registry of patients treated with etanercept and other RA therapies in the United States ($N = 10,061$ in 2 cohorts) [26, 27]. Although safety data have not yet been reported, patients treated with etanercept, with ($p < 0.01$) or without ($p < 0.05$) methotrexate, were significantly more likely to have a modified ACR 20% response at 12 months compared with those receiving only methotrexate. In another PMS study involving TNF-α antagonists, Feltelius et al. [23] collected safety and effectiveness data from 1999 to 2003 in the cohort of all etanercept-treated Swedish patients with RA ($N = 1073$). The 24-month incidence rates of ADRs and SAEs of 27 and 7%, respectively, in that study are both similar to those observed in the current PMS study. A good or moderate EULAR response rate was observed in 86% of 517 patients, which is similar to the rate reported in our analysis (84.3%) at week 24.

Because the registered patients in the current PMS study had varied backgrounds, multivariate analyses were conducted to ascertain risk factors related to safety and effectiveness in a real-world setting. The current PMS study identified several factors that improved the safety and effectiveness outcomes of patients treated with etanercept. Patients were more likely to achieve DAS28 remission if they had moderate disease activity, better Steinbrocker functional class, shorter disease duration, and received concomitant methotrexate treatment. Importantly, patients who had a combination of these factors showed a higher probability of achieving remission.

Cox proportional hazard model results also demonstrated several risk factors for serious infection. A combination of Steinbrocker functional class 4, no use of concomitant methotrexate, and the presence of any comorbidities significantly increased the risk for developing serious infection. Thus, the combined use of etanercept and methotrexate in patients with early moderate RA with less comorbidity and better physical function appears to provide patient benefit for the achievement of remission and lowering of SAE occurrences.

Interpretation of these data is somewhat limited by the fact that no control arm was included in this large PMS study. This makes it difficult to distinguish outcomes relating to etanercept treatment from those caused by other factors (e.g., patient expectations, natural history of the disease, or concomitant treatments). The study length (6 months) allowed for the collection of important safety and effectiveness data, but longer-term studies would also be useful. Additionally, evaluations of effectiveness did not include radiographic analysis to confirm the effectiveness of treatment.

This PMS study collected safety and effectiveness data for every Japanese patient with RA receiving etanercept at the participating study sites for a 2-year period. With nearly 14,000 patients registered, this represents one of the largest observational surveillance studies conducted to date in RA patients treated with biologics. The safety and effectiveness data reported here support data from previous clinical trials with etanercept and are also consistent with the data from the interim analysis of this study. Additional subgroup analyses from this study may enable the identification of important factors affecting the safety and effectiveness of etanercept so that treatment decisions can be further optimized.

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Conflict of interest Doctors T. Koike, M. Harigai, S. Inokuma, N. Ishiguro, J. Ryu, T. Takeuchi, Y. Tanaka, and H. Yamanaka are all members of the Etanercept Postmarketing Surveillance Committee of the Japan College of Rheumatology. It is the belief of the first author that this position does not constitute a Conflict of Interest. The doctors participated in the review and analysis of the PMS data in their capacity as Committee members and are so listed. The financial relationships of the authors with all manufacturers of biological products used in the management of RA are as follows. #1 is a research grant to the institute to which they are affiliated, #2 is a consulting fee, #3 is membership of a speakers' bureau, #4 is a full-time employee, and #5 is a previous employee of Pfizer. T. Koike, Abbott Japan, 1; Bristol-Myers Squibb, 1; Chugai Pharmaceutical Co. Ltd, 1; Eisai Co. Ltd, 1; Mitsubishi Tanabe Pharma, 1; Takeda Pharmaceutical Co. Ltd, 1; Wyeth KK, 1; Otsuka Pharmaceutical Co. Ltd, 2; Abbott Japan, 3; Bristol-Myers Squibb, 3; Chugai Pharmaceutical Co. Ltd, 3; Eisai Co. Ltd, 3; Mitsubishi Tanabe Pharma, 3; Takeda Pharmaceutical Co. Ltd, 3; Wyeth KK, 3; M. Harigai, Abbott Japan, 1; Bristol-Myers Squibb, 1; Chugai Pharmaceutical Co. Ltd, 1; Eisai Co. Ltd, 1; Mitsubishi Tanabe Pharma, 1; Pfizer Japan Inc., 1; Takeda Pharmaceutical Co. Ltd, 1; Abbott Japan, 2; Chugai Pharmaceutical Co. Ltd, 2; Mitsubishi Tanabe Pharma, 2; Abbott Japan, 3; Bristol-Myers Squibb, 3; Chugai Pharmaceutical Co. Ltd, 3; Eisai Co. Ltd, 3; Mitsubishi Tanabe Pharma, 3; Pfizer Japan Inc., 3; Takeda Pharmaceutical Co. Ltd, 3; S. Inokuma, None; N. Ishiguro, Abbott, 1; Chugai Pharmaceutical Co. Ltd, 1; Daiichi-Sankyo Pharmaceutical Co. Ltd, 1; Eisai Co. Ltd, 1; Mitsubishi Tanabe Pharma, 1; Takeda Pharmaceutical Co. Ltd, 1; Wyeth KK, 1; Abbott, 3; Bristol-Myers Squibb, 3; Chugai Pharmaceutical Co. Ltd, 3; Daiichi-Sankyo Pharmaceutical Co. Ltd, 3; Eisai Co. Ltd, 3; Mitsubishi Tanabe Pharma, 3; Takeda Pharmaceutical Co. Ltd, 3; Wyeth KK, 3; J. Ryu, None; T. Takeuchi, Bristol-Myers Squibb, 2; Mitsubishi Tanabe Pharma, 2; Novartis, 2; Abbott, 3; Chugai Pharmaceutical Co. Ltd, 3; Eisai Pharma, 3; Mitsubishi Tanabe Pharma, 3; Takeda Pharmaceutical Co. Ltd, 3; Y. Tanaka, Abbott, 1; Astellas Pharma Inc., 1; Chugai Pharmaceutical Co. Ltd, 1; Eisai Co. Ltd, 1; Mitsubishi Tanabe Pharma, 1; MSD KK, 1; Pfizer Inc., 1; Takeda Pharmaceutical Co. Ltd, 1; Mitsubishi Tanabe Pharma, 2; Abbott, 3; Astellas Pharma Inc., 3; Chugai Pharmaceutical Co. Ltd, 3; Eisai Co. Ltd, 3; Mitsubishi

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EXTENDED REPORT

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

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

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ABSTRACT

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

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

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

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

INTRODUCTION

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

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

METHODS

Patients

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

Study design

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

Eligible patients were randomly (1:1:1) assigned to receive placebo injection + oral MTX (Group 1), golimumab 50 mg injection + oral MTX (Group 2) or golimumab 100 mg injection + oral MTX (Group 3). Golimumab and placebo were supplied as sterile liquid (Janssen Biotech Inc, Horsham, Pennsylvania, USA) for subcutaneous injection at week 0 and every 4 weeks to week 24. MTX doses were not adjusted unless dose reduction was required because of MTX toxicity.

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

Study endpoints

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

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

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

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

Statistical analyses

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

Treatment group differences in dichotomous variables were assessed with a 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).

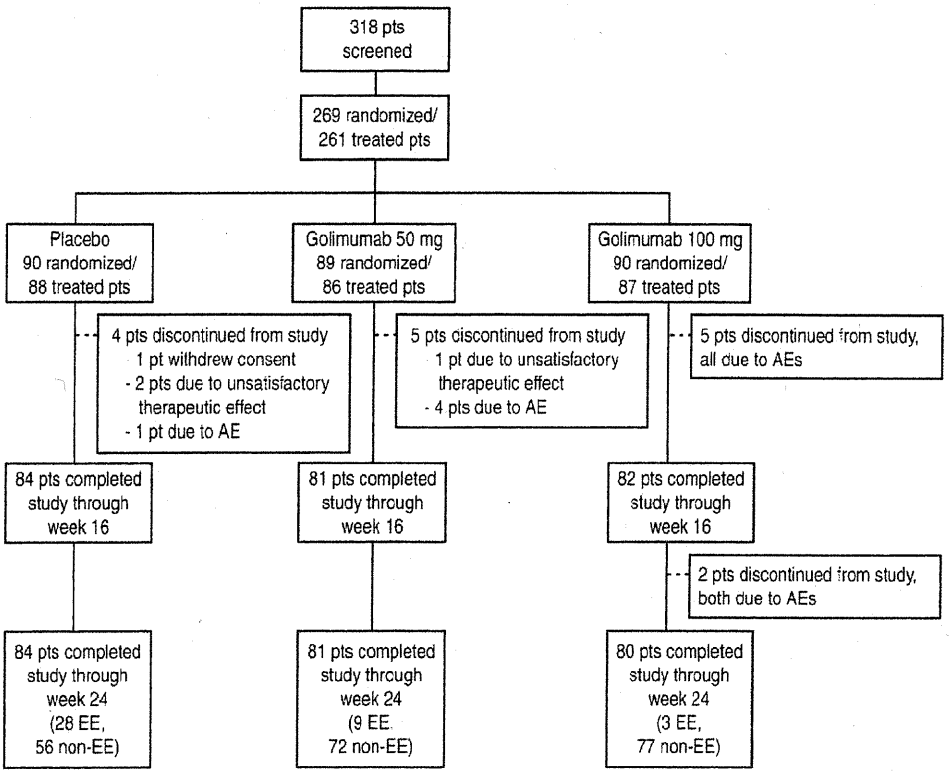

Figure 1 Patient disposition through week 24; randomised patients. Note that 'worsening of rheumatoid arthritis' is included in 'unsatisfactory therapeutic response' and not as an AE. AE, adverse event; EE, early escape; pts, patients.

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.

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 greater median improvement in the HAQ-DI score was observed in patients who received golimumab + MTX (median

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

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

Values are number (%) of patients or mean (SD), median [range].

*The full analysis patient population excluded patients who did not meet the study eligibility criteria, who did not receive study treatment and/or who had no efficacy data, following randomisation. With the exception of vdH-S scores, which were not determined at week 16, patients who qualified for early escape were grouped according to randomised treatment group and had week 24 data replaced with week 16 data.

†Based on the 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.

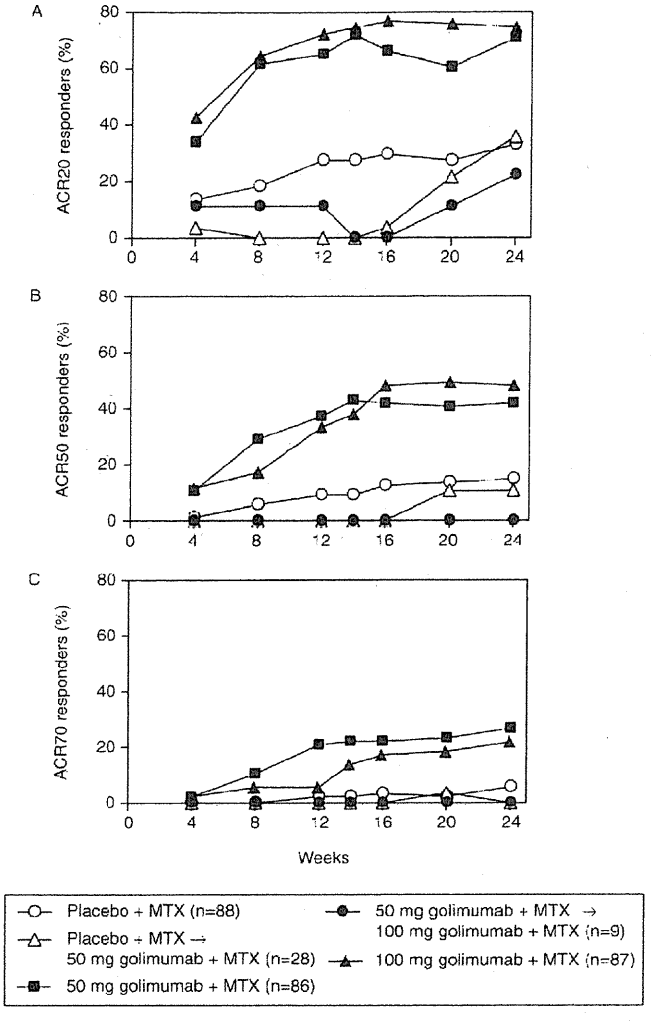

Figure 2 (A) American College of Rheumatology 20% (ACR20), (B) 50% (ACR50) and (C) 70% (ACR70) improvement from baseline through week 24. Note that patients who met the early escape criteria at week 16 and crossed over to golimumab 50 mg or dose escalated from golimumab 50 mg to 100 mg are shown with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

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).

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

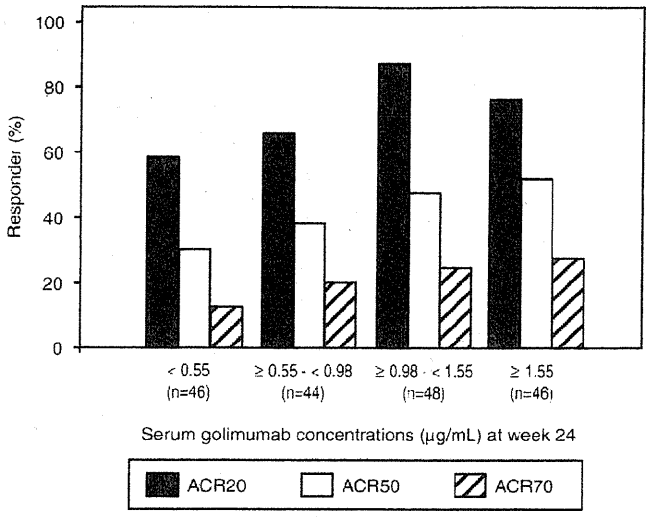

Figure 3 Proportions of patients achieving at least 20%, 50% and 70% improvement in the American College of Rheumatology (ACR20, ACR50, ACR70) response criteria by serum golimumab concentration quartiles (µg/ml) at week 24. The results are from a post hoc analysis of ACR responders in the combined Group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

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

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

Golimumab pharmacokinetics and antibodies to golimumab

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

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

Adverse events

AEs reported at week 16 (fixed treatment regimen study period) and week 24 are summarised in table 3. By week 16, 72.7% (64/88), 75.6% (65/86) and 78.2% (68/87) of patients in Groups 1, 2 and 3, respectively, had AEs. Infections were the

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

Week 16

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

Week 24

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

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

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

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

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

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

DISCUSSION

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

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

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

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

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

This could have resulted in study enrolment of patients with relatively inactive disease.

Golimumab was generally well tolerated with no unexpected safety issues observed in Japanese patients with RA. By week 24, approximately 10% of all patients treated with golimumab + MTX had an injection site reaction. A variety of dermatological adverse effects, including injection site reactions and dermatitis, have been reported for TNF antagonists such as adalimumab, etanercept and infliximab,[20] as well as for anakinra, a recombinant human form of interleukin-1 receptor antagonist.[21] These dermatological complications typically are well-tolerated, respond to antihistamines and do not necessitate treatment discontinuation.

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

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

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

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ORIGINAL ARTICLE

Discontinuation of adalimumab treatment in rheumatoid arthritis patients after achieving low disease activity

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Abstract
Objective We implemented a retrospective study to explore discontinuation of therapy with adalimumab (ADA) without exacerbation in rheumatoid arthritis (RA) patients who had achieved low disease activity (LDA) with the biological agent.
Methods We enrolled 46 RA patients who had completed open extension of a double-blind, placebo-controlled trial of ADA monotherapy in Japan and who had LDA (DAS28-CRP <2.7) at the last administration of ADA in the extension trials; this date was defined as week 0 in the present study. Treatment of RA was at the discretion of the attending physician after week 0. The primary endpoint of this study was the percentage of patients who maintained discontinuation of biological agents and LDA for 52 weeks.
Results Twenty-four of the enrolled patients continued ADA while the rest discontinued ADA after the administration of the drug at week 0. Fourteen of the 22 patients did not restart biological agents, and 4 (18.2%) of these maintained LDA through week 52. All 4 of these patients had received ADA monotherapy before week 0.
Conclusion Some RA patients who have achieved LDA with ADA monotherapy can discontinue the biologic without incurring increased disease activity. A prospective randomized study is required to confirm the results of our study.

Keywords Adalimumab · Biological disease-modifying antirheumatic drug · Low disease activity · Rheumatoid arthritis

For the BRIGHT Study Investigators Group.

The members of the BRIGHT Study Investigators Group are listed in the "Appendix."

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Introduction

Recent advances in treatment strategies for rheumatoid arthritis (RA) have enabled us to target remission, especially in patients with early disease [1, 2]. Clinical trials of tumor necrosis factor (TNF) inhibitors have shown their excellent efficacy for alleviating the signs and symptoms of RA, as well as for inhibiting the progression of structural damage to affected joints [3, 4]. Despite this recognized efficacy, some drawbacks to the use of these drugs have been found, including adverse drug reactions, such as serious infections, high drug costs, and moderate drug retention rates. One solution to these problems would be to discontinue TNF inhibitors when the treatment target is achieved.

Several investigators have reported promising results from studies of discontinuation of biologic therapies, including the TNF20 study [5], the Behandel Strategieen (BeSt) study [6–11], and the Remission Induction by Remicade in RA (RRR) study [12]. The TNF20 and BeSt studies enrolled RA patients with early disease, while the RRR study enrolled established RA patients; all three studies used infliximab (IFX). A similar attempt has been reported in RA patients using the anti-interleukin-6 receptor antibody tocilizumab, with successful discontinuation of the biological agent in a subset of the enrolled patients without incurring significant elevation of disease activity [13].

Adalimumab (ADA), a fully human monoclonal anti-human TNF antibody, has shown good clinical efficacy and tolerability in clinical trials both in Japan [14] and worldwide [15–20]. ADA was approved for treatment of RA in the United States in 2002, in Europe in 2003, and in Japan in 2008. In a randomized, double-blind, placebo-controlled phase II/III trial of ADA in Japan (M02-575 or CHANGE; Clinical Investigation in Highly Disease-Affected Rheumatoid Arthritis Patients in Japan with Adalimumab Applying Standard and General Evaluation) [14], RA patients ($n = 352$) with a mean disease duration of 9.8 years were enrolled and allocated to either ADA monotherapy or placebo arms for 24 weeks. After completing the trial, 309 patients were enrolled into open extension trials, one requiring the administration of ADA by medical staff (M03-651), and one requiring self-injection by patients (M03-775). Taking advantage of the termination of these extension trials (M03-651 and M03-775) and the launch of ADA into the market in Japan, we implemented a retrospective study, the Biologics-free RemIssion and low disease activity after stoppinG adalimumab in Japanese patients with rHeumatoid arThritis (BRIGHT) study, to explore the possibility of discontinuing ADA without incurring exacerbation in RA patients who had achieved a low disease activity (LDA) with the biological agent.

Materials and methods

Patients

We identified 61 RA patients who had completed the open extension trials (M03-651 or M05-775) and had LDA at the last administration of ADA. Disease activity was assessed using DAS28-CRP, a formula requiring a tender joint count of 28 joints (TJC28), a swollen joint count of 28 joints (SJC28), and C-reactive protein (CRP) serum levels, and a general health visual analog scale assessed by patients (GH-VAS) [21]. LDA was defined as DAS28-CRP <2.7, as established by a large-scale cohort study in Japan [21]. Invitation letters to the BRIGHT study were sent to the investigators from M03-651 and M05-775 who had treated those 61 patients. Forty-six patients from 29 facilities were enrolled in the BRIGHT study. Among the 46 patients enrolled in the BRIGHT study, 34/46 (73.9%) were treated with ADA alone, while the remaining 12 had received ADA plus disease-modifying antirheumatic drugs (DMARDs) during the extension trials.

Therapeutic regimes

Among the 46 patients enrolled in BRIGHT, at the attending physicians' discretion, 24 continued ADA (the continued group), while the remaining 22 discontinued the biological agent after the last administration of ADA in the M05-775 and M03-651 open extension trials (the stopped group). The patients were assessed in a clinical practice setting and treatments were adjusted accordingly. The protocol for the BRIGHT study required no treatment change or modification.

Data collection

The date of the last administration of ADA in each patient in the M05-775 or M03-651 trials was defined as week 0 of this study. We evaluated TJC28, SJC28, CRP, GH-VAS, the Health Assessment Questionnaire—Disability Index (HAQ-DI), the use of DMARDs, and the use of corticosteroid (CS) 26 and 13 weeks before the ends of those trials (week −26 and week −13) and at the ends of those trials (week 0 of the BRIGHT study). TJC28, SJC28, CRP, GH-VAS, and treatments at weeks 26 and 52 of the BRIGHT study were retrospectively evaluated from medical records in the participating facilities (Fig. 1).

Statistical analysis

The primary endpoint of this study was the percentage of patients who maintained discontinuation of ADA for

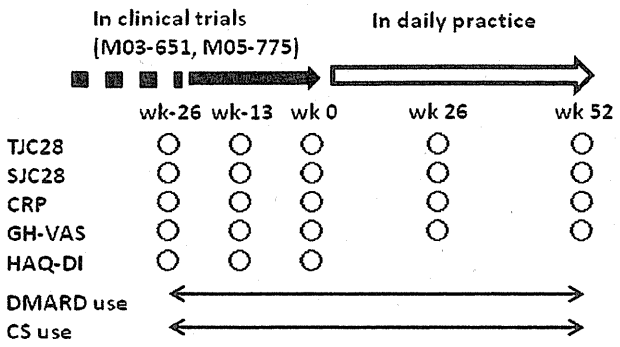

Fig. 1 Design of the BRIGHT study. Patients with RA who participated in the M03-651 or M05-775 open extension trials and had low disease activity (DAS28-CRP <2.7) at the last administration of adalimumab in the clinical trials (i.e., week 0 of the BRIGHT study) were enrolled. These 46 patients continued ($n = 24$) or discontinued ($n = 22$) adalimumab after the last administration of the drug in the trials at their attending physicians' discretion, and were followed up in daily practice. Data at weeks −26, −13, and 0 were collected from the trial databases, and the data at weeks 26 and 52 were collected retrospectively from medical records. *TJC28* tender joint count 28, *SJC28* swollen joint count 28, *CRP* C-reactive protein, *GH-VAS* general health Visual Analog Scale by patients, *HAQ-DI* Health Assessment Questionnaire—Disability Index, *DMARD* disease-modifying antirheumatic drug, *CS* corticosteroid

52 weeks without incurring elevation of DAS28-CRP to >2.7. Because this was a retrospective study, we anticipated that some patients would have missing data. Therefore, the DAS28-CRP of patients with missing data for TJC, SJC, CRP or GH-VAS at weeks 26 or 52 was regarded as ≥2.7. In some analyses, we replaced the missing data with 0 in order to calculate the theoretical minimum DAS28-CRP at that time point. Demographic data and baseline data at week 0 were compared between the two groups using Fisher's direct probability test for categorical variables and Student's *t* test or the Mann–Whitney test for continuous variables, depending on the data distribution. Changes in disease activity over time were compared visually between the two groups using observed data without statistical assessment. Treatments for RA between week 0 and 52 were compared using Fisher's direct probability test. We used SPSS 17.0 (Tokyo, Japan) for statistical analyses.

Ethics

The Helsinki Declaration (revised in 2008) and the ethical guidelines for epidemiologic research in Japan were followed. The ethical committee of the Tokyo Medical and Dental University Hospital and those of the participating facilities approved the study. Written informed consent was obtained from each patient enrolled in the BRIGHT study.

Table 1 Clinical characteristics of the patients enrolled in the BRIGHT study at week 0

Characteristics	Continued group ($n = 24$)	Stopped group ($n = 22$)
Age (years)	60.1 ± 12.7	55.7 ± 14.2
Female (%)	79.2	63.6
Disease duration[a] (years)	10.3 ± 7.3	10.3 ± 9.0
Steinbrocker's stage 1/2/3/4[a]	1/5/5/13	2/6/7/7
Steinbrocker's class 1/2/3/4[a]	7/11/5/0	3/14/5/0
Rheumatoid factor positive (%)[a]	87.5	81.8
DAS28-CRP	1.8 ± 0.5	1.6 ± 0.3
TJC28 (number)	0.4 ± 0.7	1.5 ± 2.1
SJC28 (number)	0.4 ± 1.1	0.6 ± 0.9
CRP (mg/dl)	0.4 ± 0.8	0.1 ± 0.1
GH-VAS by patients (mm)	11.9 ± 10.8	9.9 ± 8.6
HAQ-DI	0.4 ± 0.5	0.2 ± 0.5
Dosage of ADA		
40 mg/2 weeks	23	20
80 mg/2 weeks	1	2
Treatment duration of ADA (months)	46.0 ± 4.2	45.8 ± 3.3
Use of MTX between weeks −26 and 0 (%)	29.2	*13.6*
ADA monotherapy between weeks −26 and 0 (%)	62.5	*86.4*
Dosage of MTX (mg/week)	6.9 ± 1.6	*6.0 ± 2.0*
Use of CS between weeks −26 and 0 (%)	62.5	40.9
Dosage of CS (mg/day) (PSL equivalent)	4.3 ± 1.6	3.7 ± 1.3

Data are expressed as the mean ± standard deviation unless otherwise mentioned. Mean dosages of methotrexate and corticosteroid are calculated among the users of each drug at the last administration of ADA in the extension trials

DAS28-CRP disease activity score 28 with C-reactive protein, *TJC28* tender joint counts of 28 joints, *SJC28* swollen joint counts of 28 joints, *CRP* C-reactive protein, *GH-VAS* general health Visual Analog Scale, *HAQ-DI* Health Assessment Questionnaire—Disability Index, *ADA* adalimumab, *MTX* methotrexate, *CS* corticosteroid, *PSL* prednisolone

There was no statistical difference between the two groups. *P* ($P > 0.05$) values of continuous variables were calculated using the Mann–Whitney test or Student's *t* test according to the distribution of the data, and those of categorical variables were calculated using Fisher's direct probability test

[a] Data at the start of adalimumab in the extension trials (M03-651 or M05-775)

Results

Baseline characteristics of the enrolled patients

Demographic and clinical characteristics for the continued group and the stopped group are compared in Table 1. The initial trial (CHANGE) compared ADA monotherapy and

placebo in RA patients who showed an inadequate response to DMARDs, but the open extension trials of ADA therapy also allowed investigators to use DMARDs at their discretion. However, 86.4% of the continued group and 62.5% of the stopped group were still treated without nonbiological DMARDs and methotrexate (MTX) between weeks −26 and 0 (the beginning of the BRIGHT study). There was no significant difference in baseline characteristics between the two groups.

Maintenance of LDA after stopping adalimumab

Fourteen patients in the stopped group did not restart any biological agents, but 3 started ADA, 3 etanercept, 1 tocilizumab, and 1 ocrelizumab before week 52. Four out of the 14 patients who maintained discontinuation of ADA without starting other biological DMARDs for 52 weeks had DAS28-CRP <2.7 at weeks 26 and 52, and achieved the primary endpoint of this study. Among the remaining 10 patients who maintained discontinuation of ADA for 52 weeks, 4 had DAS28-CRP ≥2.7 at week 26 or 52, while the rest of the patients ($n = 6$) did not report either GH-VAS or CRP at week 26 or 52, and were therefore deemed to have DAS28-CRP ≥2.7 at those times. Among the 24 patients who continued ADA after week 0, 2 had discontinued ADA by week 52: 1 patient discontinued because of remission of RA, and the other developed cerebellar infarction and discontinued ADA. Sixteen of the 22 RA patients who continued ADA for 52 weeks maintained DAS28-CRP <2.7 at weeks 26 and 52 (Fig. 2).

Disease activity of RA after discontinuing adalimumab

Changes in the DAS28-CRP score and those of its individual components (TJC, SJC, CRP, GH-VAS) over time are compared between the two groups in Fig. 3. It should be noted that the mean DAS28-CRP in both groups was <2.0 from week −26 to the end (week 0) of the extension trials, suggesting that these patients were well controlled by ADA, which was the monotherapy in the majority (73.9%) of the patients. All components of the DAS28-CRP of the stopped group were numerically higher than those of the continued group at weeks 26 and 52, as was the DAS28-CRP itself.

Treatment of RA after stopping adalimumab

We next compared treatment modification between weeks 0 and 52. MTX was started or the dosage of MTX was increased in 6 patients in the continued group and 12 in the stopped group, ($P = 0.040$, Fisher's direct probability test). Percentages of patients who started new DMARDs, except for MTX, and those of patients who started or

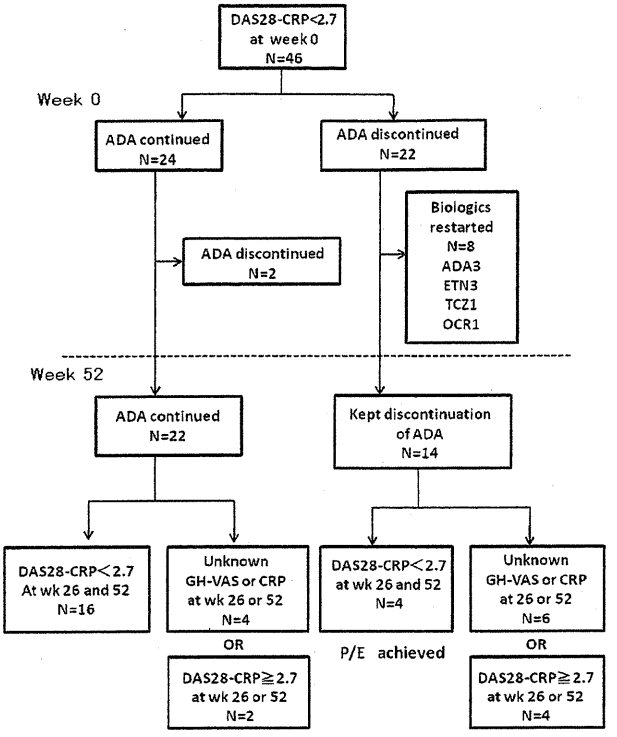

Fig. 2 BRIGHT study patient disposition through week 52. Adalimumab was continued ($n = 24$) or discontinued ($n = 22$) after the last administration of the drug in the open extension studies (i.e., week 0 of the BRIGHT study) and the patients were followed for 52 weeks. The patients were categorized according to the use of adalimumab and DAS28-CRP values. Four patients who had DAS28-CRP <2.7 at week 26 and 52 achieved the primary endpoint. *ADA* adalimumab, *ETN* etanercept, *TCZ* tocilizumab, *OCR* ocrelizumab, *CRP* C-reactive protein, *GH-VAS* general health Visual Analog Scale by patients, *P/E* primary endpoint

increased the dosage of CS were numerically, but not significantly, higher in the stopped group compared to the continued group (Table 2).

None of the patients who achieved the primary endpoint used MTX between weeks −26 and 0, but 3 patients used low-dose PSL (2.5–5 mg/day). The concomitant drugs used by these patients during weeks 0–52 were as follows: the first patient did not start any DMARDs, tapered off PSL at week 32, and was in drug-free remission from week 32 to week 52; the second and third patients started MTX (6 and 4 mg/week, respectively) at week 0 and continued both MTX and PSL until week 52; the fourth patient started PSL (7.5 mg/day) at week 0 and MTX (8 mg/week) at week 8, and continued both drugs until week 52. There was 1 patient who did not use DMARDs (including MTX, biologics, and CS) for 52 weeks. The patient, however, did not achieve the primary endpoint because of a lack of CRP data at week 26. There was no statistical difference in the use of MTX and CS at week 52 between the two groups (Table 2).

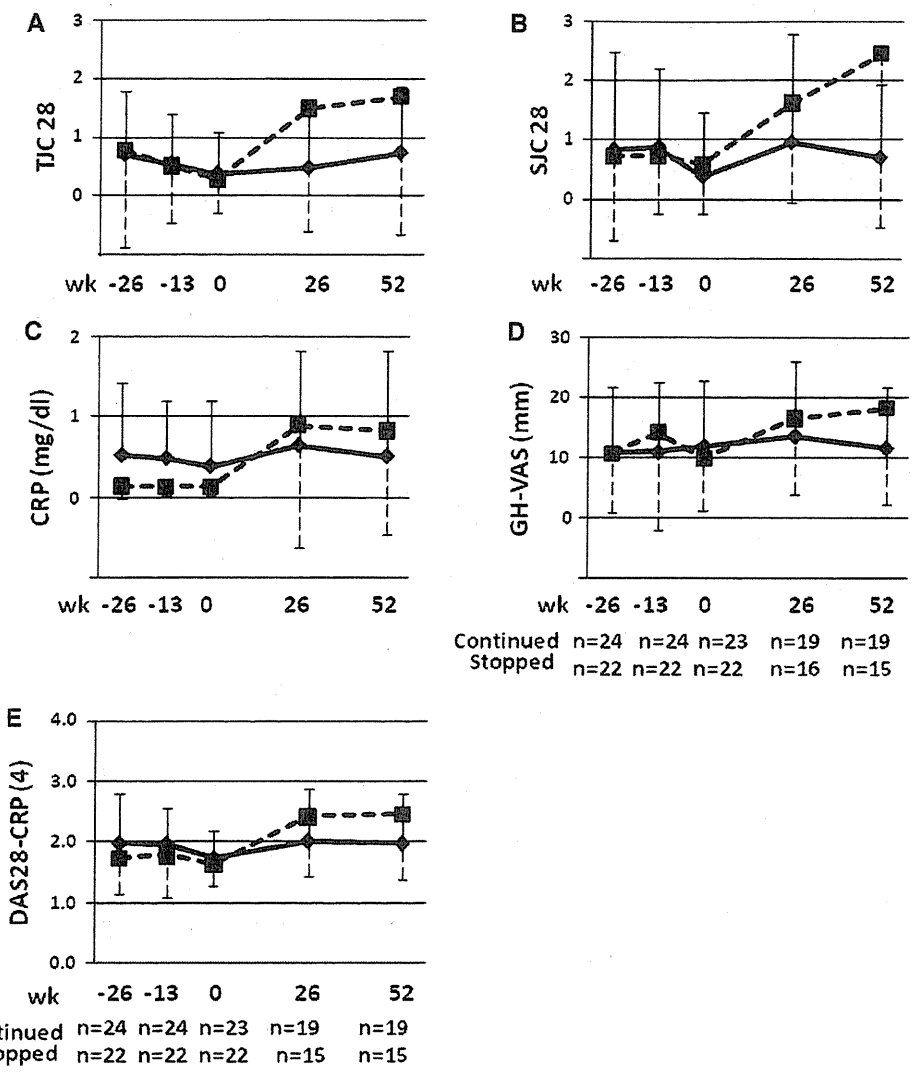

Fig. 3 Changes in the rheumatoid arthritis disease activity of patients enrolled in the BRIGHT study from week −26 to week 52. Tender joint count 28 (*TJC28*) (**a**), swollen joint count 28 (*SJC28*) (**b**), C-reactive protein (*CRP*) serum levels (**c**), general health Visual Analog Scale by patients (*GH-VAS*) (**d**), and disease activity score 28-CRP (*DAS28-CRP*) (**e**) were measured from week −26 to week 52 for the continued group ($n = 24$, *diamonds with solid line*) and the stopped group ($n = 22$, *squares with dashed line*). The mean and standard deviation at each time point are shown. The number of patients is shown when there were patients with missing data (**d**, **e**)

Comparison between patients who did and did not achieve the primary endpoint

To explore the characteristics of patients who maintained LDA after stopping ADA for 52 weeks, we compared the baseline data of patients who did and did not achieve the primary endpoint. Although 6 patients who had missing data for GH-VAS or CRP at week 26 or 52 were deemed to have not achieved the primary endpoint (Fig. 2), 3 of them had none or only one TJC28 or SJC28 and did not seem to be appropriate for this comparison. We therefore calculated the theoretical minimum DAS28-CRP for the 6 patients with missing data by replacing the missing values with 0. Patients who restarted biologics ($n = 8$), who had DAS28-CRP >2.7 at week 26 or 52 ($n = 4$), who had missing data for CRP or VAS-GH, and had a theoretical minimum DAS28-CRP of >2.7 at week 26 or 52 ($n = 3$) were included in this analysis. Because we had only 4 patients who achieved the primary endpoint, we deliberately did not perform statistical analyses (Table 3). Patients who achieved the primary endpoint had a longer duration of RA and used CS more frequently at week 0, and they had higher mean and median titers of rheumatoid factor at the beginning of the M03-651 or M05-775 trials.

Discussion

In the BRIGHT study, we demonstrated that 4 of the 22 RA patients (18.2%) who discontinued ADA after achieving LDA maintained the same disease activity status for at least 1 year without restarting biological agents. The majority (73.9%) of the patients who enrolled onto the BRIGHT study had received ADA monotherapy in the extension trials. The stopped group had a higher DAS28-CRP at

Table 2 Use of DMARDs and corticosteroid from week 0 to week 52 of the BRIGHT study

Treatment	Continued group ($n = 24$)	Stopped group ($n = 22$)	P value
Change of MTX dosage between week 0 and 52			
Increased or started	6 (25.0)	12 (54.5)	0.040*
No change	3 (12.5)	2 (9.1)	
Decreased	3 (12.5)	0 (0.0)	
Not used	12 (50.0)	8 (36.4)	
Use of MTX at week 52	11 (45.8)	13 (59.1)	NS†
Dosage of MTX at week 52 (mg/week)	6.8 ± 2.8	6.3 ± 2.4	NS
Starting DMARD except for MTX	1 (4.2)	5 (22.7)	NS†
Use of DMARD except for MTX at week 52	1 (4.2)	5 (22.7)	NS†
CS dosage			
Increased or started	3 (12.5)	8 (36.4)	NS*
No change	10 (41.7)	4 (18.2)	
Decreased	5 (20.8)	3 (13.6)	
Not used	6 (25.0)	7 (31.8)	
Use of CS at week 52	15 (62.5)	15 (68.2)	NS
Dosage of CS at week 52 (mg/day) (PSL equivalent)	4.7 ± 1.5	4.9 ± 2.0	NS

Percentages are shown in parentheses. Mean dosages of methotrexate and corticosteroid and their standard deviation at week 52 are calculated among the users of each drug

P values of continuous variables were calculated using the Mann–Whitney test or Student's t test according to the distribution of the data

MTX methotrexate, *DMARD* disease-modifying antirheumatic drug, *CS* corticosteroid

* Percentages of patients who increased or started methotrexate or corticosteroid were compared between the two groups using Fisher's direct probability test

† Percentages of patients who used MTX at week 52, who started new DMARDs except for MTX, and who used DMARDs except for MTX at week 52 were compared between the two groups using Fisher's direct probability test

Table 3 Comparison of patients who did not did not achieve the primary endpoint in the stopped group

Characteristics	Patients who achieved the primary endpoint ($n = 4$)	Patients who did not achieve the primary endpoint ($n = 15$)
Age (years)	58.3 ± 12.3	54.9 ± 13.6
Female (%)	75.0	60.0
Disease duration[a] (years)	4.4 ± 4.3	18.1 ± 9.8
Steinbrocker's stage 1/2/3/4[a]	0/0/3/1	4/2/4/5
Steinbrocker's class 1/2/3/4[a]	0/3/1/0	2/9/4/0
Rheumatoid factor titer[a], mean ±SD (median)	78.8 ± 69.4 (73.0)	259.8 ± 423.6 (90.0)
DAS28-CRP	1.5 ± 0.1	1.7 ± 0.4
HAQ-DI	0.2 ± 0.3	0.3 ± 0.6
Use of MTX between weeks −26 and 0 (%)	0	13.3
Use of CS between weeks −26 and 0 (%)	75	33.3
Dosage of CS (mg/day) (PSL equivalent)	3.8 ± 1.3	3.4 ± 1.5

Four patients who maintained discontinuation of ADA without starting other biological DMARDs for 52 weeks and had a DAS28-CRP of <2.7 at weeks 26 and 52 were included in the "Patients who achieved the primary endpoint" group. Fifteen patients who restarted biologics ($n = 8$), who had a DAS28-CRP of >2.7 at week 26 or 52 ($n = 4$), and who had missing data for CRP or VAS-GH and had a theoretical minimum DAS28-CRP of >2.7 ($n = 3$) were included in the "Patients who did not achieve the primary endpoint" group. Because we had only 4 patients who achieved the primary endpoint, we deliberately did not perform statistical analyses. Data are expressed as the mean ± standard deviation unless otherwise mentioned. Mean dosages of corticosteroid are calculated among the users of each drug at the last administration of ADA in the extension trials

DAS28-CRP disease activity score 28 with C-reactive protein, *HAQ-DI* Health Assessment Questionnaire—Disability Index, *MTX* methotrexate, *CS* corticosteroid, *PSL* prednisolone

[a] Data at the start of adalimumab in the extension trials (M03-651 or M05-775)

week 26 and 52 than the continued group, despite the increased use or start of MTX therapy in this group.

The first clinical trial that evaluated discontinuation of biological agents was the TNF20 study [5]. Six of 10 early RA patients who received MTX + IFX for the first 52 weeks and who discontinued IFX thereafter showed DAS28-ESR <2.6 at week 104 [5]. The sustained benefits of IFX therapy for early RA following withdrawal of the drug was confirmed in the BeSt study, which enrolled a larger number of patients with a longer study period [6–11]. Among 128 RA patients who received MTX + IFX as initial therapy, 54 (42%) of them were in clinical remission (DAS <1.6) at year 4, and 23 (18%) stopped all antirheumatic drugs without incurring an increase in disease activity and progression of structural joint damage [11]. Recently, Tanaka et al. [12] reported that 56% of RA patients with a mean disease duration of 5.9 years who achieved LDA (DAS28-ESR <3.2) for more than 24 weeks with IFX + MTX maintained DAS28-ESR <3.2 for 1 year after discontinuing IFX. These results show that there is substantial evidence that the benefits of IFX are sustained after the withdrawal of the drug in RA patients who had achieved remission or LDA with the biological agent and concurrent MTX therapy.

Emery et al. [22] recently reported the results of their study of the discontinuation of ADA, the Optimal Protocol for Treatment Initiation with Methotrexate and Adalimumab (OPTIMA). Early RA patients who responded (DAS28-CRP <3.2) to treatment with MTX + ADA at weeks 22 and 26 were randomly allocated into placebo + MTX ($n = 102$) or ADA + MTX ($n = 105$) groups and followed for an additional 52 weeks. The percentage of patients who achieved DAS28-CRP <3.2 was 81%, DAS28-CRP <2.6 was 66%, and simplified disease activity index (SDAI) <3.3 was 51% at week 78 in the placebo + MTX group, similar to the results reported in the BeSt study [5], but apparently better than the corresponding figure for the BRIGHT study. Three important differences in the characteristics of the enrolled patients between the OPTIMA and the BRIGHT study should be mentioned. First, the mean disease durations of the enrolled patients were 3.9 months for the OPTIMA and 10.3 years for the BRIGHT study. A significant association of disease duration with the discontinuation of IFX has been reported in the RRR study [12], while an association of symptom duration with drug-free remission has been reported in the BeSt study [11]. The longer mean disease duration of our patients may be relevant to the lower rate of discontinuation of ADA without exacerbation in the BRIGHT study compared to the OPTIMA study. This possibility may be supported by the finding that the disease durations of the four RA patients who met the primary endpoint were 0.8, 1.3, 5.6, and 9.9 years, and the mean value was numerically smaller than that of the patients who did not achieve the primary endpoint of our study (Table 3). Second, OPTIMA had predefined criteria for the discontinuation of biologics, just as the BeSt study and the RRR study did, while discontinuation was determined at the discretion of the attending physicians and/or according to patient preference in the BRIGHT study. It is plausible that lack of criteria for discontinuation affected the success rate upon the discontinuation of biologics. Third, the concomitant use of non-biological DMARDs before discontinuing ADA should be discussed. In the stopped group of the BRIGHT study, only 3 out of 22 patients received MTX before ADA discontinuation (Table 1), and no patients who achieved the primary endpoint used concomitant DMARDs, including MTX, before discontinuing ADA, a marked difference from the OPTIMA study, where all patients received concomitant MTX. Because only 3 patients received MTX before ADA discontinuation, we could not analyze the possible effect of MTX on realizing the primary endpoint in this study.

Stringency of disease control was associated with the successful discontinuation of IFX without incurring an RA flare in the RRR study [12], but we could not find a difference in DAS28-CRP at week 0 between those who did and those who did not achieve the primary endpoint (Table 3). It is difficult to analyze the association between stringency of disease control and discontinuation of treatment with ADA in the BRIGHT study because of the small number of patients enrolled.

Among the 14 patients who maintained discontinuation of biological agents for 1 year without restarting biological agents, there were 6 patients with missing data in components of the DAS28-CRP. Based on our predefined criteria, these patients were deemed to have DAS28-CRP $\geq$2.7 at the corresponding time point. In actuality, 3 of these patients had very low disease activity; 2 patients had TJC28 $\leq$1, SJC28 $\leq$1, and CRP $\leq$1 without GH-VAS at weeks 26 and 52, and 1 patient had TJC28 = 0, SJC28 = 0, and GH-VAS = 10/100 mm without CRP at week 26 and a DAS28-CRP of 1.92 at week 52. These were the patients who had a theoretical minimum DAS28-CRP of <2.7 and were excluded from the analyses in Table 3. These data suggest that we can expect a higher probability of ADA discontinuation without RA disease activity elevation than the 18.2% resulting from our study.

Some limitations of this study should be mentioned. The study design was retrospective and open, the number of patients enrolled was small, and no data were collected to evaluate structural changes in joints. These limitations should be considered when interpreting the results of this study.

In conclusion, this study suggests that once continuous good control is achieved with ADA monotherapy, it is

possible to discontinue ADA but maintain LDA status without biological DMARDs, even in patients with established RA. Further studies are warranted to confirm this possibility.

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Appendix

The following rheumatologists are the members of the BRIGHT Study Investigators Group: T. Koike (Hokkaido University); H. Takahashi (Sapporo Medical University); M. Mukai (Sapporo City General Hospital); S. Ohta (Taga General Hospital); T. Sumita (Tsukuba University); N. Watanabe (Chiba University); R. Matsumura (NHO Chiba East Hospital); T. Mimura (Saitama Medical University); T. Hanyu (Nagaoka Red Cross Hospital); T. Kasama (Showa University); H. Yamagata (NHO Murayama Medical Center); H. Yamada (St. Marianna University School of Medicine); S. Nagaoka (Yokohama Minami Kyousai Hospital); S. Toma (NHO Sagamihara National Hospital); S. Hirohata (Kitasato University); H. Taki (Toyama University); K. Sugimoto (Fukui General Hospital); T. Tsuji (Fukui Onsen Hospital); N. Ishiguro (Nagoya University); Y. Eto (NHO Nagoya Medical Center); T. Fujii (Kyoto University); Y. Kawahito (Kyoto Prefectural University); S. Kumagai (Kobe University); H. Wakabayashi (Okayama University); E. Suematsu (NHO Kyusyu Medical Center); T. Fukuda (Kurume University); R. Koike, T. Nanki, M. Tanaka, K. Watanabe, H. Yamazaki, R. Sakai (Tokyo Medical and Dental University).

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