

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 RA⁴ 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 ($\geq 4/66$ swollen joints and $\geq 4/68$ 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 pre-specified 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),



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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 criteria⁹ at week 14, prior to any change in treatment at week 16. Additional efficacy assessments included ACR50 and ACR70 responses, ACR-N Index of Improvement¹⁰ 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 χ^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 χ^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

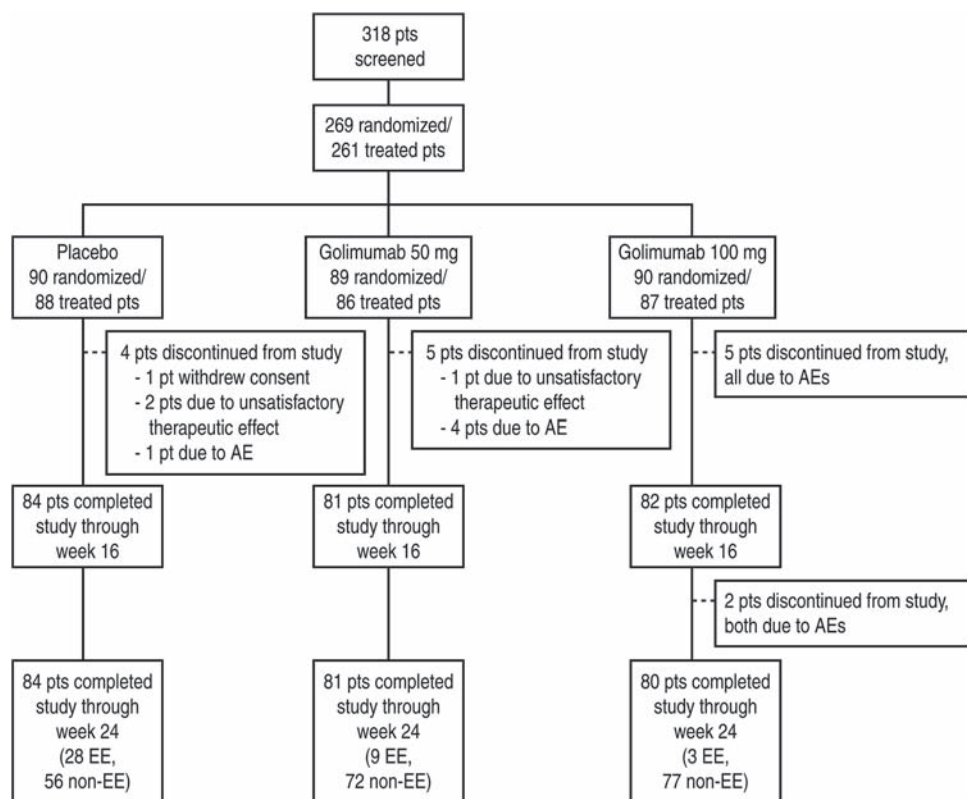


Figure 1 Patient disposition through week 24; randomised patients. Note that 'worsening of rheumatoid arthritis' is included in 'unsatisfactory therapeutic response' and not as an AE. AE, adverse event; EE, early escape; pts, patients.

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
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
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	<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	<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	<0.0001	0.0050	0.0003	0.0002	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 (30.77)	44.17 (30.78)
p value† vs Group 1	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	<0.0001	<0.0001
DAS28(ESR) responses								
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	<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	<0.0001	0.0020	<0.0001	<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	<0.0001	0.0014	<0.0001	<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]
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)
p value† vs Group 1	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]
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	0.0094	0.1678	0.1678	<0.0001	0.0014
Change from baseline in vdH-S score								
Total vdH-S score								
p value† vs Group 1					2.51 (5.52)	1.05 (3.71)	0.33 (2.66)	0.69 (3.23)
Erosion score					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	0.0006	0.0009
JSN score								
p value† vs Group 1					N=84	N=81	N=82	N=163
JSN score					1.66 (3.73)	0.54 (1.62)	0.03 (1.44)	0.28 (1.55)
p value† vs Group 1					0.00 [-2.5, 22.5]	0.00 [-2.5, 8.0]	0.00 [-3.5, 9.0]	0.00 [-3.5, 9.0]
JSN score					0.0044	0.0044	<0.0001	<0.0001
JSN score					N=84	N=81	N=82	N=163
p value† vs Group 1					0.83 (2.31)	0.71 (2.91)	0.29 (1.49)	0.50 (2.31)
JSN score					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	0.2836
Change in vdH-S > SDC (3.23)					44 (50.0%)	51 (59.3%)	61 (70.1%)	112 (64.7%)
p value† vs Group 1					0.2179	0.0066	0.0066	0.0217
p value† vs Group 1					19 (21.6%)	14 (16.3%)	5 (5.7%)	19 (11.0%)
p value† vs Group 1					0.3715	0.0023	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 χ^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.

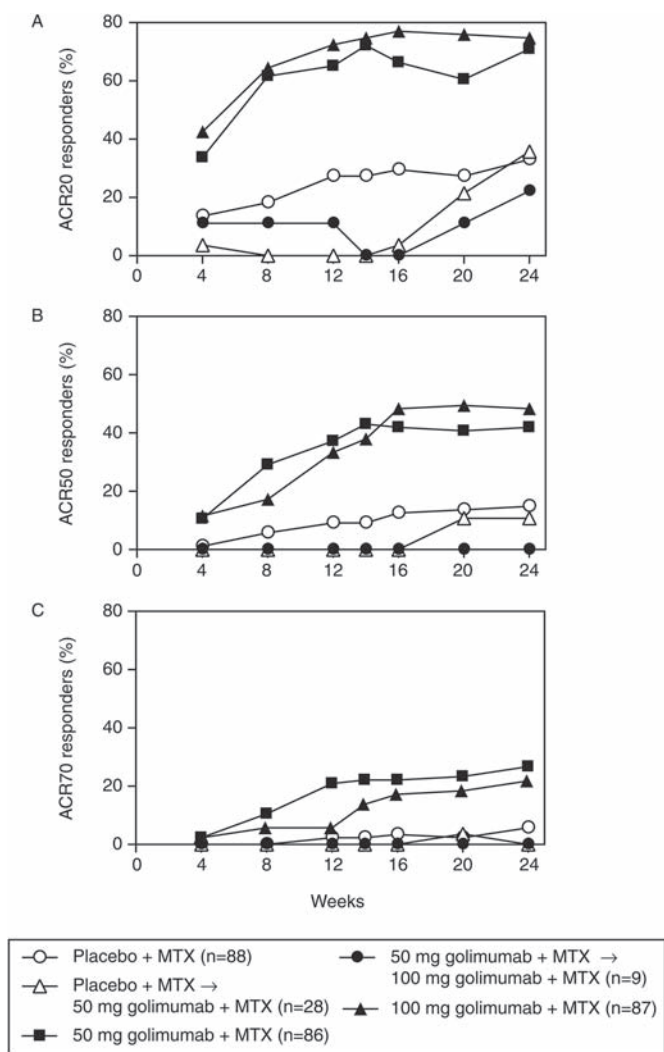


Figure 2 (A) American College of Rheumatology 20% (ACR20), (B) 50% (ACR50) and (C) 70% (ACR70) improvement from baseline through week 24. Note that patients who met the early escape criteria at week 16 and crossed over to golimumab 50 mg or dose escalated from golimumab 50 mg to 100 mg are shown with 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

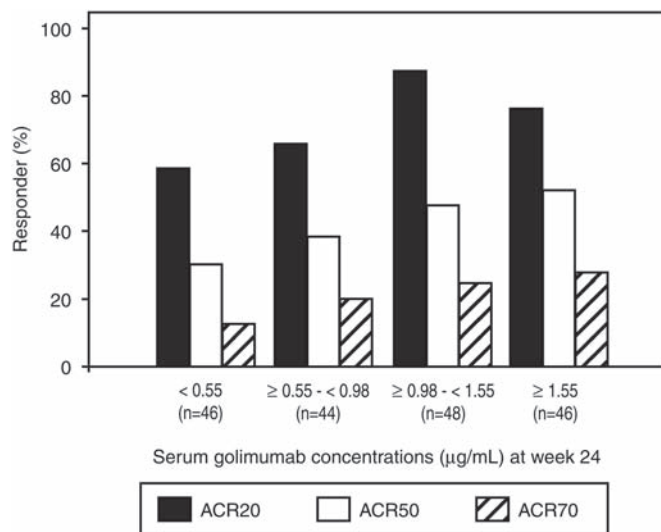


Figure 3 Proportions of patients achieving at least 20%, 50% and 70% improvement in the American College of Rheumatology (ACR20, ACR50, ACR70) response criteria by serum golimumab concentration quartiles ($\mu\text{g}/\text{mL}$) at week 24. The results are from a post hoc analysis of ACR responders 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 <math>< 0</math>) 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 $\mu\text{g}/\text{mL}$, respectively, for Group 2 and 1.28 and 1.16 $\mu\text{g}/\text{mL}$, 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 <math>< 0.55</math> $\mu\text{g}/\text{mL}$, followed by concentrations \mu\text{g}/\text{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

	Group 1: Placebo + MTX		Group 2: Golimumab 50 mg + MTX		Group 3: Golimumab 100 mg + MTX		Combined Groups 2 and 3	
Week 16								
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: Golimumab 100 mg + MTX		All	
	With or without EE	With EE Placebo + MTX → Golimumab 50 mg + MTX	With or without EE	With EE Golimumab 50 mg + MTX 50 mg → 100 mg + MTX	With or without EE	With EE Golimumab 100 mg + MTX	Combined Groups 2 and 3	Group 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; 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 elsewhere¹⁸ 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 profile¹⁹ 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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ONLINE SUPPLEMENTAL TEXT

Concomitant medication and tuberculosis screening criteria

Concurrent nonsteroidal anti-inflammatory drug, RA analgesic, and oral corticosteroid (≤ 10 mg prednisolone/day or equivalent) use was allowed with stable doses prior to (≥ 2 weeks) and during the study. Prior receipt of anti-TNF biological therapy, alkylating agents (cyclophosphamide), or any investigational agents within the previous 4 months excluded patients.

Patients who met the third criteria listed below could be enrolled into this study only if administration of anti-tuberculosis (isoniazid) therapy was started within 3 weeks prior to the initial administration of study agent. Patients who had received preventive anti-tuberculosis therapy over the prior 6 months were also allowed to enter the study.

- 1) A history of tuberculosis or active tuberculosis based upon screening medical history.
- 2) Not “1)” but thoracic (posterior-anterior and side) radiographic or thoracic computed tomography imaging performed within 1 month of study registration, and results of such testing revealed tuberculosis findings, including fibrotic scarring of the lungs or pleura, tuberculosis nodules, swelling of the hilus or diaphragmic lymph nodes, reduced volume of upper pulmonary lobe, vacuole formation, and/or shadows consistent with old pulmonary tuberculosis (pleural thickening, tram line shadows, and darkening in excess of 5mm).

3) Not “2)” but with evidence as outlined above in 2), red indurations of 20 mm or larger observed via tuberculin reaction testing performed either at the time of study registration or within 1 month of registration.

Prespecified data handling rules and sample size determination

ACR response rates and HAQ were calculated employing last-observation-carried-forward methodology at weeks 14 and 24. In the analysis of DAS28 response at weeks 14 and 24, observed data were used with no imputation for missing data, with the exception of the DAS28 remission analysis for which patients with missing data were deemed nonresponders. Observed data were employed in analyses of erosion scores, joint space narrowing scores and pharmacokinetic data.

For any ACR component, DAS28 component and HAQ scores, missing values were replaced by the last non-missing observation (including baseline). Patients who were missing data for all ACR components were considered to be nonresponders. Similarly, patients who were missing data for all DAS components were considered to not be in remission and were treated as missing for DAS response status.

Patients were also considered nonresponders if they met any one of the following treatment failure criteria: (1) initiated treatment with any disease-modifying antirheumatic agent, systemic immunosuppressive agents, or biologics agents for RA; (2) increased the MTX dose above the baseline dose for treatment of RA; (3) initiated treatment with oral corticosteroids for RA, increased the dose of oral corticosteroids for RA above the baseline dose, or received intravenous or intramuscular administration of corticosteroids for RA; or (4) discontinued study agent injections due to lack of efficacy.

Week-16 efficacy data for patients in Groups 1 and 2 who entered early escape were carried forward to week 24. No treatment adjustment options were available for patients in Group 3 even if they met the criteria for early escape. Therefore, actual observed data at week 24 were used for these patients with the normal data imputation rules applied as described above.

For erosion and JSN scores, no imputation rule was applied. For changes in total vdH-S scores, if either the baseline or week-24 score was missing, but scores were available for two other time points between baseline and week 24 (including at the time of discontinuation), linear extrapolation was used to impute the missing score. If both of the baseline and week 24 total vdH-S scores were missing, the change from baseline to week 24 was imputed with the median change from baseline to week 24 among all patients.

The planned sample size (n=255) provided >90% power to detect a difference in ACR20 response between Combined Groups 2&3 vs. Group 1 ($\alpha=0.05$) at week 14. This power calculation assumed ACR20 response rates similar to those observed in a previously conducted Phase 3 golimumab trial in a similar population of RA patients receiving background MTX therapy (33.1%, 55.1% and 56.2% of patients who received placebo+MTX, golimumab 50mg+MTX and golimumab 100mg+MTX, respectively).[5]

