Table 2. Demographic indicators and baseline disease characteristics in GLM-50 + MTX with high disease activity (DAS28 (ESR) > 5.1).

	DAS28 (ESR) > 5.1			
	All	ΔTSS ≤ 0	ΔTSS > 0	*p* value
Number of patients	51	22	29	
Female patients, *n* (%)	43 (84.3)	22 (100.0)	21 (72.4)	0.0072*
Age (years)	53.5 (8.9), 55 [30, 72]	54.8 (8.7), 55 [39, 72]	52.5 (9.0), 55 [30, 60]	0.3728**
Average duration of RA (years)	9.3 (9.6), 6.5 [0.4, 36.8]	12.8 (9.6), 10.4 [0.7, 36.8]	6.7 (8.9), 3.6 [0.4, 35.8]	0.0221**
Swollen joint count (0–68)	14.6 (7.0), 13 [4, 33]	13.9 (6.5), 12 [5, 26]	15.1 (7.5), 15 [4, 33]	0.5422**
Tender joint count (0–68)	16.6 (8.6), 15 [4, 40]	16.1 (7.1), 15 [6, 33]	16.9 (9.7), 14 [4, 40]	0.7588**
Time of morning stiffness (min)	168.8 (3444.3), 60 [0, 1440]	74.1 (84.3), 60 [0, 300]	240.7 (440.4), 60 [0, 1440]	0.0870**
HAQ-DI (0–3)	1.2 (0.57), 1.3 [0.0, 2.4]	1.3 (0.63), 1.5 [0.1, 2.4]	1.2 (0.53), 1.3 [0.0, 2.4]	0.3875**
CRP (mg/dl)	2.8 (3.05), 1.9 [0.07, 13.9]	2.1 (3.05), 1.4 [0.07, 13.9]	3.4 (2.98), 3.0 [0.13, 12.1]	0.1466**
ESR (mm/h)	63.0 (28.7), 56 [19.0, 134.0]	61.5 (29.8), 59.5 [19.0, 127.0]	62.1 (28.2), 55 [28.0, 134.0]	0.7379**
Rheumatoid factor	45 (90.0)	19 (86.4)	29 (92.9)	0.6428*
Anti CCP antibody, *n* (%)	50 (98.0)	22 (100)	28 (96.6)	1.0000*
DAS28 (ESR)	6.3 (0.76), 6.3 [5.1, 8.8]	6.3 (0.58), 6.3 [5.3, 7.5]	6.3 (0.88), 6.2 [5.1, 8.8]	0.9163**
TSS (baseline)	69.5 (71.9), 41 [0.0, 300.5]	93.9 (84.1), 65.8 [4.0, 300.5]	51.1 (55.6), 27.5 [0.0, 187.5]	0.0336**
TSS/duration	9.7 (7.1), 7.8 [0.0, 26.1]	8.0 (5.9), 6.5 [0.7, 26.1]	11.0 (7.8), 10.5 [0.0, 25.0]	0.1343**

*Fisher's exact test.
**t-test.
Data shown mean (SD) and median (min, max).
ΔTSS: change from baseline to week 24 of the modified total Sharp score.

Table 3. Demographic indicators and baseline disease characteristics in GLM-50 + MTX with high CRP (≥1.5 mg/dL).

	CRP ≥ 1.5			
	All	ΔTSS ≤ 0	ΔTSS > 0	*p* value
Number of patients	34	13	21	
Female patients, *n* (%)	26 (76.5)	12 (92.3)	14 (66.7)	0.1164*
Age (years)	53.6 (7.7), 55 [36, 66]	55.2 (5.0), 55 [47, 63]	52.6 (9.0), 55 [36, 66]	0.3490**
Average duration of RA (years)	8.8 (9.7), 4.5 [0.4, 35.8]	11.4 (8.6), 9.6 [2.3, 27.8]	7.2 (10.3), 2.8 [0.4, 35.8]	0.2316**
Swollen joint count (0-68)	15.0 (7.6), 15.5 [4, 33]	12.9 (7.1), 10 [4, 24]	16.3 (7.7), 16 [4, 33]	0.2060**
Tender joint count (0-68)	16.0 (9.7), 14 [4, 40]	13.6 (8.6), 11 [4, 33]	17.5 (10.2), 17 [4, 40]	0.2576**
Time of morning stiffness (min)	234.3 (407.9), 60 [0, 1440]	99.2 (106.3), 60 [0, 300]	317.9 (498.5), 60 [0, 1440]	0.1308**
HAQ-DI (0–3)	1.2 (0.62), 1.3 [0.0, 2.4]	1.1 (0.74), 1.3 [0.1, 2.1]	1.3 (0.53), 1.4 [0.0, 2.4]	0.2599**
CRP (mg/dl)	4.1 (3.07), 3.0 [1.6, 13.9]	3.6 (3.4), 2.5 [1.6, 13.9]	4.4 (2.89), 3.5 [1.6, 12.1]	0.4717**
ESR (mm/h)	71.5 (28.7), 64 [33.0, 134.0]	70.2 (30.4), 69.0 [33.0, 127.0]	72.3 (28.3), 63 [38.0, 134.0]	0.8333**
Rheumatoid factor	31 (93.9)	12 (92.3)	19 (95.0)	1.0000*
Anti CCP antibody, *n* (%)	34 (100.0)	13 (100.0)	21 (100.0)	–
DAS28 (ESR)	6.3 (0.93), 6.3 [4.5, 8.8]	6.1 (0.93), 6.3 [4.5, 7.5]	6.5 (0.93), 6.4 [5.1, 8.8]	0.2853**
TSS (baseline)	69.4 (67.4), 53.8 [3.5, 243.8]	78.6 (78.9), 59 [5.0, 243.8]	63.6 (60.6), 48.5 [3.5, 187.5]	0.5358**
TSS/duration	11.4 (7.7), 11.2 [0.5, 26.1]	7.5 (7.1), 5.3 [1.1, 26.1]	13.9 (7.1), 14.5 [0.5, 25.0]	0.0166**

*Fisher's exact test.
**t-test.
Data shown mean (SD) and median (min, max).
ΔTSS: change from baseline to week 24 of the modified total Sharp score.

study of adalimumab [19], a duration of RA < 3 years was classified as early disease and a duration > 3 years was defined as established disease. In our analysis, ΔTSS was larger for patients with early disease duration than for patients with established disease according to these criteria, but treatment with 100 mg of golimumab significantly prevented joint destruction regardless of disease duration.

RRP was recently defined as an annual ΔTSS of 5 or more, and the necessity of predicting RRP and starting appropriate treatment at an early stage was pointed out [16,20]. In the GO-FORTH study, ΔTSS at 24 weeks was >2.5 in 26, 17, and 5 patients from the PBO, GLM-50, and GLM-100 groups, respectively, and there were significantly fewer such patients in the GLM-100 group than in the GLM-50 group. The results of the ATTRACT trial using infliximab [21] and the PREMIER study using adalimumab [13] have suggested that anti-TNF therapy + MTX is effective for preventing RRP in patients with RA.

Regarding the other clinical effects of golimumab apart from preventing joint destruction, baseline disease activity and CRP had no significant influence on the changes of ACR20, ACR50, ACR70, DAS (ESR), and HAQ-DI in the GLM-50 and GLM-100 groups (data not shown). These results confirm that disease activity and CRP are more closely related to the risk of progressive joint destruction than are symptoms and physical activity. In a study with an 8-year follow-up period [22], van den Broek et al. showed that RRP during the first year affected function over time and that HAQ could not decrease to match RRP without suppression of joint destruction. They also reported that early RRP did not decrease subsequent annual progression of joint damage, suggesting that determining the baseline characteristics of patients with and without RRP is important. Emery et al. have also suggested that CRP and ESR are significant parameters for predicting RRP [7].

For the safety profile of golimumab, Tanaka et al. reported that the most common AEs on theGO-FORTH study was infection and the incidence rate of each group were PBO (39.8%), GLM-50(38.4%) and GLM-100(33.3%), respectively [8]. However, Kay et al. recently reported golimumab 3-year safety result [23]. This

report was analysis of pooled data from long-term extensions of RA, psoriatic arthritis or ankylosing spondylitis trials and Golimumab 100 mg was possibly associated with an increased incidence of lymphoma and other infrequently occurring safety events compare with 50 mg [23]. The postmarketing registry study of golimumab continuing in Japan will explain the detail safety.

In conclusion, the preventive effect of golimumab on joint destruction in patients with RA is influenced by disease activity and CRP. More rapid progression of joint destruction occurs in patients with HDA or high CRP than in patients with MDA or low CRP. Although further studies will be required to verify the factors related to progression, the present results suggest that treating RA patients with golimumab (50 mg or 100 mg) and MTX will reduce disease activity and suppress progressive joint destruction. However, starting golimumab therapy at a dose of 100 mg should be considered to prevent rapid progression of joint destruction in patients with HDA or a high CRP level.

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Conflict of interest

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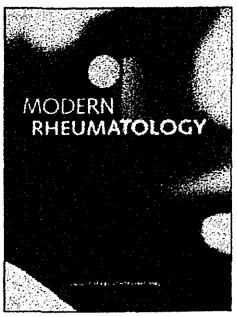

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ORIGINAL ARTICLE

Clinical efficacy, radiographic progression, and safety through 156 weeks of therapy with subcutaneous golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis despite prior methotrexate therapy: final results of the randomized GO-FORTH trial

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Abstract

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

Methods: Japanese patients with active RA despite MTX were randomized to placebo + MTX (Group 1, $n = 88$), golimumab 50 mg + MTX (Group 2, $n = 86$), or golimumab 100 mg + MTX (Group 3, $n = 87$). Patients with <20% improvement in swollen/tender joint counts entered early escape at week 16. At week 24, all remaining placebo patients crossed over to golimumab 50 mg. Efficacy assessments included ACR20, DAS28-ESR, and HAQ-DI. Radiographic progression was assessed with the van der Heijde-modified Sharp (vdH-S) score.

Results: ACR20 response rates in Group 1, Group 2, and Group 3 were 67.9, 86.1, and 82.4%, respectively, at week 52 and were maintained through week 104 (87.1, 94.0, and 88.7%) and week 156 (97.1, 94.1, and 89.5%). Proportions of patients with good/moderate DAS28-ESR response or clinically meaningful improvement in HAQ-DI were also maintained through week 156. The majority of patients did not experience radiographic progression through week 156. Among 257 golimumab-treated patients, 251 (97.7%) had ≥1 AE; 54 (21.0%) had ≥1 serious AE through week 156. Infections were the most common type of AE.

Conclusions: Response to golimumab + MTX was maintained over 3 years in Japanese patients with active RA despite MTX. Safety results were consistent with the known safety profile of golimumab.

Keywords

Anti-tumor necrosis factor, Asian, Golimumab, Rheumatoid arthritis

History

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Introduction

It is estimated that approximately 0.6–1.0% of the Japanese population has rheumatoid arthritis (RA), a chronic inflammatory joint disease [1]. The joint destruction that is characteristic of RA can lead to a substantial loss of physical function [2]. In addition, patients with RA often experience extra-articular manifestations including pulmonary, kidney, and cardiovascular disease [3,4]. Timely and adequate treatment for RA with the goal of low disease activity or remission may prevent long-term radiographic damage and disability [5–7].

Golimumab is a human monoclonal antibody that binds to and blocks the effects of tumor necrosis factor α (TNFα), one of the key inflammatory cytokines involved in the pathogenesis of RA. The safety and efficacy of subcutaneous (SC) golimumab with and without methotrexate (MTX) were evaluated in three large global trials of patients with RA who were MTX-naïve (GO-BEFORE) [8], MTX-experienced (GO-FORWARD) [9], or had been previously treated with anti-TNF agents (GO-AFTER) [10]. The Phase

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2/3 GO-FORTH trial further evaluated the safety and efficacy of SC golimumab plus MTX in Japanese patients with active RA despite treatment with MTX [11]. Through 24 weeks of the GO-FORTH trial, patients treated with golimumab plus MTX had significantly greater improvements in the signs and symptoms of RA and less radiographic progression than did patients who received MTX monotherapy [11]. We now report the final safety and efficacy results from the GO-FORTH trial through 156 weeks.

Materials and methods

Patients

The patient eligibility criteria have been previously reported in detail [11]. Briefly, Japanese patients with active RA despite prior MTX therapy were eligible. Active RA was defined as at least four swollen joints (0–66) and at least four tender joints (0–68) and at least two of the following criteria: (1) C-reactive protein (CRP) > 1.5 mg/dL or erythrocyte sedimentation rate (ESR) by Westergren method > 28 mm/h, (2) morning stiffness ≥ 30 min, (3) radiographic evidence of bone erosion, or (4) positive test for anti-cyclic citrullinated peptide antibody or rheumatoid factor. Patients had to have been receiving a stable dose of MTX (6–8 mg/week) for at least 4 weeks prior to the first study agent administration.

Study design

The GO-FORTH trial was a Phase 2/3, multicenter, randomized, placebo-controlled trial (ClinicalTrials.gov NCT00727987). Details of the trial design have been previously reported [11]. Briefly, eligible patients were randomly assigned (1:1:1) to receive placebo plus MTX (Group 1), golimumab 50 mg plus MTX (Group 2), or golimumab 100 mg plus MTX (Group 3). Subcutaneous placebo and golimumab injections were administered at baseline and every 4 weeks thereafter. All patients were to continue receiving concomitant MTX at a dose of 6–8 mg/week, with dose adjustments permitted only when required for cases of MTX toxicity. At week 16, patients with <20% improvement from baseline in swollen and tender joint counts entered early escape in a double-blinded fashion such that patients in Group 1 switched from placebo to golimumab 50 mg, and patients in Group 2 had their golimumab dose increased to 100 mg. No changes in golimumab dose were permitted for patients in Group 3 regardless of early escape status. At week 24, all patients in Group 1 who were still receiving placebo crossed over to golimumab 50 mg. After week 52, patients who were receiving golimumab 100 mg could have their dose reduced to 50 mg at the investigator's discretion. The final golimumab administration was at week 152.

This study was performed in accordance with the principles in the Declaration of Helsinki and Good Clinical Practice guidelines in Japan. The protocol was reviewed by the institutional review board or ethics committee at each site. All patients gave written informed consent before any study-related procedures were performed.

Assessments

The primary endpoint was the proportion of patients with ≥20% improvement from baseline in the American College of Rheumatology criteria (ACR20) at week 14. Other clinical efficacy assessments included the ACR-N Index of Improvement and the proportions of patients with ACR50 and ACR70 responses, a good or moderate response [12] using the 28-joint count Disease Activity Score using ESR (DAS28-ESR), or DAS28-ESR remission (<2.6). Physical function was assessed using the Health Assessment Questionnaire-Disability Index (HAQ-DI) [13], with a minimal clinically important difference defined as an improvement of at least 0.25 [14]. Efficacy assessments were collected through week 156.

Radiographs of the hands and feet were collected at weeks 0, 52, 104, and 156 and were scored using the van der Heijde modification of the Sharp (vdH-S) score [15]. The smallest detectable change (SDC) was determined using the standard deviation for the difference in absolute change in the vdH-S scores between the readers. Readers were blinded to patient identity, treatment group, and time point at which the radiograph was obtained. An exploratory *post-hoc* analysis was performed to compare baseline characteristics of patients who did and did not have a clinically relevant progression in total vdH-S score (i.e., change in vdH-S ≥ 3) [16] from baseline to week 104. This analysis was not performed at week 156 due to the small patient numbers in each group at that time point.

In a *post-hoc* analysis, remission rates were determined through week 156 using the simplified disease activity index (SDAI ≤ 3.3) [17], clinical disease activity index (CDAI ≤ 2.8) [18], and Boolean criteria [17]. Comprehensive remission (defined as DAS28-ESR < 2.6, HAQ-DI < 0.5, and change in vdH-S ≤ 0) was also evaluated as a *post-hoc* analysis. In addition, a Pearson correlation analysis was performed to examine the relationship between clinical response at week 12 (DAS28-ESR, DAS28-CRP, SDAI, and CDAI) and response at week 104.

Safety assessments were performed through week 156 and included adverse event (AE) reporting and laboratory tests. Blood samples were collected at weeks 0, 24, 52, 104, and 156 for evaluation of the presence of antibodies to golimumab [19]; if patients discontinued treatment, samples were collected at the final visit and at 8 and 12 weeks after the last golimumab administration. On days when study agent was administered, blood samples were collected before the golimumab administration.

Statistical analysis

Clinical efficacy, including the *post-hoc* remission analyses, and radiographic results from week 52 to week 156 were summarized using descriptive statistics according to randomized treatment group. For clinical efficacy and radiographic outcomes, observed data were reported with no imputation for missing data, and no adjustments were made for early escape status at week 16. As all patients were receiving golimumab + MTX after week 24, no statistical comparisons were performed among the treatment groups.

Adverse events were summarized by actual treatment received (i.e., placebo plus MTX, golimumab 50 mg plus MTX, or golimumab 100 mg plus MTX). Due to the planned crossover from placebo to golimumab and the early escape design, some patients may be included in more than one group if they experienced AEs with more than one treatment regimen.

Results

Baseline characteristics and patient disposition

Baseline demographics and disease characteristics were generally well balanced among the three treatment groups and have been previously reported [11]. Of the 269 patients who were randomized, 261 (Group 1, $n = 88$; Group 2, $n = 86$; Group 3, $n = 87$) received at least one dose of study agent. Patient disposition through week 24 has been previously described in detail [11]. At week 16, 28 patients in Group 1 and 9 patients in Group 2 entered early escape. A total of 245 patients (Group 1, $n = 84$; Group 2, $n = 81$; Group 3, $n = 80$) completed study treatment through week 24 [11], and 225, 208, and 191 completed the study through weeks 52, 104, and

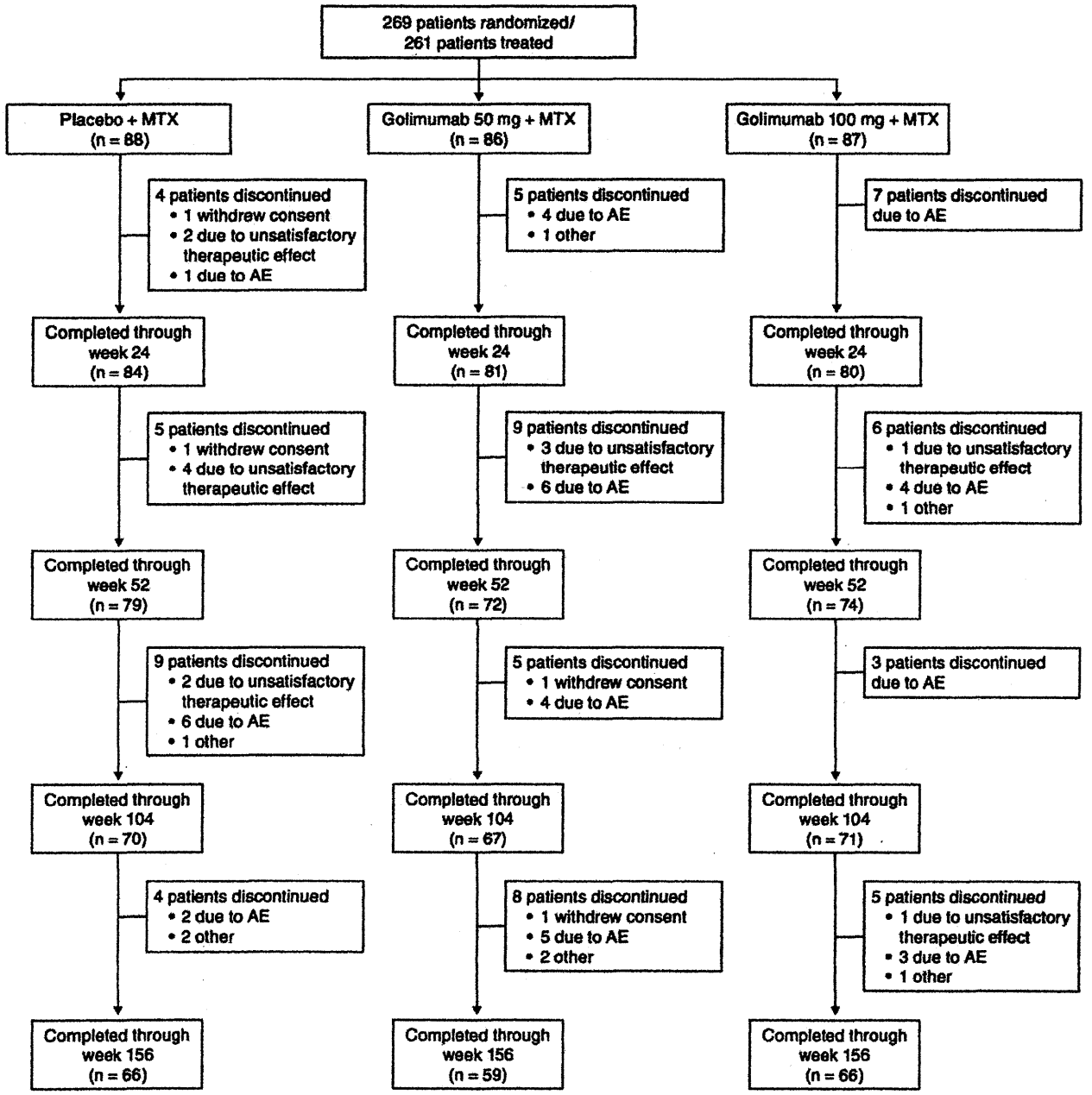

Figure 1. Patient disposition through 156 weeks. AE, adverse event.

156, respectively (Figure 1). Due to local regulations, the trial was discontinued when golimumab was approved by the Ministry of Health, Labor and Welfare in Japan. Patients for whom the study was terminated before the week 156 visit (Group 1, $n=32$; Group 2, $n=25$; Group 3, $n=28$) were counted as having completed the study; however, they did not have available observed data at the final time point. Thus, at week 156, 66 patients in Group 1, 59 patients in Group 2, and 66 patients in Group 3 were counted as having completed the study, and among these, 34, 34, and 38 patients, respectively, had available data at the final visit (week 156).

Throughout the study, 70 patients (Group 1, $n=22$; Group 2, $n=27$; Group 3, $n=21$) discontinued golimumab therapy. The most common reasons for discontinuation were AEs ($n=45/261$ [17.2%]) and unsatisfactory therapeutic effect ($n=13/261$ [5.0%]).

Efficacy

As previously reported, the primary endpoint of the study (ACR20 response at week 14) was met, and patients in Groups 2 and 3 also had significantly greater ACR50 and ACR70 response rates than did patients in Group 1 [11]. ACR response rates in Group 1 increased following crossover from placebo to golimumab, and were similar to those in Groups 2 and 3 at weeks 52, 104, and 156 (Figure 2). ACR20 response rates in Group 1, Group 2, and Group 3 were 67.9, 86.1, and 82.4%, respectively, at week 52, and responses were maintained through week 104 (87.1, 94.0, and 88.7%, respectively) and week 156 (97.1, 94.1, and 89.5%, respectively; Table 1). A similar result was observed for ACR50 and ACR70 response rates through week 156 (Figure 2). Similar trends were also observed for ACR-N scores and changes from baseline in DAS28-ESR scores as well as the proportions of

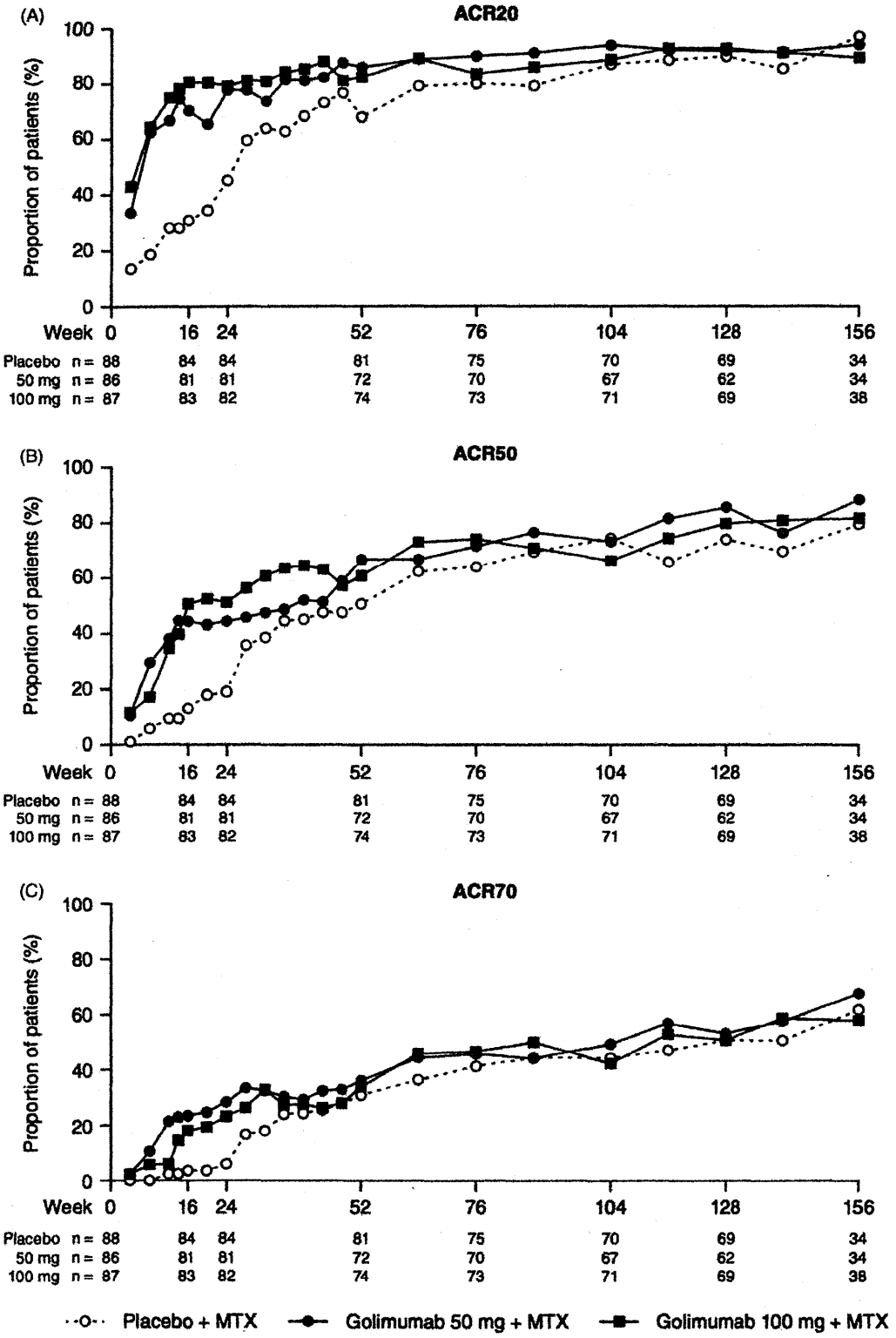

Figure 2. The proportions of patients* with an ACR20 (A), ACR50 (B), and ACR70 (C) response through week 156. *Observed data without imputation. ACR20/50/70, ≥ 20%/50%/70% improvement in American College of Rheumatology criteria; MTX, methotrexate.

patients with a moderate or good DAS28-ESR response and DAS28-ESR remission (Table 1). The proportions of patients in remission through week 24, using the SDAI, CDAI, and Boolean criteria, were numerically greater in Groups 2 and 3 than in Group 1 (Figure 3). The proportions of patients in remission were similar among the treatment groups at week 52 and were maintained through week 156. In addition, comprehensive remission was achieved at week 52 by 16 (19.8%) patients in Group 1, 18 (25.0%) patients in Group 2, and 18 (24.3%) patients in Group 3 (Table 1). Among these patients, 11 in Group 1, 13 in Group 2, and 10 in Group 3 maintained comprehensive remission at week 104 (data not shown). No significant correlations were observed between clinical response at week 12 and response at week 104 (data not shown).

At week 24, patients randomized to Groups 2 and 3 had greater mean improvements from baseline in HAQ-DI score when compared with those in Group 1, and greater proportions of these patients had an improvement in HAQ-DI score of at least

Table 1. Clinical efficacy results at weeks 52, 104, and 156.

	Placebo + MTX → Golimumab 50 mg + MTX (Group 1)	Golimumab 50 mg + MTX (Group 2)	Golimumab 100 mg + MTX (Group 3)
Patients, *n*			
Week 52*	81	72	74
Week 104	70	67	71
Week 156	34	34	38
ACR20			
Week 52	55 (67.9)	62 (86.1)	61 (82.4)
Week 104	61 (87.1)	63 (94.0)	63 (88.7)
Week 156	33 (97.1)	32 (94.1)	34 (89.5)
ACR50			
Week 52	41 (50.6)	48 (66.7)	45 (60.8)
Week 104	52 (74.3)	49 (73.1)	47 (66.2)
Week 156	27 (79.4)	30 (88.2)	31 (81.6)
ACR70			
Week 52	25 (30.9)	26 (36.1)	25 (33.8)
Week 104	31 (44.3)	33 (49.3)	30 (42.3)
Week 156	21 (61.8)	23 (67.6)	22 (57.9)
ACR-N			
Week 52	45.0 ± 32.3	57.3 ± 28.9	53.2 ± 29.0
Week 104	61.6 ± 30.0	63.2 ± 27.2	59.8 ± 26.8
Week 156	71.6 ± 27.9	70.5 ± 23.5	68.7 ± 27.1
Change from baseline in DAS28-ESR			
Week 52	−2.2 ± 1.3	−2.5 ± 1.1	−2.4 ± 1.1
Week 104	−2.7 ± 1.2	−2.7 ± 1.1	−2.6 ± 1.3
Week 156	−3.1 ± 1.1	−3.0 ± 1.0	−3.1 ± 1.1
DAS28-ESR moderate response			
Week 52	71 (87.7)	70 (97.2)	69 (93.2)
Week 104	66 (94.3)	64 (95.5)	66 (93.0)
Week 156	34 (100.0)	34 (100.0)	38 (100.0)
DAS28-ESR good response			
Week 52	41 (50.6)	38 (52.8)	37 (50.0)
Week 104	49 (70.0)	45 (67.2)	47 (66.2)
Week 156	24 (70.6)	23 (67.6)	29 (76.3)
DAS28-ESR remission (<2.6)			
Week 52	28 (34.6)	32 (44.4)	24 (32.4)
Week 104	31 (44.3)	33 (49.3)	28 (39.4)
Week 156	19 (55.9)	21 (61.8)	21 (55.3)
Improvement from baseline in HAQ-DI			
Week 52	0.37 ± 0.54	0.45 ± 0.46	0.53 ± 0.49
Week 104	0.46 ± 0.57	0.54 ± 0.51	0.58 ± 0.51
Week 156	0.54 ± 0.56	0.75 ± 0.53	0.71 ± 0.52
Patients with HAQ-DI improvement ≥0.25, *n* (%)			
Week 52	50 (61.7)	48 (66.7)	51 (68.9)
Week 104	47 (67.1)	50 (74.6)	55 (77.5)
Week 156	25 (73.5)	29 (85.3)	31 (81.6)
Comprehensive remission†			
Week 52	16 (19.8)	18 (25.0)	18 (24.3)
Week 104	14 (20.0)	19 (28.4)	14 (19.7)
Week 156	8 (23.5)	12 (35.3)	11 (28.9)

ACR-N, ACR Index of Improvement; DAS28-ESR, 28-joint count Disease Activity Score using erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; MTX, methotrexate.
Data are presented as mean ± standard deviation or *n* (%), unless otherwise noted, using observed data without imputation.
*Two patients in Group 1 discontinued the study at week 52; however, these patients had efficacy data available for this time point and were included in the week-52 efficacy analyses.
†DAS28-ESR < 2.6, HAQ-DI <0.5, and change in van der Heijde-modified Sharp score (vdH-S) ≤ 0. ACR20/50/70, ≥ 20%/50%/70% improvement in the American College of Rheumatology criteria.

0.25 [11]. Physical function continued to improve in all three groups after week 24 when all patients were receiving golimumab plus MTX, and these improvements were maintained through weeks 52, 104, and 156 (Table 1).

The mean changes from baseline in total vdH-S score in Groups 1, 2, and 3 at weeks 52, 104, and 156 are shown in Table 2. These changes appeared to be smaller in Groups 2 (1.6) and 3 (0.6) than in Group 1 (2.0) at week 52; although no statistical testing between treatment groups was conducted at this time point. The mean changes for Groups 1, 2, and 3 were 1.5, 2.3, and 1.6, respectively, at week 104 and −0.2, 4.1, and 1.7, respectively, at week 156. The median change from baseline in all three groups was 0 at weeks 52, 104, and 156, indicating that half of all patients had minimal radiographic progression. The proportions of patients in each treatment group who had a change from baseline in total vdH-S score greater than the SDC ranged from 9.6% to 17.9% at week 52, from 10.1% to 16.4% at week 104, and from 9.1% to 20.6% at week 156 (Table 2), with numerically greater proportions observed in Groups 2 and 3 when compared with Group 1 at weeks 104 and 156. Similar trends among the treatment groups were seen for changes in total vdH-S score from week 52 to week 104 and from week 104 to week 156 (Table 2).

An exploratory analysis showed that patients with clinically relevant radiographic progression (i.e., a change in total vdH-

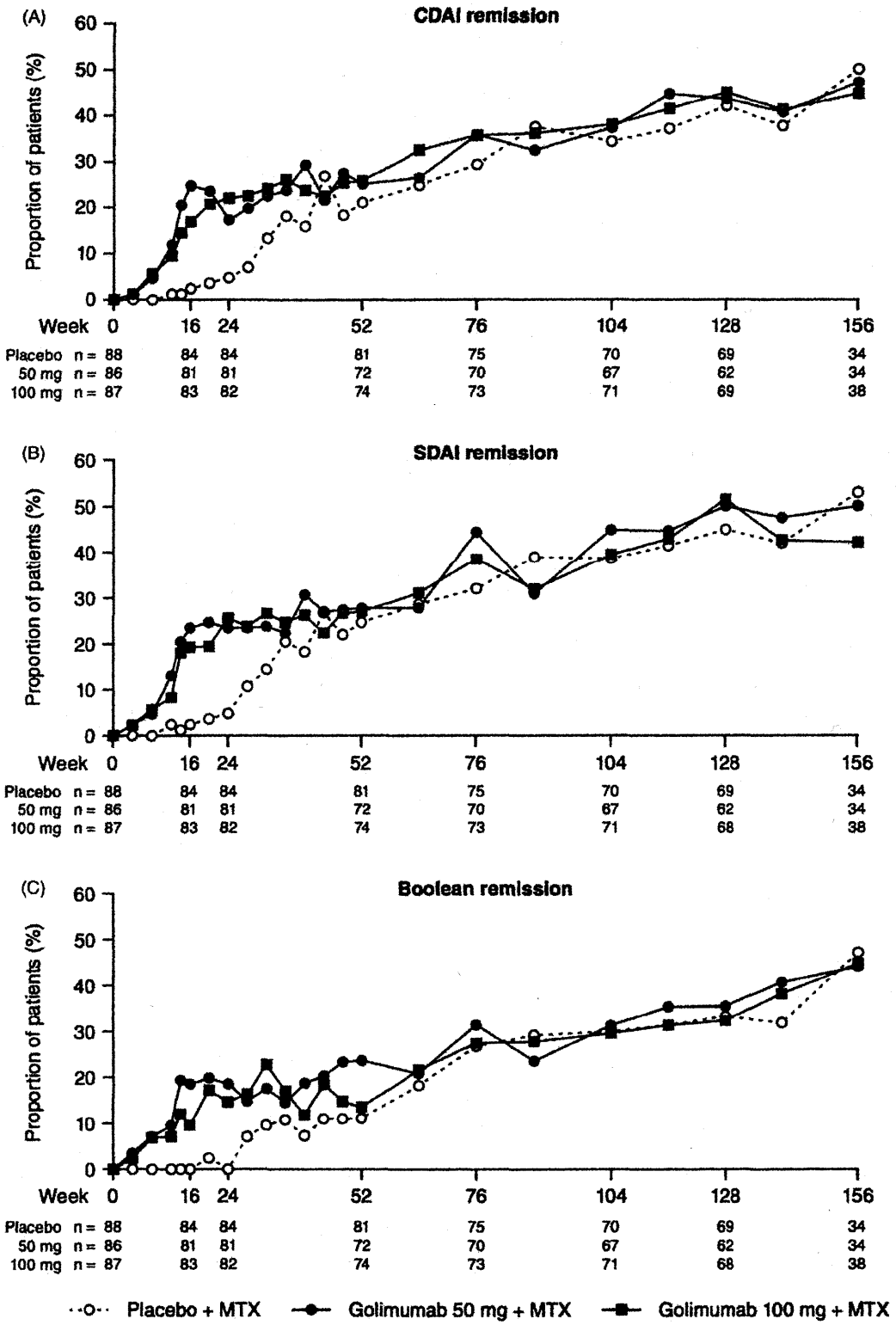

Figure 3. The proportions of patients* with remission as defined by the CDAI (A), SDAI (B), and Boolean (C) criteria through week 156. *Observed data without imputation. CDAI, clinical disease activity index; MTX, methotrexate; SDAI, simplified disease activity index.

S ≥ 3) from baseline to week 104 generally had higher disease activity and a higher annual rate of radiographic progression at baseline when compared with patients who had a change in total vdH-S < 3 (Supplemental Table S1).

Table 2. Radiographic results through 156 weeks.

	Placebo + MTX → Golimumab 50 mg + MTX (Group 1)	Golimumab + MTX	
		Golimumab 50 mg + MTX (Group 2)	Golimumab 100 mg + MTX (Group 3)
Patients, *n*			
Week 52	78	72	73
Week 104	69	67	71
Week 156	33	34	38
Change from baseline in total vdH-S score			
Total			
Week 52	2.0 ± 8.7 [0.0]	1.6 ± 7.4 [0.0]	0.6 ± 6.0 [0.0]
Week 104	1.5 ± 12.0 [0.0]	2.3 ± 10.0 [0.0]	1.6 ± 7.2 [0.0]
Week 156	−0.2 ± 8.1 [0.0]	4.1 ± 13.4 [0.0]	1.7 ± 5.9 [0.0]
Patients with change from baseline in total vdH-S score > SDC*	14 (17.9)	10 (13.9)	7 (9.6)
Week 52	7 (10.1)	11 (16.4)	9 (12.7)
Week 104	3 (9.1)	7 (20.6)	6 (15.8)
Week 156			
Patients with change from week 52 to week 104 in total vdH-S score > SDC†	1/69 (1.4)	9/67 (13.4)	12/71 (16.9)
Patients with change from week 104 to week 156 in total vdH-S score > SDC‡	0/33 (0.0)	1/34 (2.9)	2/38 (5.3)

Data are presented as mean ± standard deviation [median] or *n* (%) using observed data without imputation. MTX, methotrexate; SDC, smallest detectable change; vdH-S score, van der Heijde modification of the Sharp score.
*SDC at week 52 = 4.31, SDC at week 104 = 5.54, SDC at week 156 = 5.63.
†SDC = 2.87.
‡SDC = 2.83.

Table 3. Adverse events through 156 weeks.

	Placebo + MTX (Weeks 0–24)	Golimumab + MTX	
		Golimumab 50 mg + MTX	Golimumab 100 mg + MTX
Patients, *n*	88	170	96
Mean duration of follow-up, weeks	20.8	116.0	127.1
Patients with ≥ 1 AE, *n* (%)	67 (76.1)	163 (95.9)	95 (99.0)
Incidence per 100-patient years (95% CI)	591.9 (510.3, 682.8)	382.3 (362.7, 402.8)	376.5 (351.9, 402.5)
Patients who discontinued due to AEs, *n* (%)	1 (1.1)	25 (14.7)	18 (18.8)
Common AEs			
Nasopharyngitis	22 (25.0)	82 (48.2)	50 (52.1)
Pharyngitis	3 (3.4)	26 (15.3)	18 (18.8)
Gastroenteritis	4 (4.5)	11 (6.5)	10 (10.4)
Bronchitis	2 (2.3)	16 (9.4)	6 (6.3)
Infections and infestations	39 (44.3)	128 (75.3)	73 (76.0)
Tuberculosis	0 (0)	0 (0)	0 (0)
Pneumonia	1 (1.1)	3 (1.8)	3 (3.1)
Anaphylactic reactions or serum sickness	0 (0)	0 (0)	0 (0)
Patients with ≥ 1 SAE, *n* (%)	2 (2.3)	36 (21.2)	19 (19.8)
Incidence per 100 patient-years (95% CI)	5.7 (0.7, 20.7)	11.5 (8.2, 15.5)	11.4 (7.4, 16.7)
Serious infections, *n* (%)	0 (0)	12 (7.1)	7 (7.3)
Incidence per 100 patient-years (95% CI)	0 (0.0, 8.5)	3.2 (1.7, 5.6)	3.0 (1.2, 6.2)
Malignancies	0 (0)	5 (2.9)	1 (1.0)
Patients with ≥ 1 injection site reaction, *n* (%)	7 (8.0)	30 (17.6)	24 (25.0)

AE, adverse event; CI, confidence interval; MTX, methotrexate; SAE, serious adverse event.

Safety

Adverse events among patients receiving placebo plus MTX (up to week 24) have been previously reported in detail [11]. A total of 257 patients received at least one administration of golimumab through week 156. Through weeks 52 and 104, 89.1% (*n* = 229/257) and 96.9% (*n* = 249/257) of golimumab-treated patients had at least one AE, and 52.1 and 69.3%, respectively, had an AE in the system organ class (SOC) of infections and infestations. The cumulative proportion of patients with at least one AE through week 156 was 95.9% among patients who received the 50-mg dose and 99.0% among those receiving the 100-mg dose (Table 3). The most commonly reported AEs among golimumab-treated patients were in the SOC of infections and infestations (Table 3). The most common infections among golimumab-treated patients were nasopharyngitis (50 mg, *n* = 82 [48.2%]; 100 mg, *n* = 50 [52.1%]) and pharyngitis (50 mg, *n* = 26 [15.3%]; 100 mg, *n* = 18 [18.8%]).

The cumulative proportions of patients with at least one serious AE (SAE) through week 156 were similar for the two golimumab doses (50 mg, *n* = 36 [21.2%]; 100 mg, *n* = 19 [19.8%]; all golimumab plus MTX, *n* = 54 [21.0%]). There was no significant difference in the adjusted incidence of SAEs per 100 patient-years

for the two golimumab doses (Table 3). Serious infections were reported by 12 (7.1%) and 7 (7.3%) patients receiving golimumab 50 and 100 mg, respectively, with the most common being gastroenteritis (50 mg, $n=2$), herpes zoster (100 mg, $n=2$), and pneumonia (100 mg, $n=2$). There were no cases of tuberculosis.

Six malignancies in six patients were reported. Uterine cancer ($n=1$), extranodal marginal zone B-cell lymphoma ($n=1$), testicular neoplasm ($n=1$), diffuse large B-cell lymphoma ($n=1$), and colon cancer ($n=1$) occurred in patients receiving golimumab 50 mg, and one case of breast cancer was reported in a patient receiving golimumab 100 mg. One death occurred during the trial (community-acquired pneumonia and amyloidosis) in a patient receiving golimumab 100 mg plus MTX.

Injection site reactions were reported by seven (8.0%) patients receiving placebo plus MTX and 54 (21.0%) patients receiving golimumab plus MTX (50 mg, $n=30$ [17.6%]; 100 mg, $n=24$ [25.0%]). The most common injection site reaction was erythema (placebo, $n=4$ [4.5%]; 50 mg, $n=19$ [11.2%]; 100 mg, $n=20$ [20.8]). All injection site reactions were considered to be mild, and no patient discontinued the study agent due to an injection site reaction. No anaphylactic reactions or serum sickness-like reactions occurred throughout the trial.

Immunogenicity

A total of 257 patients received at least one administration of golimumab and had at least one post-golimumab treatment serum sample for the analysis of antibodies to golimumab. Two (0.8%) patients (Group 1, $n=1$; Group 3, $n=1$) tested positive for antibodies to golimumab; both patients had an antibody titer of 1:20.

Discussion

Through 24 weeks of the GO-FORTH trial, Japanese patients with active RA despite prior MTX therapy had significantly greater improvements in the signs and symptoms of RA when treated with golimumab 50 mg or 100 mg plus MTX compared with MTX monotherapy [11]. These improvements were maintained through weeks 52, 104, and 156, the final efficacy evaluation. At week 104, 94% of patients in Group 2 and 89% of patients in Group 3 had an ACR20 response; these rates were further maintained at week 156. Through 3 years, response rates for ACR and DAS28-ESR outcomes and improvements in physical function in Group 2 were generally comparable to or slightly higher than those in Group 3.

Golimumab plus MTX-treated patients also had less radiographic progression through 24 weeks when compared with those receiving MTX monotherapy [11]. Throughout the trial, radiographic progression was inhibited in all treatment groups, with a median change from baseline in total vdH-S score of 0 at weeks 52, 104, and 156. Mean increases in vdH-S scores tended to be smaller in Group 3 than in Group 2; however, no formal statistical comparisons were performed between the two golimumab dose groups. In addition, most patients did not experience progression when assessed using the SDC from baseline to weeks 52, 104, and 156, from week 52 to week 104, or from week 104 to week 156.

At week 52, the proportion of patients with an increase from baseline in vdH-S score that was greater than the SDC was numerically lower among patients who had received golimumab from week 0 (Groups 2 and 3) than in patients initially randomized to placebo (Group 1); however, this trend was reversed at week 104. Although the proportion of patients with radiographic progression greater than the SDC appeared to increase from week 52 to week 104 in Groups 2 and 3, and was numerically greater than that observed in Group 1, the actual number of patients in Groups 2 and 3 who were classified as progressors remained stable during this time period. In contrast, the proportion of patients in Group 1 with progression from baseline greater than the SDC decreased from 17.9% at week 52 to 10.1% at week 104, suggesting that the inhibition of radiographic progression in Group 1 patients was continuing to stabilize following early escape/crossover from placebo plus MTX to golimumab plus MTX. In an exploratory analysis, patients with higher levels of disease activity and radiographic progression at baseline generally had more radiographic progression at week 104 than did patients with less active disease at baseline. This is consistent with a previous analysis of progressors and non-progressors [20] and further supports the concept that earlier treatment of RA may result in prevention of long-term radiographic damage [7].

Adverse events reported during the trial were consistent with those of the known safety profile of golimumab [21–23]. Of the 257 patients included in the safety analysis, 97.7% reported an AE through week 156, the majority of which were considered to be mild, and no disproportionate increase in the cumulative incidence of AEs was observed over time among golimumab-treated patients. Infections were the most commonly reported AE, with nasopharyngitis being the most common. All injection site reactions were considered mild, and none led to discontinuation from treatment. There were no cases of anaphylactic reactions, or serum sickness-like reactions. Approximately 7% of golimumab-treated patients had a serious infection through week 156, which was similar to the cumulative rates reported through 2 years of the global GO-BEFORE [21] and GO-FORWARD [23] golimumab trials and that observed through 3 years in a pooled analysis of golimumab-treated patients with RA, ankylosing spondylitis, and psoriatic arthritis in five phase 3 trials [22]. There were no cases of tuberculosis during the trial. Approximately 21% of golimumab-treated patients experienced at least one SAE through week 156, which was generally consistent with previous studies of golimumab in patients with rheumatic diseases [22]. There was no significant difference between the two golimumab doses in the incidence of SAEs per 100 patient-years. Six malignancies were reported, including breast cancer, colon cancer, extranodal marginal zone B-cell lymphoma, and diffuse large B-cell lymphoma. The observed incidence of malignancies in golimumab-treated patients through 3 years was comparable to that observed in a pooled analysis of golimumab-treated patients with rheumatologic diseases [22]. One death occurred (community-acquired pneumonia and amyloidosis) in a patient receiving golimumab 100 mg plus MTX.

As in other studies, the long-term results of the GO-FORTH study are limited by selection bias over time and the lack of a control group, and the use of observed data may overestimate the proportion of patients in response over time. In addition, changes to golimumab dose after week 52 and the small number of patients with available data at week 156 limit the interpretation of the results. As previously noted [11], although the MTX dose used in the trial was consistent with the approved dose of MTX in Japan at the time the trial was planned, this dose was generally lower than doses commonly used for RA in other regions. No unexpected safety events were observed; however, this study was not powered to detect rare safety events.

In conclusion, the results demonstrate that treatment with golimumab 50 or 100 mg in combination with MTX provided sustained efficacy with no unexpected safety findings through 3 years of therapy in MTX-experienced Japanese patients with active RA.

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Conflicts of interest

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ORIGINAL RESEARCH

Effect of Methotrexate Plus Adalimumab on the Achievement of Rheumatoid Arthritis Therapeutic Goals: Post Hoc Analysis of Japanese Patients (MELODY Study)

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ABSTRACT

Introduction: There is insufficient evidence regarding the appropriate dose of methotrexate (MTX) required to achieve specific treatment goals in patients with rheumatoid arthritis (RA) receiving biologic drugs in Japan. The present study aimed to assess the dose–response effect of MTX in combination with adalimumab (ADA) to achieve low disease activity (LDA) and/or remission at 24 weeks in RA patients.

Methods: This analysis used data of the ADA all-case survey in Japan ($n = 7740$), and 5494 patients who received ADA and MTX were classified into five groups by weighted average MTX dose (>0–<4, 4–<6, 6–<8, 8–< 10, and ≥10 mg/week). Of the 5494 patients, 3097 with baseline 28-joint disease activity score based on erythrocyte sedimentation rate >3.2 were analyzed for effectiveness by MTX dose.

Results: In biologic-naïve patients ($n = 1996$/3097), LDA/remission rates increased with MTX up to 6–<8 mg/week and then plateaued at

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higher doses (LDA, $p = 0.0440$; remission, $p = 0.0422$). In biologic-exposed patients ($n = 1101/3097$), LDA/remission rates increased with MTX dose (LDA, $p = 0.0009$; remission $p = 0.0143$). The incidences of serious adverse drug reactions (ADRs) and serious infections did not differ by MTX dose, but total ADRs and infections were significantly higher ($p < 0.05$) with increased MTX doses.

Conclusion: The appropriate MTX doses in combination with ADA to achieve LDA and/or remission at week 24 were different between biologic-naïve and biologic-exposed patients with RA, suggesting that 8 mg/week of MTX would be enough for biologic-naïve patients.

Trial Registration: ClinicalTrials.gov identifier, NCT01076959.

Funding: AbbVie and Eisai Co., Ltd.

Keywords: Adalimumab; Doses; Effectiveness; Methotrexate; Rheumatoid arthritis; Safety

INTRODUCTION

Adalimumab (ADA; Humira®, AbbVie Inc., North Chicago, IL, USA), a fully human monoclonal antibody to tumor necrosis factor-α, was approved in Japan in 2008 for the treatment of rheumatoid arthritis (RA) [1–4]. The safety and effectiveness of ADA has been confirmed with the results of an all-case postmarketing surveillance study that enrolled 7740 Japanese patients with RA (ClinicalTrials.gov identifier, NCT01076959) [5, 6]. Methotrexate (MTX) was approved in Japan in 1999 for the treatment of RA at the dose of ≤8 mg/week, and higher doses up to 16 mg/week, which is lower than the maximum weekly dose in Western countries, were additionally approved in 2011 [7]. Clinical studies conducted in and outside of Japan have shown that the combination of ADA and MTX is more effective than monotherapy with either drug [8–12]. In fact, the 2013 updates of the EULAR recommendations for the management of RA with synthetic and biological disease-modifying antirheumatic drugs describe that biological disease-modifying antirheumatic drugs (DMARDs) should be used preferentially in combination with MTX or other conventional synthetic DMARDs [8]. However, evidence is lacking in terms of the optimal dose of MTX used in combination with TNF inhibitors. While the CONCERTO trial (ClinicalTrials.gov identifier, NCT01185301) [11] has described the dose–response profile of MTX in bio-naïve patients with early stage RA, no studies have reported the corresponding data in patients with established RA in the clinical setting. In the present (MELODY) study, we conducted an analysis of data from the all-case postmarketing surveillance of ADA in 7740 Japanese patients with RA [6] by stratifying patients according to the clinical MTX dosages used in order to evaluate the effects of MTX dose in patients receiving ADA. Patients were classified as biologic-naïve and biologic-exposed patients, and the effects of MTX dose on the rates of achievement of low disease activity (LDA) and remission as determined by 28-joint Disease Activity Score (DAS28) as efficacy measures were analyzed using the maximum-contrast method [13].

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METHODS

In the MELODY study, we conducted secondary analyses of central registry data from an all-case postmarketing surveillance study with follow-up periods of 24 weeks for efficacy and 28 weeks for safety [6]. These analyses had been requested by the Ministry of Health, Labour and Welfare of Japan (MHLW) as a condition for approval of ADA, in accordance with the Pharmaceutical Affairs Law of Japan, and were conducted in compliance with the Good Post-marketing Study Practice (Ordinance No. 171 of the MHLW dated December 20, 2004). In this all-case study, as 2241 patients (2241/7740 patients, 29%) did not use MTX concomitantly with ADA (five patients with unknown MTX dose), we excluded the data from these patients receiving ADA monotherapy to investigate the dose response profile of MTX in 5494 patients with established RA in the clinical setting. The dose of MTX used concomitantly with ADA was calculated as the weighted average adjusted for the duration of ADA therapy during the follow-up period. Patients were classified into the following five groups according to the average weekly dose of concomitant MTX: group 1, >0–<4 mg; group 2, 4–<6 mg; group 3, 6–<8 mg; group 4, 8–<10 mg; and group 5, ≥10 mg.

Among the 5494 patients who received ADA and MTX, 3097 patients who had a baseline DAS28 based on erythrocyte sedimentation rate (DAS28-ESR) of >3.2 were included in the efficacy analysis set. Low disease activity was defined as a DAS28-ESR of ≤3.2, and remission as a DAS28-ESR of <2.6. Missing DAS28-ESR data were imputed by the last observation carried forward (LOCF) method.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation and categorical variables as numbers and ratios (%). The relationships between patient background factors and groups were assessed using the Chi-square test for categorical data and the Kruskal–Wallis test for continuous data. To identify factors relevant to the dose–response profile of MTX, univariate logistic regression analysis was performed using the effectiveness analysis set ($n = 3097$) on the factors listed below (step 1), and factors with $p < 0.05$ were included in the multivariate logistic analysis (step 2). Contrast analysis of the relationship between MTX dose and effectiveness was performed by multivariate logistic regression modeling, including variables selected as factors affecting LDA achievement by week 24 (LOCF method; step 3). The data were adjusted for essential variables, including interactions. In the selected model ($n = 3097$; Akaike's information criterion, 3587.7), a maximum-contrast test [13] in each population was performed to establish the dose–response profile of MTX, adjusting for essential variables. To simplify the dose–response profile of MTX, the effectiveness analysis set was divided into biologic-naïve and biologic-exposed patients. Prior biologic treatment was determined to be a significant factor ($p < 0.0001$) in the multivariate logistic analysis.

Safety Evaluation

For safety evaluation, all adverse events (AEs) were recorded and tabulated based on preferred terms from the Medical Dictionary for Regulatory Activities, version 14.0 [14]. The

Table 1 Baseline characteristics of biologic-naïve RA patients stratified by weekly dose of concomitant MTX ($n = 1996$)

	Group 1 ($n = 97$)	Group 2 ($n = 284$)	Group 3 ($n = 580$)	Group 4 ($n = 819$)	Group 5 ($n = 216$)	p[a]
Sex, females (%)	79 (81.4)	246 (86.6)	492 (84.8)	685 (83.6)	161 (74.5)	0.0038
Age (y)	61.1 ± 13.9	63.3 ± 11.4	60.9 ± 12.5	57.6 ± 13.1	56.4 ± 13.3	<0.0001
Duration of RA (y)	12.5 ± 11.1	11.1 ± 10.4	9.9 ± 10.4	8.3 ± 8.7	7.7 ± 8.6	<0.0001
DAS28-ESR score	5.3 ± 1.3	5.4 ± 1.1	5.3 ± 1.1	5.3 ± 1.0	5.2 ± 1.1	0.2059
Comorbidities	64 (66.0)	162 (57.0)	329 (56.7)	474 (57.9)	135 (62.5)	0.3130
Cardiovascular	26 (26.8)	61 (21.5)	119 (20.5)	153 (18.7)	47 (21.8)	0.3547
Respiratory	12 (12.4)	23 (8.1)	41 (7.1)	75 (9.2)	35 (16.2)	0.0018
Hematologic	5 (5.2)	20 (7.0)	33 (5.7)	46 (5.6)	16 (7.4)	0.7839
Hepatic	9 (9.3)	20 (7.0)	40 (6.9)	34 (4.2)	14 (6.5)	0.0784
Renal	4 (4.1)	4 (1.4)	1 (0.2)	9 (1.1)	3 (1.4)	0.0083
Others	49 (50.5)	124 (43.7)	254 (43.8)	367 (44.8)	104 (48.1)	0.6240
Diabetes mellitus	9 (9.3)	15 (5.3)	44 (7.6)	6.2 (7.6)	13 (6.0)	0.5663
Pulmonary disease history or comorbidity[b]	15 (15.5)	29 (10.2)	53 (9.1)	101 (12.3)	39 (18.1)	0.0068
History of allergies	15 (15.5)	31 (10.9)	62 (10.7)	100 (12.2)	28 (13.0)	0.5719
Steinbrocker stage						
I	10 (10.3)	26 (9.2)	87 (15.0)	142 (17.3)	36 (16.7)	0.0005
II	21 (21.6)	89 (31.3)	162 (27.9)	228 (27.8)	78 (36.1)	
III	23 (23.7)	75 (26.4)	159 (27.4)	236 (28.8)	51 (23.6)	
IV	43 (44.3)	94 (33.1)	172 (29.7)	213 (26.0)	51 (23.6)	
Steinbrocker class						
I	12 (12.4)	41 (14.4)	90 (15.5)	126 (15.4)	25 (11.6)	0.0002
II	60 (61.9)	162 (57.0)	361 (62.2)	535 (65.3)	160 (74.1)	
III	19 (19.6)	75 (26.4)	118 (20.3)	150 (18.3)	30 (13.9)	
IV	6 (6.2)	6 (2.1)	11 (1.9)	8 (1.0)	1 (0.5)	
Previous biologic therapy						
None (biologic-naïve)	97 (100.0)	284 (100.0)	580 (100.0)	819 (100.0)	216 (100.0)	NR
Infliximab only	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Etanercept only	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Infliximab and etanercept	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Others	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	

Table 1 continued

	Group 1 ($n = 97$)	Group 2 ($n = 284$)	Group 3 ($n = 580$)	Group 4 ($n = 819$)	Group 5 ($n = 216$)	p^a
Other prior medication						
GCs > 5 mg/day	14 (14.4)	33 (11.6)	73 (12.6)	113 (13.8)	35 (16.2)	0.7226
GCs > 7.5 mg/day	7 (7.2)	14 (4.9)	28 (4.8)	50 (6.1)	19 (8.8)	0.4541
DMARDs (excluding MTX)	35 (36.1)	94 (33.1)	147 (25.3)	195 (23.8)	50 (23.1)	0.0036

Group 1, >0–<4 mg; group 2, ≥4–<6 mg; group 3, ≥6–<8 mg; group 4, ≥8–<10 mg; group 5, ≥10 mg/week. Values are means ± SD or *n* (%). [a]Chi-square test for categorical variables, Kruskal–Wallis test for continuous variables. [b]Includes patients with a past or current history of pulmonary disease (e.g., pneumonia, asthma, and obstructive pulmonary disease) and those with abnormal chest radiographic findings. A weighted average dose was used to calculate mean MTX dose. *DAS28-ESR* disease activity score for 28 joints based on the erythrocyte sedimentation rate, *DMARDs* disease-modifying antirheumatic drugs, *GCs* glucocorticoids, *MTX* methotrexate, *NR* not reported, *RA* rheumatoid arthritis

safety endpoints were the incidences of adverse drug reactions (ADRs) for which a causal relationship with ADA could not be ruled out, serious ADRs, infections, and serious infections. The safety analysis for the MELODY study was performed with 5494 of the 7740 patients registered in the all-case postmarketing surveillance study [6]: specifically, all patients except the 2241 patients who did not use MTX concomitantly with ADA and the five patients for whom the MTX dosage was unspecified. The safety endpoints were the incidences of ADRs, serious ADRs, infections, and serious infections. Multiplicity was not considered in the contrast test and Cox regression analysis, as this study was an explanatory study. All tests were two-sided and $p < 0.05$ was defined as significant, except for interactions ($p < 0.10$). All statistical analyses were performed with SAS 9.3 (SAS Institute, Cary, NC, USA). This article does not contain any new studies with human subjects performed by any of the authors.

RESULTS

In this post hoc analysis of the all-case survey with ADA, patients were stratified only by previous use of biologics to assess the effect of MTX dose on patients receiving ADA after the following analysis: In the selected model ($n = 3097$; Akaike's information criterion, 3587.7), the essential variables were previous use of biologics ($p < 0.0001$), baseline DAS28-ESR ($p < 0.0001$), age ($p = 0.0013$), Steinbrocker class ($p = 0.0004$), diabetes mellitus ($p = 0.0206$), sex ($p = 0.0068$), group ($p = 0.0280$), and interaction between age and diabetes mellitus ($p = 0.0558$) (Data on file, AbbVie GK, Tokyo, Japan). Although both previous use of biologics and baseline DAS28-ESR showed a highly significant effect on the dose–response profile of MTX, baseline DAS28-ESR did not differ by MTX dose.

In the 1996 biologic-naïve patients, there were significant differences among the five MTX dose groups with respect to sex, age, disease duration, renal comorbidities, and percentages in each Steinbrocker stage at baseline. In the 1101 biologic-exposed patients, there were significant differences among the five MTX dose groups with respect to respiratory comorbidities, pulmonary disease history or comorbidity, and percentages in each Steinbrocker class (Tables 1, 2). Mean

Table 2 Baseline characteristics of biologic-exposed RA patients stratified by weekly dose of concomitant MTX ($n = 1101$)

	Group 1 ($n = 84$)	Group 2 ($n = 175$)	Group 3 ($n = 349$)	Group 4 ($n = 369$)	Group 5 ($n = 124$)	p[a]
Sex, females (%)	76 (90.5)	149 (85.1)	304 (87.1)	317 (85.9)	101 (81.5)	0.4066
Age (y)	61.3 ± 11.3	61.1 ± 12.7	59.6 ± 11.9	56.8 ± 12.8	53.4 ± 13.5	<0.0001
Duration of RA (y)	13.9 ± 9.8	12.0 ± 9.4	11.9 ± 9.5	10.6 ± 8.3	8.8 ± 7.5	0.0004
DAS28-ESR score	5.4 ± 1.1	5.4 ± 1.1	5.3 ± 1.1	5.3 ± 1.1	5.4 ± 1.1	0.8663
Comorbidities	54 (64.3)	122 (69.7)	216 (61.9)	225 (61.0)	68 (54.8)	0.1132
Cardiovascular	12 (14.3)	52 (29.7)	71 (20.3)	76 (20.6)	18 (14.5)	0.0086
Respiratory	8 (9.5)	20 (11.4)	30 (8.6)	34 (9.2)	12 (9.7)	0.8894
Hematologic	6 (7.1)	16 (9.1)	33 (9.5)	33 (8.9)	11 (8.9)	0.9781
Hepatic	4 (4.8)	12 (6.9)	18 (5.2)	18 (4.9)	8 (6.5)	0.8642
Renal	5 (6.0)	7 (4.0)	3 (0.9)	5 (1.4)	0 (0.0)	0.0017
Others	45 (53.6)	105 (60.0)	174 (49.9)	187 (50.7)	55 (44.4)	0.0841
Diabetes mellitus	5 (6.0)	17 (9.7)	29 (8.3)	27 (7.3)	11 (8.9)	0.8161
Pulmonary disease history or comorbidity[b]	14 (16.7)	26 (14.9)	39 (11.2)	39 (10.6)	15 (12.1)	0.4064
History of allergies	19 (22.6)	33 (18.9)	69 (19.8)	70 (19.0)	21 (16.9)	0.9103
Steinbrocker stage						
I	6 (7.1)	7 (4.0)	15 (4.3)	32 (8.7)	16 (12.9)	0.0058
II	11 (13.1)	46 (26.3)	81 (23.2)	83 (22.5)	32 (25.8)	
III	24 (28.6)	52 (29.7)	113 (32.4)	121 (32.8)	42 (33.9)	
IV	43 (51.2)	70 (40.0)	140 (40.1)	133 (36.0)	34 (27.4)	
Steinbrocker class						
I	6 (7.1)	8 (4.6)	33 (9.5)	43 (11.7)	12 (9.7)	0.3818
II	50 (59.5)	112 (64.0)	214 (61.3)	231 (62.6)	80 (64.5)	
III	26 (31.0)	48 (27.4)	95 (27.2)	87 (23.6)	31 (25.0)	
IV	2 (2.4)	7 (4.0)	7 (2.0)	8 (2.2)	1 (0.8)	
Previous biologic therapy						
None (biologic-naïve)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Infliximab only	17 (20.2)	51 (29.1)	142 (40.7)	151 (40.9)	65 (52.4)	<0.0001
Etanercept only	41 (48.8)	80 (45.7)	126 (36.1)	131 (35.5)	28 (22.6)	
Infliximab and etanercept	9 (10.7)	17 (9.7)	51 (14.6)	50 (13.6)	19 (15.3)	
Any others	17 (20.2)	27 (15.4)	30 (8.6)	37 (10.0)	12 (9.7)	