that tofacitinib-induced specific inhibition of IL-17 and IFNγ production by CD4+ T cells (presumably Th1 and Th17 cells) resulted in the suppression of IL-6 and IL-8 production by RASFs and CD14+ monocytes, with decreased cartilage destruction in SCID-HuRAg mice.

The mechanism of tofacitinib-induced inhibition of IL-17 and IFNγ production by CD4+ T cells remains unknown. We observed that the concentration of IL-2 in the culture supernatant of CD4+ T cells stimulated with anti-CD3/anti-CD28 antibodies was apparently increased when tofacitinib was added to the culture (data not shown), as reported by other investigators (19). This suggests that tofacitinib might inhibit the consumption of IL-2, which is produced by CD4+ T cells stimulated with anti-CD3/anti-CD28 antibodies. Alternatively, IL-2 production by CD4+ T cells is also thought to be enhanced by tofacitinib, because tofacitinib might cancel the IL-2–mediated negative feedback loop through activating STAT-5 (20). Furthermore, it has been reported that tofacitinib inhibited IL-2–enhanced IFNγ production by T cells in the peripheral blood of the cynomolgus monkey (21). Our study also showed that tofacitinib significantly decreased IL-2–induced production of IL-17 and IFNγ by peripheral blood CD4+ T cells (Figure 2G). Taken together, our observations suggest that IL-2–dependent activation of CD4+ T cells may be important in the pathologic processes of RA, and that tofacitinib could inhibit the IL-2–mediated JAK/STAT signaling pathway.

Although the present study confirmed the specificity of the action of tofacitinib on CD4+ T cells, it remains possible that other immune cells expressing JAKs could be targeted. Dose-related decreases in neutrophil counts (6,8) have been observed that can be related to attenuation of inflammation (11); however, it is highly likely that neutropenia can occur through inhibition of JAK-1. Because active RA responds to rituximab, a monoclonal antibody selectively targeting CD20+ B cells (22–24), and because B cells also express JAKs, it is possible that tofacitinib directly affects B cell function. Treatment with tofacitinib was previously reported to decrease the absolute number of CD3+ CD16+CD56+ natural killer cells (25), suggesting an antiinflammatory effect through natural killer cells. Additionally, a growing body of evidence indicates the involvement of mast cells in the pathogenesis of RA (26,27), and these immune cells also express JAKs. Indeed, the majority of IL-17A–expressing cells in synovium have been reported to be mast cells (28), suggesting another possible underlying mechanism of the antiinflammatory effect.

Here, we demonstrated that tofacitinib functions through a mechanism different from that of biologic agents that target IL-6 or TNF. Our results indicate that tofacitinib is potentially useful in various autoimmune diseases involving autoreactive T cells. This JAK inhibitor could therefore be indicated widely for immunologic abnormalities and inflammatory conditions in the future. In addition to the effect of tofacitinib in RA, the clinical benefit of orally available tofacitinib in other immune diseases such as inflammatory bowel disease and psoriasis has been observed in ongoing clinical trials. We await with interest the results of these and future trials, to establish the usefulness of tofacitinib in clinical practice.

Finally, we conclude that JAKs in CD4+ T cells play an important role in RA synovitis. However, considering the dramatic effect of tofacitinib in RA, further basic and clinical research is needed to fully determine the mechanism of tofacitinib and the importance of immune cells expressing JAKs and mesenchymal cells expressing only JAK-1 and JAK-2 in RA pathology.

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## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved

the final version to be published. Dr. Y. Tanaka had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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**Analysis and interpretation of data.** Maeshima, Yamaoka, Kubo, Nakano, Iwata, Saito, Ishii, Yoshimatsu, Y. Tanaka.

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EXTENDED REPORT

# Golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis: results of the GO-FORTH study

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► Additional data are published online only. To view the files please visit the journal online at (http://ard.bmj.com/content/71/6.toc).

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## ABSTRACT

**Objective** To assess the efficacy and safety of golimumab + methotrexate (MTX) in Japanese patients with active rheumatoid arthritis (RA).

**Methods** 269 Japanese patients with active RA despite treatment with MTX were randomised (1:1:1) to placebo + MTX (Group 1), golimumab 50 mg + MTX (Group 2) or golimumab 100 mg + MTX (Group 3). Subcutaneous golimumab/placebo was injected every 4 weeks; stable doses of oral MTX (6–8 mg/week) were continued. Patients were allowed to enter early escape (Group 1 added golimumab 50 mg, Group 2 increased golimumab to 100 mg, Group 3 continued golimumab 100 mg) based on swollen/tender joint counts at week 14. The primary study endpoint was achievement of at least 20% improvement in the American College of Rheumatology (ACR20) response criteria at week 14. To control for multiplicity of testing, treatment group comparisons were first made between combined Groups 2 and 3 versus Group 1, followed by comparisons of Group 2 and Group 3 versus Group 1.

**Results** The proportion of patients with an ACR20 response at week 14 was significantly higher in combined Groups 2 and 3 (73.4%, 127/173) and in each of Group 2 (72.1%, 62/86) and Group 3 (74.7%, 65/87) compared with Group 1 (27.3%, 24/88; $p<0.0001$ for all comparisons). Golimumab + MTX also elicited a significantly better response than placebo + MTX in other efficacy parameters, including disease activity score (DAS28) response/remission and radiographic assessments. During the 16-week fixed treatment regimen study period, 72.7%, 75.6% and 78.2% of patients had adverse events and 1.1%, 1.2% and 2.3% had serious adverse events in Groups 1, 2 and 3, respectively.

**Conclusion** In Japanese patients with active RA despite MTX therapy, golimumab + MTX was significantly more effective than MTX monotherapy in reducing RA signs/symptoms and limiting radiographic progression with no unexpected safety concerns.

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease mediated by overproduction of cytokines such as tumour necrosis factor α (TNF).[1 2] Golimumab, a newer human anti-TNF monoclonal antibody that binds with high affinity and specificity to soluble and transmembrane TNF,[3] antagonises the effects of TNF.[1] Golimumab + methotrexate (MTX) has demonstrated statistically significant efficacy versus MTX monotherapy in MTX-naïve patients with RA[4] and in patients with active RA despite prior MTX therapy.[5 6]

In a phase 1 study of healthy age- and dose-matched Japanese men (n=24) and Caucasian subjects (n=27), the pharmacokinetics of golimumab were comparable between ethnic groups.[7] A phase 2/3 study was conducted to examine the efficacy and safety of golimumab in Japanese patients with active RA despite MTX therapy.

## METHODS

### Patients

Eligible patients were adults (age 20–75 years) with RA diagnosed according to the American College of Rheumatology (ACR) 1987 revised criteria,[8] with disease duration of ≥3 months who had received ≥6 mg/week oral MTX for RA for ≥3 months before study agent initiation. Stable MTX doses (6–8 mg/week) were required for ≥4 weeks before the start of the study. Patients had to have active RA (≥4/66 swollen joints and ≥4/68 tender joints at screening/baseline) and had to meet at least two of the following criteria at screening/baseline: (1) C-reactive protein (CRP) >1.5 mg/dl or erythrocyte sedimentation rate (ESR) by the Westergren method of >28 mm/h, (2) morning stiffness lasting ≥30 min, (3) radiographic evidence of bone erosion, or (4) anti-cyclic citrullinated peptide antibody-positive or rheumatoid factor-positive. Eligible patients also met prespecified concomitant medication and tuberculosis screening criteria (see online supplement).

### Study design

This multicentre phase 2/3 study (ClinicalTrials.gov NCT00727987) had a 24-week, randomised, double-blind, placebo-controlled phase followed by an open-label extension continuing through 3 years. This report presents clinical data through week 24. The study was conducted according to Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was reviewed and approved by all institutional review boards. All patients provided written informed consent prior to study participation.

Eligible patients were randomly (1:1:1) assigned to receive placebo injection + oral MTX (Group 1),

golimumab 50 mg injection + oral MTX (Group 2) or golimumab 100 mg injection + oral MTX (Group 3). Golimumab and placebo were supplied as sterile liquid (Janssen Biotech Inc, Horsham, Pennsylvania, USA) for subcutaneous injection at week 0 and every 4 weeks to week 24. MTX doses were not adjusted unless dose reduction was required because of MTX toxicity.

At week 16, patients with <20% improvement from baseline in tender and swollen joint counts at week 14 could enter double-blind early escape (EE). Group 1 added golimumab 50 mg, Group 2 increased the golimumab dose to 100 mg and Group 3 continued golimumab 100 mg.

### Study endpoints

The primary study endpoint was response according to achievement of at least 20% improvement in the ACR response criteria[9] at week 14, prior to any change in treatment at week 16. Additional efficacy assessments included ACR50 and ACR70 responses, ACR-N Index of Improvement[10] and Disease Activity Score using 28 joints and ESR (DAS28(ESR)). DAS28(ESR) response (moderate and good ratings) and remission (DAS28(ESR) score <2.6) were also determined.[11 12] Physical function was assessed using the disability index of the Health Assessment Questionnaire (HAQ-DI).[13] All efficacy assessments were conducted at baseline (week 0) and at weeks 4, 8, 12, 14, 16, 20 and 24.

Hand and feet x-rays were obtained before administration of study agent at weeks 0 and 24 or upon premature discontinuation. They were scored by the BioClinica Corporation (Newtown, Pennsylvania, USA) using the Sharp score as modified by van der Heijde and colleagues (vdH-S).[14] Two primary readers who were blinded to patient identity, treatment group assignment and x-ray time point read the x-rays. If the readers' scores differed by ≥10 points or data were unavailable for one reader, a third reader evaluated the x-rays. In the former case, the reader score that differed the least from the adjudicator's score was used.

In a post hoc analysis, the relationship between efficacy and serum study agent concentrations was examined, whereby ACR response rates were categorised by serum golimumab concentration quartiles: <0.55 μg/ml (n=46), ≥0.55–<0.98 μg/ml (n=44), ≥0.98–<1.55 μg/ml (n=48) and ≥1.55 μg/ml (n=46).

Safety assessments included adverse events (AEs) and routine laboratory analyses. Serum golimumab concentrations and antibodies to golimumab were determined.[15]

### Statistical analyses

Efficacy and pharmacology parameters were primarily assessed according to a modified intent-to-treat approach in which patients who did not meet the study eligibility criteria, did not receive study treatment and/or had no efficacy- or pharmacology-related data following randomisation were excluded from the full analysis patient population. Safety analyses included all randomised treated patients. Further details of prespecified data handling rules and sample size calculations are provided in the online supplement.

Treatment group differences in dichotomous variables were assessed with a $\chi^2$ test. Type I error at the 0.05 level of significance was preserved with a hierarchical approach to control for multiplicity when testing, wherein the comparison between combined Groups 2 and 3 versus Group 1 was made first. If this difference was significant, pairwise comparisons between Group 2 versus Group 1 and Group 3 versus Group 1 were performed. In data summaries that did not present patients who entered EE separately, such patients were grouped by randomised group and had week 24 data replaced with week 16 data. For continuous variables, treatment group differences were assessed using analysis of covariance (ANCOVA) with treatment as a factor and baseline value as a covariate or analysis of variance (ANOVA) with treatment as a factor. For comparisons of changes in vdH-S score, ANCOVA based on least squares mean and accompanying two-sided 95% confidence intervals was detailed a priori, and ANOVA based on van der Waerden normal scores was conducted post hoc for ease of comparison with the radiographic results of the GO-FORWARD study.[16] ANCOVA results are presented herein. A cumulative probability plot depicting changes in the vdH-S score (shown in ascending order of magnitude with smaller changes indicating greater inhibition of disease progression) was also constructed. The proportions of patients with no change in the vdH-S score and with changes in excess of the smallest detectable change (SDC=3.23) were also determined and compared among treatment groups with a $\chi^2$ test. Agreement between the two primary readers for vdH-S scores was assessed by determination of intraclass correlation coefficients (ICCs).

## RESULTS

### Patient disposition and baseline characteristics

Data for this report were collected beginning in May 2008 and the week 24 database was locked in September 2009. Two hundred and sixty-nine patients were enrolled at 89 investigational sites in Japan and randomised to Group 1 (n=90), Group 2 (n=89) or Group 3 (n=90); 261 patients received at least one study treatment (n=88, 86 and 87 in Groups 1, 2 and 3, respectively). Eight patients discontinued the study before receiving study treatment. Similar proportions of treated patients completed subcutaneous administration of the study agent through the week 24 visit in Group 1 (95.5%), Group 2 (94.2%) and Group 3 (92.0%) (figure 1).

The overall mean (SD) baseline vdH-S score was 55.1 (58.1) and duration of RA was 8.5 (7.9) years. Baseline demographic and disease characteristics were generally consistent across the three treatment groups, with the exception of shorter mean disease duration (8.1 years) and lower mean baseline CRP level (1.5 mg/dl) in Group 3 compared with Group 1 (8.7 years and 2.2 mg/dl, respectively) and Group 2 (8.8 years and 1.9 mg/dl, respectively) (table 1).

### Efficacy results

*ACR response*

Analysis of the primary endpoint (ie, ACR20 response at week 14) demonstrated a significant difference between combined Groups 2 and 3 (73.4%, 127/173) and Group 1 (27.3%, 24/88) (p<0.0001; table 2). Significantly higher ACR20 response rates were also observed in Group 2 (72.1%, 62/86; p<0.0001) and Group 3 (74.7%, 65/87; p<0.0001) versus Group 1. Consistent findings were observed for ACR50 and ACR70 responses (table 2).

Differences in ACR response between golimumab + MTX and placebo + MTX were evident as early as week 4 and maintained through week 24 (figure 2). Patients in Group 1 who crossed over to golimumab 50 mg + MTX and patients in Group 2 who increased the golimumab dose from 50 mg to 100 mg + MTX appeared to demonstrate clinical benefit following the change in study treatment (figure 2).

*Other clinical measures of RA and physical function*

Statistical comparisons of combined Groups 2 and 3 versus Group 1, as well as for Group 2 versus Group 1 and Group 3 versus Group 1, were significant for supportive clinical efficacy parameters including ACR-N Index of Improvement, DAS28(ESR) response and DAS28(ESR) remission (table 2). At week 14, a significantly

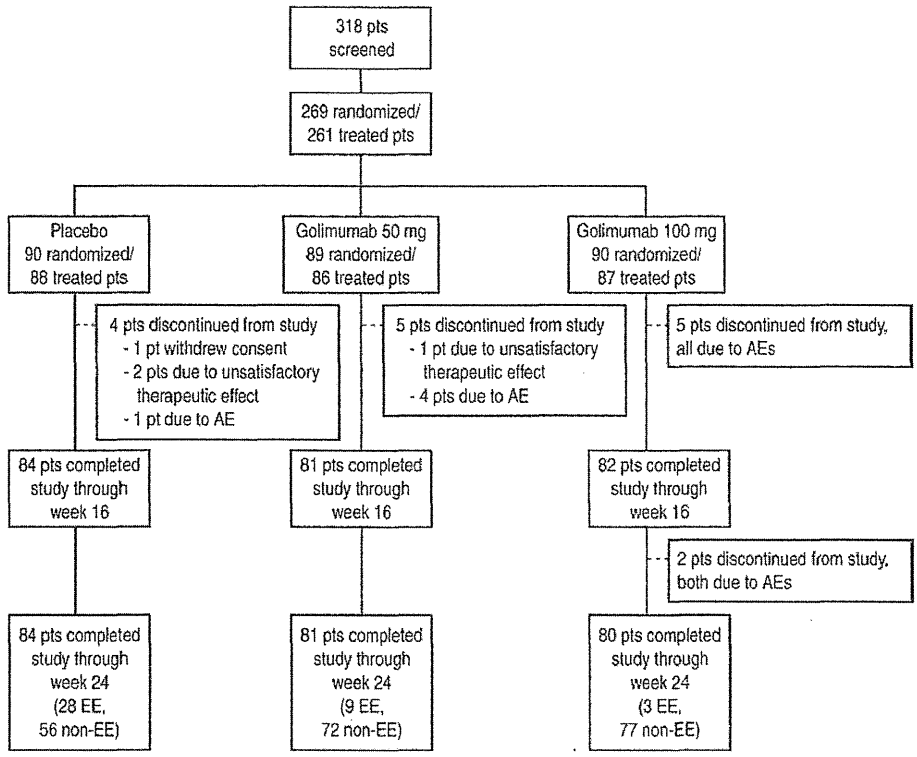


**Figure 1** Patient disposition through week 24; randomised patients. Note that 'worsening of rheumatoid arthritis' is included in 'unsatisfactory therapeutic response' and not as an AE. AE, adverse event; EE, early escape; pts, patients.

**Table 1** Baseline patient and disease characteristics: full analysis patient population*

| | Group 1: Placebo+MTX | Group 2: Golimumab 50 mg+MTX | Group 3: Golimumab 100 mg+MTX | Combined Groups 2 and 3 |
|---|---|---|---|---|
| Number of patients | 88 | 86 | 87 | 173 |
| Female patients, n (%) | 73 (83.0%) | 73 (84.9%) | 78 (89.7%) | 151 (87.3%) |
| Age (years) | 51.1 (11.6), 51.0 [24, 73] | 50.4 (9.9), 52.0 [25, 72] | 50.0 (12.2), 52.0 [21, 73] | 50.2 (11.1), 52.0 [21, 73] |
| Average duration of RA (years) | 8.7 (8.2), 6.4 [0.3, 46.1] | 8.8 (8.8), 6.4 [0.4, 36.8] | 8.1 (6.5), 6.4 [0.5, 32.4] | 8.4 (7.7), 6.4 [0.4, 36.8] |
| <1 year, n (%) | 9 (10.2%) | 8 (9.3%) | 5 (5.7%) | 13 (7.5%) |
| ≥1–<3 years, n (%) | 20 (22.7%) | 20 (23.3%) | 15 (17.2%) | 35 (20.2%) |
| ≥3–<5 years, n (%) | 13 (14.8%) | 10 (11.6%) | 14 (16.1%) | 24 (13.9%) |
| ≥5–<10 years, n (%) | 16 (18.2%) | 21 (24.4%) | 26 (29.9%) | 47 (27.2%) |
| ≥10 years, n (%) | 30 (34.1%) | 27 (31.4%) | 27 (31.0%) | 54 (31.2%) |
| Swollen joint count (0–66) | 11.4 (6.58), 9.0 [4, 36] | 11.8 (6.72), 10.0 [4, 33] | 11.5 (6.58), 9.0 [4, 32] | 11.6 (6.63), 9.0 [4, 33] |
| Tender joint count (0–68) | 13.2 (7.83), 11.0 [4, 45] | 13.1 (8.38), 11.0 [4, 40] | 12.9 (7.64), 11.0 [4, 39] | 13.0 (7.99), 11.0 [4, 40] |
| Patient's assessment of pain (VAS 0–100 mm) | 52.2 (22.86), 51.5 [2, 100] | 49.5 (23.80), 48.0 [3, 100] | 47.0 (23.88), 47.0 [6, 100] | 48.2 (23.80), 48.0 [3, 100] |
| Patient's global assessment of disease activity (VAS 0–100 mm) | 50.7 (22.63), 48.0 [2, 100] | 46.1 (23.07), 47.5 [1, 100] | 45.3 (22.90), 48.0 [4, 100] | 45.7 (22.92), 48.0 [1, 100] |
| Physician's global assessment of disease activity (VAS 0–100 mm) | 54.4 (17.97), 57.0 [22, 96] | 58.0 (18.77), 59.0 [12, 91] | 54.5 (17.81), 57.0 [14, 87] | 56.2 (18.32), 58.0 [12, 91] |
| HAQ-DI (0–3) | 1.0 (0.68), 0.9 [0.0, 2.8] | 1.0 (0.61), 1.0 [0.0, 2.4] | 0.9 (0.59), 0.9 [0.0, 3.0] | 0.9 (0.60), 0.9 [0.0, 3.0] |
| CRP (mg/dl) | 2.2 (2.44), 1.3 [0.0, 15.5] | 1.9 (2.63), 0.9 [0.0, 13.9] | 1.5 (1.68), 1.0 [0.0, 8.2] | 1.7 (2.21), 0.9 [0.0, 13.9] |
| DAS (ESR) | 5.6 (0.99), 5.6 [2.8, 8.0] | 5.5 (1.18), 5.6 [3.1, 8.8] | 5.5 (0.97), 5.4 [3.5, 8.2] | 5.5 (1.07), 5.5 [3.1, 8.8] |
| vdH-S score | | | | |
| Total score | 54.2 (62.9), 32.3 [0.0, 289.2] | 58.0 (62.4), 35.0 [0.0, 300.5] | 53.2 (48.4), 43.0 [0.0, 215.0] | 55.6 (55.7), 37.5 [0.0, 300.5] |
| JSN score | 23.4 (27.4), 13.5 [0.0, 128.0] | 25.9 (29.4), 14.5 [0.0, 127.0] | 23.9 (24.5), 16.5 [0.0, 99.0] | 24.9 (27.0), 16.0 [0.0, 127.0] |
| Erosion score | 30.8 (37.1), 17.8 [0.0, 190.0] | 32.1 (34.7), 20.8 [0.0, 185.0] | 29.3 (26.3), 21.0 [0.0, 116.0] | 30.7 (30.7), 21.0 [0.0, 185.0] |

Values are mean (SD), median [range] unless otherwise specified.
*The full analysis patient population excluded patients who did not meet the study eligibility criteria, who did not receive study treatment and/or who had no efficacy data following randomisation.
CRP, C-reactive protein; DAS 28 (ESR), disease activity score using 28-joint count and erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; JSN, joint space narrowing; MTX, methotrexate; RA, rheumatoid arthritis; VAS, visual analogue scale; vdH-S, van der Heijde-modified Sharp score.

greater median improvement in the HAQ-DI score was observed in patients who received golimumab + MTX (median of 0.25 for combined Groups 2 and 3, Group 2 and Group 3) versus placebo + MTX (median 0.13; p<0.0001 for all comparisons). Improvements in the HAQ-DI score at week 24, as well as the proportions of patients achieving a HAQ score <0.5, were also significantly greater among patients who received golimumab + MTX versus placebo + MTX (table 2).

**Table 2** Summary of clinical and radiographic efficacy at weeks 14 and 24: full analysis patient population*

| | Week 14 | | | | Week 24 | | | |
|---|---|---|---|---|---|---|---|---|
| | Group 1: Placebo+MTX | Group 2: Golimumab 50 mg+MTX | Group 3: Golimumab 100 mg+MTX | Combined groups 2 and 3 | Group 1: Placebo+MTX | Group 2: Golimumab 50 mg+MTX | Group 3: Golimumab 100 mg+MTX | Combined groups 2 and 3 |
| Number of patients | 88 | 86 | 87 | 173 | 88 | 86 | 87 | 173 |
| ACR20 response (primary endpoint) | 24 (27.3%) | 62 (72.1%) | 65 (74.7%) | 127 (73.4%) | 29 (33.0%) | 61 (70.9%) | 65 (74.7%) | 126 (72.8%) |
| p value† vs Group 1 | | <0.0001 | <0.0001 | <0.0001 | | <0.0001 | <0.0001 | <0.0001 |
| ACR50 response | 8 (9.1%) | 37 (43.0%) | 33 (37.9%) | 70 (40.5%) | 13 (14.8%) | 36 (41.9%) | 42 (48.3%) | 78 (45.1%) |
| p value† vs Group 1 | | <0.0001 | <0.0001 | <0.0001 | | <0.0001 | <0.0001 | <0.0001 |
| ACR 70 response | 2 (2.3%) | 19 (22.1%) | 12 (13.8%) | 31 (17.9%) | 5 (5.7%) | 23 (26.7%) | 19 (21.8%) | 42 (24.3%) |
| p value† vs Group 1 | | <0.0001 | 0.0050 | 0.0003 | | 0.0002 | 0.0019 | 0.0002 |
| ACR-N Index of Improvement | 12.94 (20.00) | 40.76 (30.20) | 39.99 (25.86) | 40.37 (28.02) | 16.78 (24.50) | 42.95 (32.80) | 45.37 (28.77) | 44.17 (30.78) |
| | 0.00 [0.0, 85.7] | 39.25 [0.0, 97.0] | 40.00 [0.0, 97.0] | 40.00 [0.0, 97.0] | 0.00 [0.0, 81.8] | 41.30 [0.0, 100.0] | 48.08 [0.0, 100.0] | 43.94 [0.0, 100.0] |
| p value‡ vs Group 1 | | <0.0001 | <0.0001 | <0.0001 | | <0.0001 | <0.0001 | <0.0001 |
| DAS28(ESR) response§ | | | | | | | | |
| Moderate | 32 (37.6%) | 66 (79.5%) | 71 (85.5%) | 137 (82.5%) | 41 (48.8%) | 68 (84.0%) | 74 (90.2%) | 142 (87.1%) |
| p value† vs Group 1 | | <0.0001 | <0.0001 | <0.0001 | | <0.0001 | <0.0001 | <0.0001 |
| Good | 10 (11.8%) | 35 (42.2%) | 26 (31.3%) | 61 (36.7%) | 11 (13.1%) | 38 (46.9%) | 36 (43.9%) | 74 (45.4%) |
| p value† vs Group 1 | | <0.0001 | 0.0020 | <0.0001 | | <0.0001 | <0.0001 | <0.0001 |
| DAS28(ESR) remission | 3 (3.4%) | 27 (31.4%) | 16 (18.4%) | 43 (24.9%) | 6 (6.8%) | 30 (34.9%) | 19 (21.8%) | 49 (28.3%) |
| p value† vs Group 1 | | <0.0001 | 0.0014 | <0.0001 | | <0.0001 | 0.0045 | <0.0001 |
| Change in DAS28(ESR) score | −0.43 (1.20) | −1.98 (1.25) | −1.85 (1.00) | −1.91 (1.13) | −0.60 (1.38) | −2.05 (1.23) | −2.04 (1.10) | −2.05 (1.16) |
| p value† vs Group 1 | −0.55 [−2.9, 2.5] | −2.13 [−4.5, 0.9] | −1.70 [−5.0, −0.1] | −1.80 [−5.0, 0.9] | −0.69 [−3.3, 3.1] | −2.21 [−4.6, 0.7] | −1.92 [−4.2, 0.4] | −2.07 [−4.6, 0.7] |
| | | <0.0001 | <0.0001 | <0.0001 | | <0.0001 | <0.0001 | <0.0001 |
| Improvement in HAQ-DI score | 0.07 (0.49) | 0.32 (0.40) | 0.39 (0.42) | 0.35 (0.41) | 0.03 (0.58) | 0.33 (0.42) | 0.45 (0.43) | 0.39 (0.43) |
| | 0.13 [−1.8, 1.8] | 0.25 [−0.6, 1.4] | 0.25 [−0.4, 2.0] | 0.25 [−0.6, 2.0] | 0.00 [−1.8, 2.1] | 0.25 [−0.4, 1.6] | 0.38 [−0.4, 2.0] | 0.25 [−0.4, 2.0] |
| p value¶ vs Group 1 | | <0.0001 | <0.0001 | <0.0001 | | <0.0001 | <0.0001 | <0.0001 |
| Patients achieving HAQ score <0.5 | 26 (29.5%) | 30 (34.9%) | 50 (57.5%) | 80 (46.2%) | 27 (30.7%) | 35 (40.7%) | 54 (62.1%) | 89 (51.4%) |
| p value† vs Group 1 | | 0.4511 | 0.0002 | 0.0094 | | 0.1678 | <0.0001 | 0.0014 |
| Change from baseline in vdH-S score | | | | | | | | |
| Total vdH-S score | | | | | 2.51 (5.52) | 1.05 (3.71) | 0.33 (2.66) | 0.69 (3.23) |
| | – | – | – | – | 0.25 [−8.5, 33.5] | 0.00 [−6.3, 22.5] | 0.00 [−3.5, 19.0] | 0.00 [−6.3, 22.5] |
| p value¶ vs Group 1 | | | | | | 0.0203 | 0.0006 | 0.0009 |
| Erosion score | | | | | N=84 | N=81 | N=82 | N=163 |
| | – | – | – | – | 1.66 (3.73) | 0.54 (1.62) | 0.03 (1.44) | 0.28 (1.55) |
| | | | | | 0.00 [−2.5, 22.5] | 0.00 [−2.5, 8.0] | 0.00 [−3.5, 9.0] | 0.00 [−3.5, 9.0] |
| p value¶ vs Group 1 | | | | | | 0.0044 | <0.0001 | <0.0001 |
| JSN score | | | | | N=84 | N=81 | N=82 | N=163 |
| | – | – | – | – | 0.83 (2.31) | 0.71 (2.91) | 0.29 (1.49) | 0.50 (2.31) |
| | | | | | 0.00 [−6.5, 11.0] | 0.00 [−2.5, 22.0] | 0.00 [−2.0, 10.0] | 0.00 [−2.5, 22.0] |
| *p value¶ vs Group 1* | | | | | | *0.7293* | *0.1335* | *0.2836* |
| Change in vdH-S score <0 | – | – | – | – | 44 (50.0%) | 51 (59.3%) | 61 (70.1%) | 112 (64.7%) |
| p value† vs Group 1 | | | | | | 0.2179 | 0.0066 | 0.0217 |
| Change in vdH-S >SDC (3.23) | – | – | – | – | 19 (21.6%) | 14 (16.3%) | 5 (5.7%) | 19 (11.0%) |
| p value† vs Group 1 | | | | | | 0.3715 | 0.0023 | 0.0216 |

Values are number (%) of patients or mean (SD), median [range].
*The full analysis patient population excluded patients who did not meet the study eligibility criteria, who did not receive study treatment and/or who had no efficacy data, following randomisation. With the exception of vdH-S scores, which were not determined at week 16, patients who qualified for early escape were grouped according to randomised treatment group and had week 24 data replaced with week 16 data.
†Based on the $\chi^2$ test.
‡Based on analysis of variance with treatment as a factor.
§For DAS 28 (ESR) response, the numbers of patients evaluated at week 14/24 are 85/84 in Group 1, 83/81 in Group 2, 83/82 in Group 3 and 166/163 in combined Groups 2 and 3.
¶Based on analysis of covariance on least squares mean and two-sided 95% confidence intervals with treatment as a factor and with baseline value as covariates.
ACR, American College of Rheumatology; DAS 28 (ESR), disease activity score using 28-joint count and erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; JSN, joint space narrowing; MTX, methotrexate; SDC, smallest detectable change; vdH-S, van der Heijde-modified Sharp score.

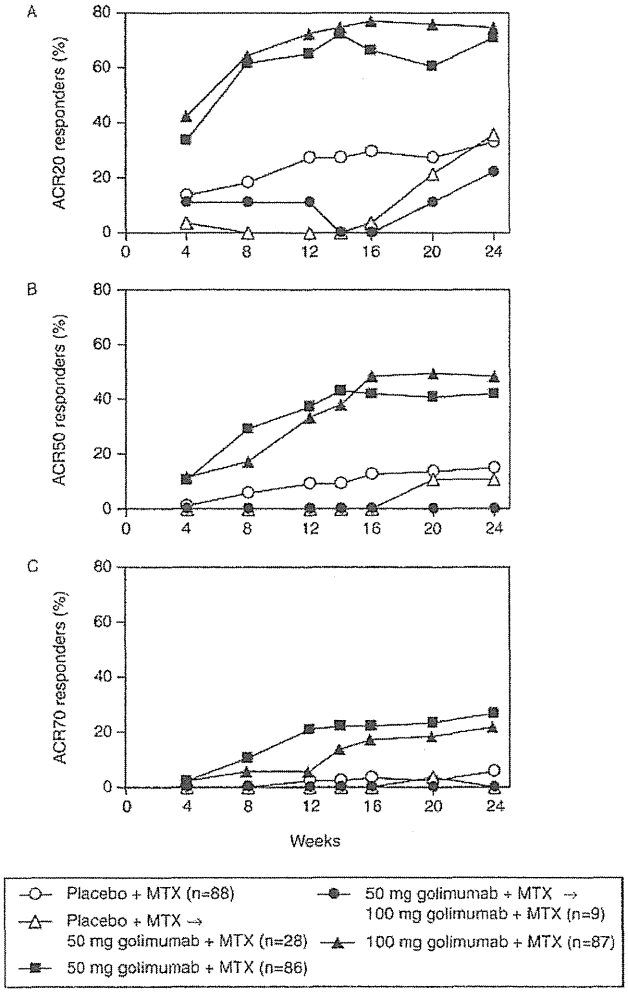


**Figure 2** (A) American College of Rheumatology 20% (ACR20), (B) 50% (ACR50) and (C) 70% (ACR70) improvement from baseline through week 24. Note that patients who met the early escape criteria at week 16 and crossed over to golimumab 50 mg or dose escalated from golimumab 50 mg to 100 mg are shown with an open triangle and closed circle, respectively. For the 28 patients in the placebo + MTX group and the nine patients in the golimumab 50 mg + MTX group who met the early escape criteria, week 20 and 24 data were imputed using last observation carried forward methodology, as were other missing data. As such, 88 patients in the placebo + MTX group and 86 patients in the golimumab 50 mg + MTX group were included in these data displays. MTX, methotrexate.

*Radiographic progression*

The primary readers exhibited good agreement with regard to vdH-S scores, with ICCs of 0.98 for baseline scores, 0.98 for week 24 scores and 0.80 for the change from baseline to week 24 in vdH-S scores.

Significantly less radiographic progression from baseline to week 24 was observed in patients who received golimumab + MTX (median changes in total vdH-S score of 0.00 (p=0.0009) for combined Groups 2 and 3, 0.00 (p=0.0203) for Group 2 and 0.00 (p=0.0006) for Group 3) versus placebo + MTX (median change 0.25). Treatment group differences in the total vdH-S score were largely attributable to significantly less change in the erosion score with golimumab + MTX therapy. As shown in the cumulative probability plot shown in figure 1 in the online supplement, changes in vdH-S scores were smaller and thus

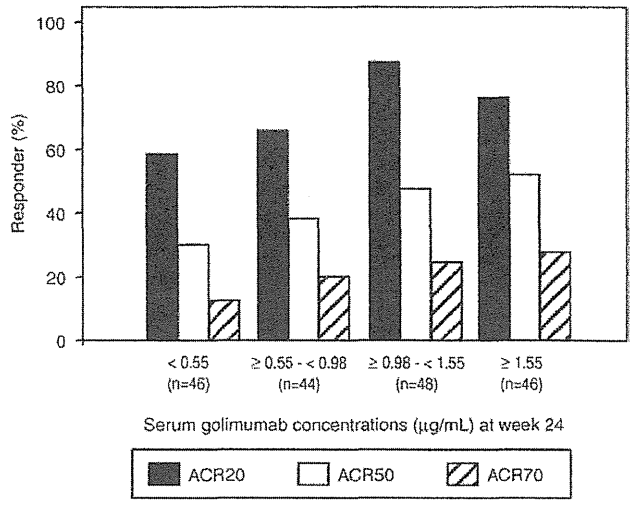


**Figure 3** Proportions of patients achieving at least 20%, 50% and 70% improvement in the American College of Rheumatology (ACR20, ACR50, ACR70) response criteria by serum golimumab concentration quartiles (µg/ml) at week 24. The results are from a post hoc analysis of ACR responders in the combined Group 2 (golimumab 50 mg + MTX) and Group 3 (golimumab 100 mg + MTX). MTX, methotrexate.

inhibition of radiographic progression was greater in patients treated with golimumab + MTX (Group 2 and Group 3) than in those given placebo + MTX (Group 1).

Significantly greater proportions of patients in combined Groups 2 and 3 (64.7%, p=0.0217) and Group 3 (70.1%, p=0.0066) did not have an increase in the total vdH-S score (ie, change from baseline to week 24 <0) compared with Group 1. The proportions of patients with a change in the total vdH-S score from baseline to week 24 greater than the SDC (3.23) were also significantly lower in combined Groups 2 and 3 (11.0%, p=0.0216) and Group 3 (5.7%, p=0.0023) compared with Group 1 (table 2).

### Golimumab pharmacokinetics and antibodies to golimumab

Median serum golimumab concentrations were approximately dose proportional and appeared to have reached steady state by week 14. Median serum golimumab concentrations at weeks 12 and 16 were 0.72 and 0.73 µg/ml, respectively, for Group 2 and 1.28 and 1.16 µg/ml, respectively, for Group 3. These steady state concentrations were maintained at week 24. In Group 2, serum golimumab concentrations in patients who met the EE criteria were approximately 45–82% of those in Group 2 patients who did not meet the EE criteria (data not shown).

In an analysis of week 24 ACR response by week 24 golimumab concentration quartiles, the lowest response rates occurred in patients with serum golimumab concentrations <0.55 µg/ml, followed by concentrations ≥0.55–<0.98 µg/ml (figure 3). No patient developed antibodies to golimumab.

### Adverse events

AEs reported at week 16 (fixed treatment regimen study period) and week 24 are summarised in table 3. By week 16, 72.7% (64/88), 75.6% (65/86) and 78.2% (68/87) of patients in Groups 1, 2 and 3, respectively, had AEs. Infections were the most common AEs in Group 1 (35/88, 39.8%), Group 2 (33/86, 38.4%) and Group 3 (29/87, 33.3%) through week 16 and were also the most common AEs at week 24 (table 3).

Serious AEs were relatively uncommon through week 16, occurring in one patient (1.1%) in Group 1 (intervertebral disc protrusion), one patient (1.2%) in Group 2 (ileus) and two patients (2.3%)

**Table 3** Summary of safety through weeks 16 and 24 in all randomised patients who received at least one injection of study agent

**Week 16**

| | Group 1: Placebo+MTX | Group 2: Golimumab 50 mg+MTX | Group 3: Golimumab 100 mg+MTX | Combined Groups 2 and 3 |
|---|---|---|---|---|
| Number of patients | 88 | 86 | 87 | 173 |
| Patients with AEs | 64 (72.7%) | 65 (75.6%) | 68 (78.2%) | 133 (76.9%) |
| Patients with SAEs | 1 (1.1%) | 1 (1.2%) | 2 (2.3%) | 3 (1.7%) |
| Patients with AEs causing study agent d/c | 1 (1.1%) | 3 (3.5%) | 6 (6.9%) | 9 (5.2%) |
| Patients with infections | 35 (39.8%) | 33 (38.4%) | 29 (33.3%) | 62 (35.8%) |
| Patients with serious infections | 0 (0.0%) | 0 (0.0%) | 1 (1.1%) | 1 (0.6%) |
| Patients with injection site reactions* | 6 (6.8%) | 7 (8.1%) | 9 (10.3%) | 16 (9.2%) |
| Patients with: | | | | |
| Neoplasia | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Malignancy | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |

**Week 24**

| | Group 1: Placebo+MTX | | Group 2: Golimumab 50 mg+MTX | | Group 3: | Combined | All |
|---|---|---|---|---|---|---|---|
| | With or without EE Placebo+MTX | With EE Placebo+MTX→ Golimumab 50 mg+MTX | With or without EE Golimumab 50 mg+MTX | With EE Golimumab 50 mg→100 mg+MTX | Golimumab 100 mg+MTX | Groups 2 and 3 | Golimumab +MTX |
| Number of patients | 88 | 28 | 86 | 9 | 87 | 173 | 201 |
| Patients with AEs | 67 (76.1%) | 14 (50.0%) | 70 (81.4%) | 1 (11.1%) | 72 (82.8%) | 142 (82.1%) | 156 (77.6%) |
| Patients with SAEs | 1 (1.1%) | 0 (0.0%) | 2 (2.3%) | 0 (0.0%) | 3 (3.4%) | 5 (2.9%) | 5 (2.5%) |
| Patients with AEs leading to d/c of study agent | 1 (1.1%) | 0 (0.0%) | 4 (4.7%) | 0 (0.0%) | 7 (8.0%) | 11 (6.4%) | 11 (5.5%) |
| Patients with infections | 39 (44.3%) | 4 (14.3%) | 36 (41.9%) | 0 (0.0%) | 34 (39.1%) | 70 (40.5%) | 74 (36.8%) |
| Patients with serious infections | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (1.1%) | 1 (0.6%) | 1 (0.5%) |
| Patients with injection site reactions* | 7 (8.0%) | 3 (10.7%) | 8 (9.3%) | 0 (0.0%) | 10 (11.5%) | 18 (10.4%) | 21 (10.4%) |
| Patients with: | | | | | | | |
| Neoplasia | 0 (0.0%) | 0 (0.0%) | 2 (2.3%)† | 0 (0.0%) | 0 (0.0%) | 2 (1.2%) | 2 (1.0%) |
| Malignancy | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |

Data shown are number (%) of patients.
*Injection site reactions were defined as any adverse reaction at a subcutaneous study agent injection site. In the placebo column the reactions are to a placebo injection; in all other columns the reactions are to a golimumab injection.
†The neoplasias included were a non-serious benign breast neoplasm and a serious bone neoplasm determined by histopathological examination to be 'borderline' malignant.
AE, adverse event; d/c, discontinuation; EE, early escape; MTX, methotrexate; SAE, serious adverse event.

in Group 3 (herpes zoster/tendon rupture and aortic dissection). Two additional patients had serious AEs between weeks 16–24, including bone neoplasm (thoracic vertebra tumour (haemangioendothelioma) with 'borderline' or low malignancy potential) in Group 2 and humeral fracture/cruciate ligament injury in Group 3, yielding a total of five (2.5%) patients treated with golimumab + MTX with serious AEs through week 24. No deaths or malignancies were reported.

In addition, by week 16, one (1.1%), three (3.5%) and six (6.9%) patients in Groups 1, 2 and 3, respectively, discontinued the study agent because of an AE. By week 24, 11 (5.5%) of the 201 patients treated with golimumab + MTX had discontinued golimumab due to AEs; these included infection (n=2), skin disorders (n=2), liver function abnormality (n=2), injury (n=2), bone neoplasm (n=1), aortic dissection (n=1), gastrointestinal disorder (n=1) and elevated blood pressure (n=1 in combination with skin disorder).

As noted, infection was the most common system organ class of AEs, occurring in 35 (39.8%), 33 (38.4%) and 29 (33.3%) patients in Groups 1, 2 and 3, respectively, up to week 16. By week 24, 74 (36.8%) patients treated with golimumab + MTX had an infection, most commonly rhinopharyngitis (19.4%, 39/201), gastroenteritis (3.5%, 7/201) and pharyngitis (3.0%, 6/201). No patient developed tuberculosis.

Injection site reactions were reported in six (6.8%), seven (8.1%) and nine (10.3%) patients in Groups 1, 2 and 3, respectively, up to week 16. By week 24, 10.4% (21/201) of all patients treated with golimumab + MTX had an injection site reaction. Erythema at the injection site was the most common of these AEs. All injection site reactions were considered mild and none required cessation of the study agent. No cases of anaphylactic reaction or serum sickness-like reactions were observed.

## DISCUSSION

This study evaluated the efficacy of golimumab 50 mg and 100 mg administered subcutaneously every 4 weeks in combination with MTX (6–8 mg/week) versus MTX (6–8 mg/week) monotherapy in Japanese patients with active RA despite MTX therapy. A significantly higher proportion of patients randomised to golimumab 50 mg or 100 mg + MTX (combined Groups 2 and 3) achieved an ACR20 response at week 14 than those receiving MTX monotherapy (73.4% versus 27.3%; $p<0.0001$). Significantly higher ACR20 response rates were also observed for the individual golimumab dose groups. While the primary endpoint at week 14 did not coincide with trough golimumab concentrations, ACR20 response rates at the time of trough concentrations (week 16) were comparable to those observed at week 14 (ie, 71.7% and 29.5%, respectively, in combined Groups 2 and 3 and Group 1, respectively; data not shown).

These primary endpoint results were consistent with the results of the GO-FORWARD study, a large phase 3 multicentre trial of golimumab encompassing a similar design (primary endpoint at week 14 and treatment change due to EE from week 16 onwards) and a comparable population of patients with RA (approximately 15% of whom were Asian; data on file, Centocor Research & Development) with an inadequate response to MTX.[5] Consistency between our findings and those of the GO-FORWARD study was also observed for improvements in HAQ-DI at week 24.[5]

Significantly less radiographic progression was observed at week 24 with golimumab + MTX than with placebo + MTX, and findings of a post hoc ANOVA analysis of vdH-S scores based on the van der Waerden normal scores were consistent (data not shown). In the GO-FORWARD study, however, minimal radiographic progression was observed in all treatment groups during the same time period, yielding no significant differences between golimumab + MTX and placebo + MTX.[5 16] Minimal radiographic progression was probably related to minimal baseline active inflammation (median CRP 0.8–1.0 mg/dl).[5 16] In a separate study of golimumab, MTX-naïve patients with RA had higher baseline CRP levels (median 1.3–1.4 mg/dl), greater radiographic progression than in the GO-FORWARD study despite less baseline radiographic damage and significantly less radiographic progression at week 28 with golimumab + MTX versus placebo + MTX.[5 16] Thus, CRP is likely to be a more important predictor of radiographic progression than the baseline radiographic score since radiographic progression is less likely if there is no active inflammation, regardless of the amount of baseline radiographic damage.[16] The CRP concentration has also been shown to predict ACR20 response.[17] In this context, the participants in the current study had an intermediate amount of active inflammation at baseline (median CRP 0.9–1.3 mg/dl) and also demonstrated significantly less radiographic progression at week 24 with golimumab + MTX compared with placebo + MTX. In evaluating the radiographic data, it is important to note that the statistically significant differences between the groups are driven by a subset of patients who progress more rapidly than the overall population, and it is in those patients that the treatment effect becomes clinically relevant.

Of note, the MTX dose used in this trial, while consistent with that approved in Japan at the time the trial was planned, was suboptimal (6–8 mg/week) in the context of customary doses elsewhere[18] and as used in the GO-FORWARD study (15–25 mg/week).[16] Evaluation of the efficacy and safety of MTX doses >8 mg/week in Japanese patients with RA has yielded a favourable benefit/risk profile[19] and approved dosing is now extended to up to 16 mg/week. It would therefore be prudent to reassess the responses to golimumab as approved MTX doses in Japan are harmonised with those approved in North America and Europe for RA. These suboptimal MTX doses may explain the higher ACR20 response rates observed in the current golimumab trial (~70%) compared with previously conducted trials of golimumab in RA (~60%) in which more robust ongoing MTX treatment regimens (10–15 mg/week) could have resulted in less room for improvement from baseline.[4 5] It is noteworthy that, when assessing response according to the more stringent ACR50 and ACR70 response criteria, the background MTX dose does not appear to affect the clinical response.[4 5] Similar reasoning may be applied to explain the highly significant difference in radiographic progression observed between placebo + MTX and golimumab + MTX despite only an intermediary level of baseline inflammation compared with previously conducted trials of golimumab.[4 5 16] Finally, more patients met the EE criteria in the golimumab 50 mg + MTX group (Group 2) than in the golimumab 100 mg + MTX group (Group 3), indicating the potential for a dose response.

In interpreting the efficacy findings of this study, it is important to bear in mind that patients could enter this study based on measures of disease activity generally considered to be subjective in nature (ie, tender and swollen joint counts and morning stiffness) or reported from each trial site (ESR) without confirmation by centrally determined parameters such as CRP or erosions. This could have resulted in study enrolment of patients with relatively inactive disease.

Golimumab was generally well tolerated with no unexpected safety issues observed in Japanese patients with RA. By week 24, approximately 10% of all patients treated with golimumab + MTX had an injection site reaction. A variety of dermatological adverse effects, including injection site reactions and dermatitis, have been reported for TNF antagonists such as adalimumab, etanercept and

infliximab,[20] as well as for anakinra, a recombinant human form of interleukin-1 receptor antagonist.[21] These dermatological complications typically are well-tolerated, respond to antihistamines and do not necessitate treatment discontinuation.

The incidences of serious AEs, serious infections and malignancies during the fixed treatment regimen period were low and similar with placebo + MTX (1.1%, 0.0% and 0.0%, respectively) and combined golimumab + MTX (1.7%, 0.6% and 0.0%, respectively). These findings indicate a safety profile similar to placebo + MTX (2.3%, 0.8% and 0.0%, respectively) and golimumab + MTX (7.3%, 3.9% and 1.1%, respectively) at week 16 in the GO-FORWARD study.[5] However, these safety findings must be interpreted with caution given the relatively small number of patients evaluated, the lack of power to detect treatment group differences in individual safety events and the relatively short follow-up period. No patients died and no cases of tuberculosis were documented during the 24-week study period.

Taken together, the efficacy and safety findings presented here indicate that golimumab 50 mg + MTX and golimumab 100 mg + MTX were at least as safe and effective in these Japanese patients with active RA despite MTX therapy as they were observed to be when administered to patients with RA who also had an inadequate response to MTX in the GO-FORWARD study.[5]

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ORIGINAL ARTICLE

# Significant improvement in MRI-proven bone edema is associated with protection from structural damage in very early RA patients managed using the tight control approach

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**Abstract**
*Objective* To identify the value of magnetic resonance imaging (MRI)-proven bone edema in patients with very early rheumatoid arthritis (RA).
*Methods* All of the 13 patients included in the study were positive at entry for MRI-proven bone edema of the wrist and finger joints and anti-cyclic citrullinated peptide antibodies or IgM-rheumatoid factor. A tight control approach was applied for 12 months. Plain MRI and radiographs of both wrist and finger joints were examined every 6 months. MRI was scored by the RA MRI scoring (RAMRIS) technique and plain radiographs were scored using the Genant-modified Sharp score. Variables that were correlated with plain radiographic changes at 12 months were examined.
*Results* Simplified disease activity index (SDAI) remission was achieved in 7 patients, and a significant reduction in the RAMRIS bone edema score, which declined to <33 % as compared with the baseline, was achieved in 8 out of 13 patients. Four patients showed plain radiographic progression while 9 patients did not. Significant reductions in the RAMRIS bone edema score ($p = 0.007$) and the time-integrated SDAI ($p = 0.031$) were the variables involved in plain radiographic progression.
*Conclusions* Improvement in bone edema may be associated with protection against structural damage in very early RA patients managed using the tight control approach.

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**Keywords** Very early RA · MRI · RAMRIS bone edema score · SDAI · Radiographic progression

**Abbreviations**

| | |
|---|---|
| ACR | American College of Rheumatology |
| Anti-CCP antibodies | Anti-cyclic citrullinated peptide antibodies |
| CRP | C-reactive protein |
| DMARDs | Disease-modifying antirheumatic drugs |
| IgM-RF | Immunoglobulin M-rheumatoid factor |
| MMP-3 | Matrix metalloproteinase 3 |
| MRI | Magnetic resonance imaging |
| MTX | Methotrexate |
| PIP joint | Proximal interphalangeal joint |
| RA | Rheumatoid arthritis |
| RAMRIS | RA MRI scoring |
| SDAI | Simplified disease activity index |
| T2T | Treat to target |
| TNF | Tumor necrosis factor |

## Introduction

Diagnosis and the subsequent application of the treat-to-target (T2T) strategy at an early stage are now considered crucial to the effective management of rheumatoid arthritis (RA) [1–3]. The 2010 RA classification criteria were developed in order to aid in the classification of patients at early stages of the disease who are likely to progress to persistent and/or erosive disease [4, 5]. With the same purpose in mind, we have also published a prediction rule for disease outcomes in patients with early undifferentiated arthritis based on magnetic resonance imaging (MRI) of the wrists and finger joints and serologic autoantibodies [6]. The application of the treat-to-target strategy utilizing a tight control approach in RA patients has been shown to improve the outcome of RA, especially in early or very early RA patients [1–3].

Imaging techniques have played an important role in assessing disease progression and therapeutic response in cases of RA for many years [7]. Plain radiographs have been widely used together with scoring systems that are designed to quantify disease and measure progression and response to therapies [7]. However, radiographs rely on relatively late disease features, such as bone erosion and joint space narrowing. Since structural damage in very early RA patients cannot be properly evaluated using plain radiographs [7, 8], the application of other techniques, such as MRI and ultrasonography, would be useful in these cases.

MRI detects synovitis, bone edema, and bone erosion [7, 8]. The severity of these lesions is scored by the RA MRI scoring (RAMRIS) technique, which is suitable for the qualification of joint injury [7, 8]. RAMRIS scores the synovitis, bone edema, and bone erosion in individual joints; providing a well-defined, reproducible measurement system [7, 8]. Despite this, few clinical trials to date, especially trials involving very early RA, have used RAMRIS to assess the efficacy of anti-rheumatic therapies [7]. The CIMESTRA trial at two years [9] and five years [10] identified the importance of MRI-proven bone edema at entry with respect to subsequent radiographic progression as evaluated by RAMRIS; however, the changes in the RAMRIS scores during the courses of therapy were not stated in the CIMETSTRA trial.

We recently demonstrated the excellent clinical efficacy of synthetic disease-modifying antirheumatic drugs (DMARDs) in very early RA patients with poor prognostic factors [11]. In that report, synthetic DMARDs-free remission was achieved in some patients with MRI-proven bone edema that was significantly reduced by treatment with synthetic DMARDs [11]. The present study follows on from that report, and attempts to identify the variables—including the features of an MRI-proven joint injury evaluated by RAMRIS—that are associated with radiographic changes in patients with very early RA.

## Patients and methods

### Patients

This was an investigator-initiated clinical study that attempted to examine the efficacy of the T2T strategy for very early RA patients with poor prognostic factors. Patients with very early RA were defined in the present study as those who did not meet the 1987 criteria of the American College of Rheumatology (ACR) for RA [12] but fulfilled the 2010 RA classification criteria [4, 5] at entry. We recently reported that MRI-proven bone edema and serologic autoantibodies are thought to be poor prognostic factors in early arthritis [6]. Accordingly, very early RA cases who did not meet the 1987 criteria of the ACR for RA but fulfilled the 2010 RA classification criteria at entry, in addition to having MRI-proven bone edema and serologic autoantibodies, were selected for the present study. Thirteen patients who met our inclusion criteria were serially recruited from the Early Arthritis Clinic that opened in 2001 as part of the Unit of Translational Medicine, Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical

Sciences. We excluded patients who met the international criteria for rheumatic diseases other than RA at baseline. Patients were referred from an area in the western part of Japan, Nagasaki Prefecture, which has approximately 450,000 inhabitants. These 13 patients were recruited from 2008 to 2009, and were exactly same as those in our recent report [11].

Baseline clinical manifestations and variables included gender, age, disease duration from onset to entry, morning stiffness, disease-modifying antirheumatic drugs (DMARDs), glucocorticoid, simplified disease activity index (SDAI), CRP (measured by latex turbidimetric immunosorbent assay; Daiichi Pure Chemicals, Fukuoka, Japan), matrix metalloproteinase 3 (MMP-3; measured by enzyme-linked immunosorbent assay, with cut-off values of 59.7 ng/ml for females and 121.0 ng/ml for males, Daiichi Pure Chemicals), anti-cyclic citrullinated peptide antibodies (anti-CCP Abs) (measured by enzyme-linked immunosorbent assay, cut-off value 4.5 U/ml; DIASTAT Anti-CCP; Axis-Shield, Dundee, UK), IgM rheumatoid factor (IgM-RF) (measured by latex-enhanced immunonephelometric assay, cut-off value 14 IU/ml; Dade Behring, Marburg, Germany), MRI-proven synovitis, MRI-proven bone edema, MRI-proven bone erosion, and plain radiographs of both hands and feet. All variables were examined on the same day, as we recently reported [6, 13, 14]. A signed consent form to participate in the study was provided by each patient, which was approved by the Institutional Review Board of Nagasaki University. All of the above variables were also measured every six months.

### T2T strategy for the treatment of very early RA

We applied the T2T strategy for the treatment of very early RA in an attempt to induce SDAI remission, based on previous reports [2, 3, 15]. The treatment strategy was described in our recent report [11]. In brief, synthetic DMARDs were initially introduced and SDAI was evaluated every 3 months. If the SDAI showed moderate disease activity at 3 months or low disease activity after 6 months, antirheumatic therapies were modulated. Methotrexate (MTX) was initiated in 10 out of 13 patients, salazosulfapyridine in 2 patients, and tacrolimus in 1 patient. Salazosulfapyridine and tacrolimus were introduced in 3 patients due to the presence of interstitial lung disease. Since the officially approved maximum weekly dosage of MTX in Japan was limited to 8 mg at that time, which is much less than that in Europe and the United States [16], all of the patients received 8 mg per week of MTX. In the present study, the time-integrated SDAI over 12 months was calculated by summing the SDAIs obtained every 3 months.

### Radiographic examination during the treatment

Plain radiographs of both hands and feet were taken every 6 months and evaluated based on the Genant-modified Sharp score by an experienced radiologist (M.U.), who was blinded to the clinical status. If the annual progression in the score was greater than 1, the patient was considered to show radiographic progression.

Plain MRIs of both wrists and finger joints were also examined every 6 months, as we previously described [6, 13, 14]. In brief, MRIs of both wrists and finger joints were acquired using a 1.5 T system (Sigma, GE Medical Systems, Milwaukee, WI, USA) with an extremity coil. T1-weighted spin echo (TR 450, TE 13) images and short T1 inversion recovery (STIR; TR 3000, TE 12, T1 160) images were simultaneously acquired on the same day. The images were evaluated for synovitis, bone edema, and bone erosion at 15 sites in each finger and wrist: the distal radioulnar joint, the radiocarpal joint, the midcarpal joint, the first carpometacarpal joint, the second to fifth carpometacarpal joints (together), the first to fifth metacarpophalangeal joints (separately), and the first to fifth proximal interphalangeal joints (PIP joints) separately (for a total of 30 sites in both hands), as we recently reported [6, 13, 14]. MRI was evaluated by an experienced radiologist (M.U.), who was blinded to the clinical status, and the severity of MRI-proven joint injury was evaluated by RAMRIS, according to the standard method, as the RAMRIS total score, RAMRIS synovitis score, RAMRIS bone edema score, and RAMRIS erosion score [7, 8]. As described later in the text, a significant improvement in the RAMRIS score was considered to have occurred if each RAMRIS score declined to <33 % as compared with the baseline.

### Statistical assessment

We used Fisher's exact probability test and the Mann–Whitney $U$ test to assess statistical difference. The correlation between two variables was calculated by evaluating Spearman's rank correlation coefficient. Logistic regression analysis was performed using the SAS v.9.1.3 software package (SAS Institute, Cary, NC, USA). Variables with a $p$ value of less than 0.05 were considered to be significant.

## Results

### Therapeutic response of the 13 patients

The baseline variables of the 13 patients have already been described in a recent report [11]. The crucial information is as follows: the mean disease duration at the initiation of

**Table 1** Overall therapeutic response for the 13 patients

| Month after treatment | 0 M | 3 M | 6 M | 9 M | 12 M |
|---|---|---|---|---|---|
| Fulfillment of 1987 criteria (%) | 0 (0) | 7 (53.8) | 7 (53.8) | 7 (53.8) | 7 (53.8) |
| Concomitant TNF inhibitor (%) | 0 (0) | 0 (0) | 1 (7.7) | 3 (23.1) | 3 (23.1) |
| SDAI remission (%) | 0 (0) | 4 (33.3) | 8 (61.5) | 5 (38.5) | 7 (53.9) |

**Table 2** Radiographic changes of 13 patients during the treatment

| Month after treatment | 6 M | 12 M |
|---|---|---|
| Plain radiographic progression (n, %) | 4 (30.8 %) | 4 (30.8 %) |
| Changes in RAMRIS scores from baseline (%) | | |
| Total (%) | 1.47 | −9.43 |
| Synovitis (%) | 14.4 | 11.6 |
| Bone edema (%) | −4.76 | −51.1 |
| Bone erosion (%) | 101.1 | 39.4 |

Change in RAMRIS score from baseline (%): % change in the RAMRIS score as compared with the baseline

synthetic DMARDs from the onset of symptoms was 13.7 weeks; all of the patients were seropositive toward anti-CCP Abs and/or IgM-RF; plain radiographic damage at entry was minimal, as evidenced by a mean Genant-modified Sharp score of 1.8; and all of the patients showed MRI-proven bone edema, respectively. RAMRIS scores as well as the seropositivity rate among the present cases at baseline were high as compared with those in the CIMESTRA trial [9–11].

Table 1 shows a brief summary of the overall therapeutic response for the 13 patients treated with a T2T strategy to induce SDAI remission. This therapeutic strategy proved effective, since >50 % of the patients achieved SDAI remission at 12 months. Tumor necrosis factor (TNF) inhibitors were introduced in 3 patients at >12 months, and 7 patients have fulfilled the 1987 criteria of the ACR for RA.

### MRI-proven bone edema is strongly associated with plain radiographic outcome

Table 2 shows a summary of the radiographic results. Four out of the 13 patients showed plain radiographic progression as evaluated based on the Genant-modified Sharp score. The total RAMRIS score decreased modestly at 12 months as compared with the baseline, whereas bone edema responded well to the therapy, since the RAMRIS bone edema score decreased to <50 % at 12 months. In particular, the RAMRIS bone edema score declined to <33 % from the baseline in 8 out of the 13 patients. In contrast, a decline less than 33 % in the RAMRIS total or synovitis score at 12 months was observed in only 1 patient. No patient achieved a RAMRIS bone erosion score decline less than 33 % at 12 months (Table 3).

We then tried to determine which of the variables were correlated with an absence of plain radiographic progression at 12 months. A summary of the results is given in Table 3. A significant reduction in the RAMRIS bone edema score at 12 months, which corresponded to a decrease of less than 33 % as compared with the baseline, was often seen in the no plain radiographic progression group. In addition, there was a correlation between the percentage decrease in the RAMRIS bone edema score and the change in the Genant-modified Sharp score ($rs = 0.65$, $p = 0.031$). No significant difference in the RAMRIS total score, RAMRIS synovitis score, or RAMRIS bone erosion score was observed. The similar tendency was observed in the RAMRIS bone edema score at baseline ($p = 0.10$); however, it did not reach statistical significance. The Genant-modified Sharp score at baseline did not differ between the two groups either. Neither SDAI at baseline nor the SDAI remission rate at 12 months varied significantly depending on the presence or absence of plain radiographic progression at 12 months. However, although the $p$ value for time-integrated SDAI was larger than that for the RAMRIS bone edema score, the time-integrated SDAI of the plain radiographic progression group was higher than that of the no progression group. We also tried to confirm the above result by logistic regression analysis; however, we did not obtain stabilizing data, probably due to the small number of patients (data not shown).

## Discussion

The usefulness of MRI for the evaluation of radiographic progression in RA has already been reported elsewhere [7, 8]. Hetland et al. [9, 10] screened the baseline variables and recently published the results from the CIMESTRA trial, which showed that MRI bone edema at entry is the only statistically significant predictor of further radiographic progression in very early RA treated aggressively by MTX and ciclosporin. Clinical disease activity in that previous study was evaluated based on the 28-joint disease activity score (DAS28).

**Table 3** The variables associated with the absence of plain radiographic progression as determined based in the Genant-modified Sharp score

| Variables | No radiographic progression ($n = 9$) | Radiographic progression ($n = 4$) | $p$ value |
|---|---|---|---|
| Gender (female %) | 66.7 | 75 | 1.0 |
| Age (y.o., mean ± SD) | 58.7 ± 12.8 | 60.5 ± 6.2 | 0.82 |
| Disease duration (week, mean ± SD) | 16.2 ± 14.8 | 8.1 ± 2.7 | 0.44 |
| Morning stiffness (min, mean ± SD) | 60.0 ± 76.5 | 182.5 ± 205 | 0.69 |
| SDAI at baseline | 16.5 ± 3.8 | 28.4 ± 17.4 | 0.25 |
| CRP (mg/dl) at baseline | 1.1 ± 1.0 | 1.2 ± 1.1 | 0.94 |
| Genant-modified Sharp score at baseline | 2.13 ± 2.43 | 0.98 ± 0.78 | 0.58 |
| RAMRIS MRI bone edema score at baseline | 10.3 ± 9.5 | 29.3 ± 24.9 | 0.10 |
| Time-integrated SDAI during 12 months | 30.54 ± 15.47 | 87.22 ± 89.43 | 0.031 |
| MTX use during 12 months (*N*) | 7 | 3 | 1.0 |
| Glucocorticoid use during 12 months (*N*) | 3 | 1 | 1.0 |
| TNF inhibitor use during 12 months (*N*) | 1 | 2 | 0.20 |
| SDAI remission at 12 months (*N*) | 6 | 1 | 0.27 |
| No fulfillment of 1987 criteria at 12 months (*N*) | 7 | 1 | 0.22 |
| Decrease in RAMRIS total score at 12 months (*N*) | 1 | 0 | 0.69 |
| Decrease in RAMRIS synovitis score at 12 months (*N*) | 1 | 0 | 0.69 |
| Decrease in RAMRIS bone edema score at 12 months (*N*) | 8 | 0 | 0.007 |
| Decrease in RAMRIS bone erosion score at 12 months (*N*) | 0 | 0 | 0.66 |

The present study is a similar clinical study; however, a new insight gained from this study is that therapeutic intervention is designed to achieve SDAI remission. Also, all of the subjects in the present study were found to have both MRI-proven bone edema and autoantibodies. Therefore, these clinical observations for cases of very early RA with poor prognostic factors led to the attempt to achieve SDAI remission by evaluating treatment efficacy using MRI. Although the dosage of MTX in the present study performed in Japan is quite low compared to the dosages used in Europe and the United States, its efficacy was evident when administered during the very early stages of RA. It is well known (e.g., from the results of Hetland et al.) that MRI bone edema at entry predicts further radiographic progression [7–10]. We have revealed that therapeutic modification of the RAMRIS bone edema score rather than the baseline RAMRIS bone edema score appears to be associated with radiographic progression. This may be consistent with the recent observation that time-integrated disease activity is associated with plain radiographic progression in patients with active early RA [17]. SDAI remission is believed to be more stringent than DAS28 remission [15]. However, our present data showed that a significant reduction in the RAMRIS bone edema score, which could be described as MRI bone edema remission, may be more strongly associated with an excellent radiographic outcome than SDAI remission. Our recent work, which found that MRI is able to more sensitively detect joint injuries of wrist and finger joints in early RA patients than physical examination [14], may support this observation. Other RAMRIS scores, such as the total score, synovitis score, and bone erosion score did not correlate with plain radiographic progression. These data also strengthen the prognostic value of MRI-proven bone edema in the identification of very early RA patients. This is a novel finding, and it reinforces the importance of taking serial MRIs during the application of a tight control approach in cases of RA. In terms of time-integrated clinical disease activity, the sum of SDAI over 12 months was higher in the plain radiographic progression group as compared with the no progression group, which is similar to recent observations [17]. Probably due to the very small sample size, we could not perform logistic regression analysis to examine the predictive value of MRI-proven bone edema for plain radiographic progression. Therefore, although the $p$ value for time-integrated SDAI was larger than that for decrease in RAMRIS bone edema score, we could not identify which of the variables were most strongly linked to radiographic progression. This issue can be resolved by studying more patients. Since the plain radiographic damage at study entry was minimal in the present cases, we did not find any difference between the Genant-modified Sharp score at entry and the radiographic outcome at 12 months.

A recent report by Haavardsholm et al. [18] found that the RAMRIS synovitis score responds better than the RAMRIS bone edema score during anti-TNF-α therapy. This contradicts our present observations. Both plain and contrast-enhanced MRI were used in that study [18]. Contrast-enhanced MRI is better suited to evaluating synovitis, whereas plain MRI is sufficient to evaluate bone changes, including bone edema [8]. Since we did not investigate contrast-enhanced MRI in the present study, we