Introduction

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory autoimmune disease that is characterized by progressive joint damage and disability, which severely affects quality of life [1, 2]. Increased understanding of the pathogenesis of RA and the proinflammatory cytokines that underlie its progression has led to the development of disease-modifying, anti-rheumatic drugs (DMARDs) [3]. These biological agents target T cells, B cells and proinflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1 and IL-6, and have had a profound impact on the treatment of this debilitating condition [4–8]. However, treatment is not always effective as many patients fail to respond [6, 8, 9] or maintain a response [5] to the therapies. Some patients develop antibodies against the particular agent used [7], while others experience relatively severe adverse reactions. These disadvantages of existing DMARDs highlight the need for new therapeutic agents with a different mechanism of action and improved efficacy.

The underlying pathogenesis of RA is thought to involve activated T cells that produce proinflammatory cytokines such as TNF-α, IL-1, and IL-6 [10]. T cells are one of the most abundant cell types in the RA synovium, comprising up to 50 % of all cells present [11]. Activated T cells may also work together with other cells in the connective tissue of joints to activate other immune cells, leading to the production of inflammatory mediators and metalloproteinases, such as matrix metalloproteinase-3. This process results in the degradation of bone and cartilage, and contributes to joint destruction [2, 10]. Autoreactive T cells, which react to self-antigens, have also been implicated in autoimmune disorders such as RA [12]. Therefore, inhibition of T cell activation represents a potential therapeutic strategy for RA.

At least two signals from antigen-presenting cells (APCs) are required for full T cell activation: an antigen-specific signal and a second signal transduced by the binding of a co-stimulatory receptor on the T cell to a ligand on the APC. Activation is also facilitated by the binding of CD80 or CD86 on the surface of an APC to CD28 expressed on T cells [11]. Activation is then followed by the induction of cytotoxic T-lymphocyte antigen 4 (CTLA4), a naturally occurring inhibitory molecule expressed on the surface of T cells, which has a significantly greater affinity for CD80 and CD86 than does CD28 [1, 11].

Abatacept is a recombinant fusion protein consisting of the extracellular domain of human CTLA4. It is the first in a new class of agents for RA that selectively modulates the CD80 or CD86–CD28 co-stimulatory signal involved in full T cell activation. Abatacept binds to CD80 and CD86 on T cells and thereby inhibits the binding of these molecules to CD28, preventing T cell activation [13]. This approach has therapeutic benefits in individuals with RA [10, 13, 14] and was shown to be safe and efficacious in a Phase I study conducted in Japanese patients with RA [15]. Of note, abatacept was effective in patients with an inadequate response to methotrexate (MTX) [10, 16–18], those who are MTX-naive [19] and those with an inadequate response to TNF-α inhibition [14, 20]. Furthermore, a global Phase II study showed good efficacy of abatacept in patients with active RA despite MTX therapy [10, 17]. To date, however, there are limited data in Japanese patients with RA.

Here, we conducted a Phase II bridging study to assess the efficacy and dose–response of abatacept in Japanese patients with active RA despite MTX therapy. We also evaluated whether the results of Phase III studies in Western patients [14, 18, 21] can be extrapolated to Japanese patients.

Materials and methods

Objectives

The primary objective of this bridging study was to assess the efficacy and dose response of abatacept by comparing the administration of abatacept at 2 and 10 mg/kg with placebo. Japanese patients with active RA despite MTX therapy fulfilling the American College of Rheumatology 20 % response (ACR20) criteria received either abatacept or placebo for 12 weeks, while continuing MTX therapy. Secondary objectives included ACR50 and ACR70 response rates at week 24; ACR20, ACR50, and ACR70 responses within 24 weeks; improvement in Health Assessment Questionnaire (HAQ); Disease Activity Score 28 based on C-reactive protein concentrations (DAS28-CRP); and the safety and immunogenicity of abatacept.

Patients

The study enrolled Japanese males and females aged ≥20 years. Enrollment criteria included fulfillment of the ACR 1987 criteria for the diagnosis of RA with a functional status of Class I, II or III [22, 23]; previous treatment with MTX at 6–8 mg weekly for at least 12 weeks, with a stable dose for at least 4 weeks before registration; and one or more of the following: ≥10 swollen joints (66-joint count), ≥12 tender joints (68-joint count), or CRP ≥1.0 mg/dL.

Exclusion criteria included females of childbearing age who were unwilling or unable to use an acceptable method of contraception for the duration of the study and for

10 weeks after the study; females who were either pregnant or breastfeeding; active vasculitis of a major organ system other than rheumatoid nodules; current symptoms of severe, progressive, or uncontrolled renal, hepatic, hematologic, gastrointestinal, pulmonary, cardiac, neurologic or cerebral disease; evidence of HIV, hepatitis B or hepatitis C; evidence of opportunistic infections, serious infections (e.g., pneumonia, renal infection, sinusitis) or chronic infections within 3 months before preliminary or formal registration in this study; or active tuberculosis requiring treatment within 3 years before registration. Patients with severe asthma, cancer, or a history of cancer within 5 years before the study, body weight >125 kg, treatment with any investigational drug within 8 weeks before formal registration, or prior administration of abatacept were also excluded.

Study design

This multicenter, placebo-controlled, double-blind, parallel-group, dose–response study was conducted at 42 sites in Japan from June 2006 to November 2007 (ClinicalTrials.gov identifier: NCT00345748). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, applicable regulatory requirements, and the study protocol. Written informed consent was obtained from all patients.

All patients continued prior MTX therapy (6–8 mg/week) throughout the study. Patients were randomized 1:1:1 to receive 2 mg/kg abatacept, 10 mg/kg abatacept, or placebo. DMARDs other than MTX or biologic therapies at study enrollment were stopped with an appropriate wash out before randomization. Abatacept was intravenously infused in a fixed volume of 100 mL saline or 5 % glucose over 30 min on weeks 0, 2, 4, 8, 12, 16 and 20 of the study. Administration of other DMARDs was prohibited, but stable doses of corticosteroids (≤10 mg/day) or non-steroidal anti-inflammatory drugs were allowed. No change in the dose or mode of administration of MTX was permitted throughout the study, unless safety concerns necessitated dose reduction. Patients who discontinued the study were assessed at an early termination visit.

Evaluation of clinical efficacy

Clinical efficacy was assessed by the ACR response rate criteria at enrollment and at each visit before study drug administration during the double-blind treatment period. Briefly, an ACR20 response requires a 20 % reduction in the number of swollen and tender joints and in three of the following parameters: physician global assessment of disease, patient global assessment of disease, patient assessment of pain, CRP or erythrocyte sedimentation rate (ESR), and degree of disability on the HAQ score. The ACR50 and ACR70 responses are defined as reductions of 50 and 70 %, respectively [24, 25].

Response to treatment was assessed based on DAS28-CRP values. A response was defined as a reduction in DAS28 from week 0 to week 24 of ≥1.2. A DAS28 value of ≤3.2 at week 24 was classified as low disease activity and a DAS28 value of <2.6 was considered to indicate disease remission.

Safety

All adverse events (AEs) that occurred within the dosing period and within 8 weeks after the last dose of study drug were analyzed. All reported AEs and serious AEs (SAEs) were reviewed at each visit.

Immunogenicity evaluation

Immunogenicity of abatacept was assessed by measuring serum anti-abatacept and anti-CTLA4-T antibody titers using enzyme-linked immunosorbent assays. As none of the samples tested showed positive signals for either antibody after the first dose of the study drug, the neutralizing activity of these antibodies was not analyzed.

Statistical analyses

Frequency distribution or descriptive statistics of all demographic variables were summarized according to treatment group. The primary efficacy analysis was designed to test the non-zero slope of the dose–response relationship using the Cochran–Armitage χ^2 trend test for proportions. Differences in ACR20, ACR50, and ACR70 response rates between the abatacept groups and the placebo group were summarized using point estimates and 95 % confidence intervals (CI). For safety evaluation, summary statistics were tabulated, with frequency distribution and individual listing of all AEs generated for each treatment group. Immunogenicity was summarized using descriptive statistics for each group, and the positive immunogenicity response rate was calculated.

Results

Patient disposition is summarized in Fig. 1. Of 195 patients, 62 were randomized to 10 mg/kg abatacept, 67 to 2 mg/kg abatacept, and 66 to placebo. Of these patients, 194 received at least one dose of study medication (61 in the 10 mg/kg abatacept group, 67 in the 2 mg/kg abatacept group, and 66 in the placebo group). One patient in the 10 mg/kg abatacept group withdrew consent and

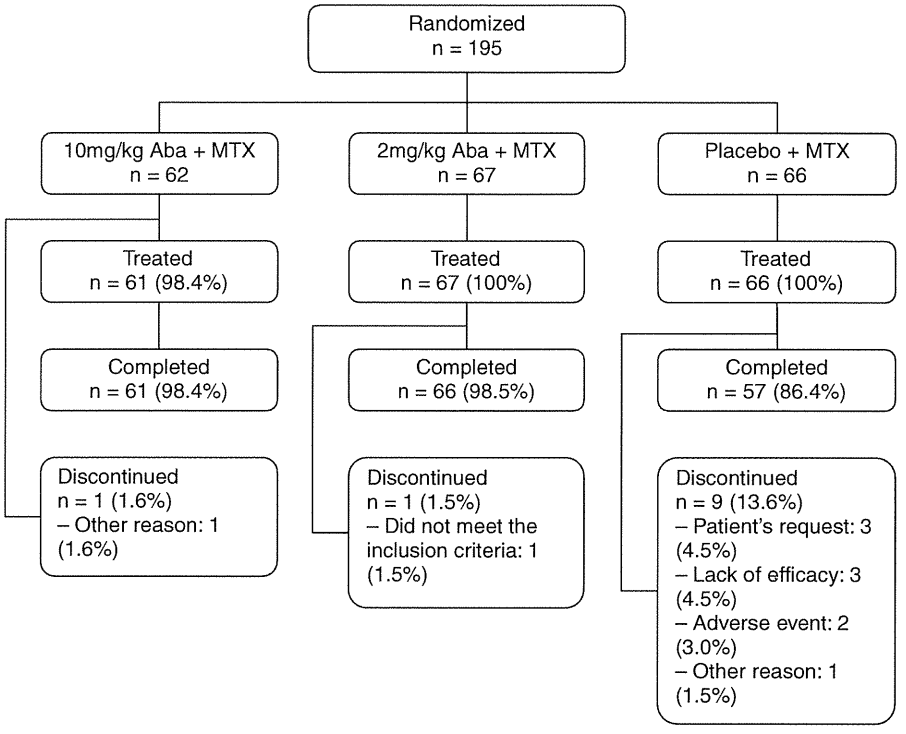

Fig. 1 Patient disposition. *Aba* abatacept, *MTX* methotrexate

discontinued the study before receiving the first dose of study medication. The rate of discontinuation during the 24-week treatment period was higher in the placebo group than in both abatacept groups (placebo 13.6 %, 10 mg/kg abatacept 1.6 % and 2 mg/kg abatacept 1.5 %). The main reasons for discontinuation included lack of efficacy, AEs, and withdrawal of consent. As few doses were missed in each treatment group, this was deemed unlikely to have affected either the administration period or dosage. There were no significant differences between baseline patient demographics, including duration of RA, painful joint count, swollen joint count, physical function, and DAS28-CRP across all three treatment groups. The majority of patients were female (Table 1).

Clinical efficacy

The study met its primary endpoint, with a dose–response relationship evident for the ACR20 response rate in the 10 and 2 mg/kg abatacept groups relative to the placebo group at week 24 (Fig. 2). Analysis using the Cochran-Armitage trend test confirmed that the ACR20 response rates at week 24 were significantly higher in the 10 mg/kg (77.0 %; 47/61 patients) and 2 mg/kg (62.7 %, 42/67 patients) abatacept-treated groups than in the placebo group (21.2 %; 14/66 patients) (Fig. 2). The differences in the ACR20 response rate between the abatacept and placebo groups were 55.8 % (95 % CI 41.4, 70.3) for 10 mg/kg abatacept and 41.5 % (95 % CI 26.3, 56.7) for 2 mg/kg abatacept (Fig. 2).

The Cochran-Armitage trend test also showed that the ACR50 and ACR70 were significantly greater in both abatacept groups compared with the placebo group at week 24 (Fig. 2). The ACR50 response rates at week 24 were 45.9 % (28/61 patients) for 10 mg/kg abatacept, 37.3 % (25/67 patients) for 2 mg/kg abatacept and 6.1 % (4/66 patients) for placebo. The corresponding ACR70 response rates were 21.3 % (13/61 patients), 16.4 % (11/67 patients) and 0 % (0/66 patients). The differences in ACR50 response rates between the abatacept and placebo groups were 39.8 % (95 % CI 26.1, 53.6 %) for 10 mg/kg abatacept and 31.3 % (95 % CI 18.3, 44.2 %) for 2 mg/kg abatacept, while the differences in ACR70 response rates were 21.3 % (95 % CI 11.0, 31.6 %) and 16.4 % (95 % CI 7.5, 25.3 %), respectively (Fig. 2). Both the ACR50 and ACR70 response rates showed a statistically significant dose–response relationship between the treatment groups at week 24, with the greatest efficacy in the 10 mg/kg abatacept group followed by the 2 mg/kg abatacept group, with the lowest response in the placebo group.

Analysis of the ACR response rates over time (with last observation carried forward) showed consistently higher ACR20 response rates in the 10 mg/kg abatacept group compared to the placebo group from week 2 to week 24, with a marked difference (41 %) as early as week 4. The 95 % CI for the difference between the 10 mg/kg abatacept

Table 1 Patient characteristics

	Abatacept (10 mg/kg)	Abatacept (2 mg/kg)	Placebo
Female, *n* (%)	49 (80.3)	57 (85.1)	52 (78.8)
Age (years)	53.4 ± 11.3	52.5 ± 11.1	53.4 ± 12.0
Weight (kg)	53.8 ± 8.0	56.2 ± 10.1	57.7 ± 9.6
Duration of RA, *n* (%)			
≤2 years	12 (19.7)	10 (14.9)	10 (15.2)
>2 to ≤5 years	14 (23.0)	26 (38.8)	18 (27.3)
>5 to ≤10 years	15 (24.6)	14 (20.9)	21 (31.8)
>10 years	20 (32.8)	17 (25.4)	17 (25.8)
Duration of RA (years)	7.4 ± 5.7	8.5 ± 9.0	7.3 ± 6.2
Tender joint count	21.8 ± 9.3	21.0 ± 8.2	21.6 ± 8.2
Swollen joint count	16.6 ± 6.7	17.6 ± 6.5	17.5 ± 6.1
HAQ physical function[a]	1.33 ± 0.59	1.24 ± 0.69	1.50 ± 0.73
CRP (mg/dL)	3.40 ± 2.74	2.98 ± 2.37	3.39 ± 2.28
DAS28-CRP	6.0 ± 0.7	5.8 ± 0.7	6.0 ± 0.7
Biologics-history, *n* (%)			
Prior use of infliximab (recombinant)	9 (14.8)	11 (16.4)	17 (25.8)
Prior use of etanercept (recombinant)	5 (8.2)	5 (7.5)	13 (19.7)
Prior use of adalimumab (recombinant) (study drug)	1 (1.6)	2 (3.0)	5 (7.6)
Prior use of tocilizumab (recombinant)	1 (1.6)	2 (3.0)	2 (3.0)
MTX dose (mg/week)	7.11 ± 1.00	7.11 ± 0.98	7.26 ± 0.96
Other DMARDs-history, *n* (%)			
Prior use of other DMARDs[a]	21 (34.4)	18 (26.9)	15 (22.7)
Concomitant adrenocorticosteroid[a], *n* (%)	47 (77.0)	54 (80.6)	56 (84.8)
Adrenocorticosteroid dose[b] (mg/day)	5.68 ± 2.21	5.81 ± 2.45	5.58 ± 2.47

Values are mean ± standard deviation or *n* (%)

CRP C-reactive protein, *DAS28* Disease Activity Score 28, *HAQ* Health Assessment Questionnaire, *MTX* methotrexate, *RA* rheumatoid arthritis

[a] other DMARDs = Salazosulfapyridine, Bucillamine, Tacrolimus hydrate, Auranofin, D-penicillamine, Gold sodium thiomalate, Mizoribine and Actaritused

[b] Oral adrenocorticosteroids were converted to the equivalent dose of prednisolone

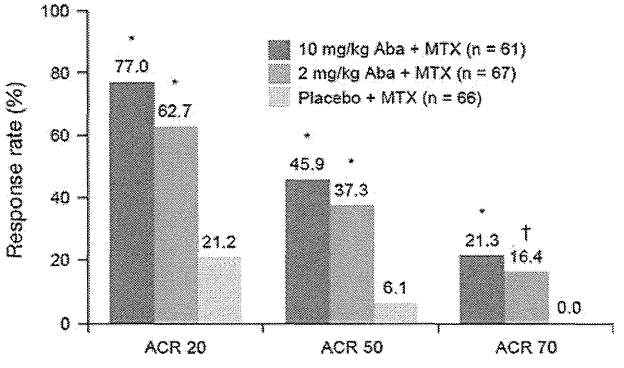

Fig. 2 ACR response rates at week 24. ACR20/50/70, 20, 50, or 70 % improvement from baseline in ACR score. Patients who discontinued treatment because of lack of efficacy were considered ACR non-responders at all subsequent time points. For all patients who discontinued treatment for other reasons, their last ACR response was carried forward. *$p < 0.001$ versus placebo (Cochran-Armitage χ^2 trend test); †$p = 0.002$ versus placebo (χ^2 test with continuous correction). *Aba* abatacept, *ACR* American College of Rheumatology, *MTX* methotrexate

group and the placebo group did not include 0 (Fig. 3a). A difference in ACR50 between the 10 mg/kg abatacept and placebo groups was also observed at week 4, with response rates of 13.1 and 1.5 %, respectively. The 10 mg/kg group showed higher ACR response rates than the placebo group that persisted until week 24 (Fig. 3b). The ACR70 response rate was 11.5 % in the abatacept 10 mg/kg group versus 0 % in the placebo group at week 12, which was maintained from week 12 to week 24 (Fig. 3c).

The 2 mg/kg abatacept group showed a clear improvement in the ACR20 response rate at week 8 compared to the placebo group (52.2 vs. 27.3 %) (Fig. 3a). At week 12, the 2 mg/kg abatacept group showed clear improvements in the ACR50 (23.9 vs. 6.1 %, respectively) and ACR70 (6.0 vs. 0 %, respectively) response rates (Fig. 3b, c) compared to the placebo group.

The DAS28-CRP values at baseline indicated high disease activity, with values of 6.0 ± 0.7, 5.8 ± 0.7, and 6.0 ± 0.7 in the 10 mg/kg abatacept, 2 mg/kg abatacept

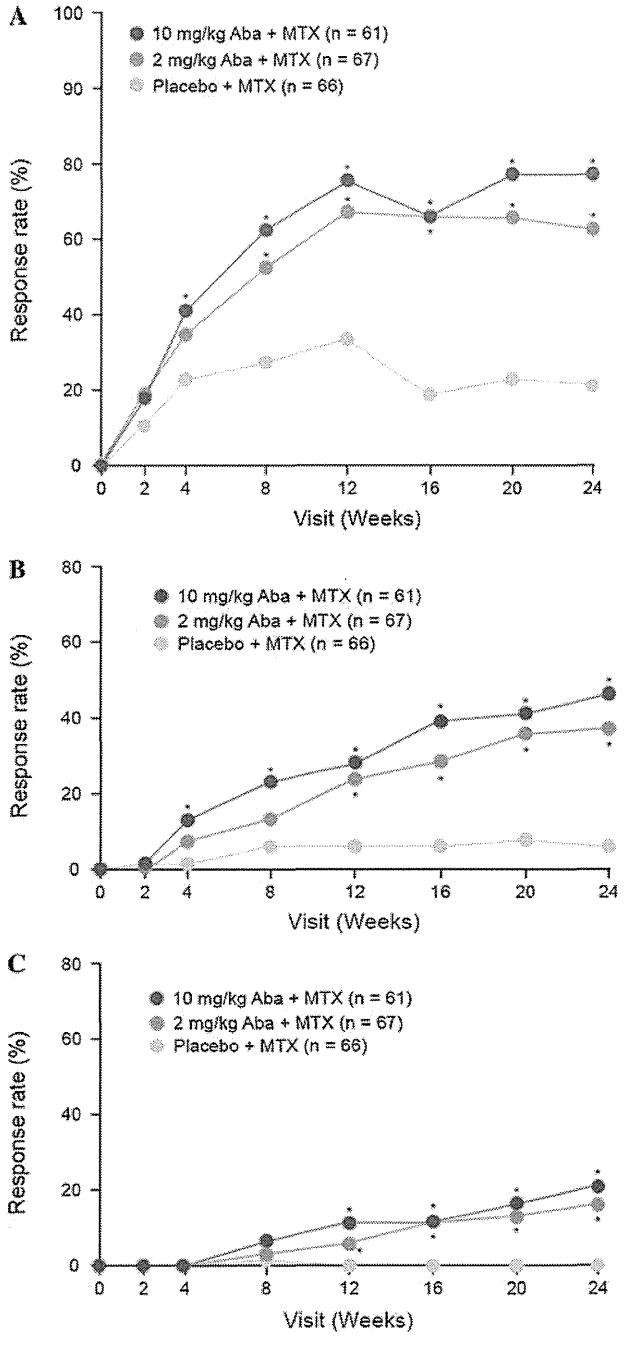

Fig. 3 ACR response rates over time (last observation carried forward). **a** ACR20, **b** ACR50, and **c** ACR70. ACR20/50/70, 20, 50,or 70 % improvement from baseline in ACR score. The 95 % confidence interval versus placebo did not include zero (*asterisk*). *Aba* abatacept, *ACR* American College of Rheumatology, *MTX* methotrexate

and placebo groups, respectively (Table 2). Individual components of the DAS28-CRP, including the number of swollen joints, number of tender joints, patient global assessment and serum CRP concentrations, showed similar trends. At week 24, DAS28-CRP decreased significantly in both abatacept groups compared with the placebo group (3.5 ± 1.3 in the 10 mg/kg abatacept group, 4.0 ± 1.2 in the 2 mg/kg abatacept group, and 5.3 ± 1.2 in the placebo group) (Table 2). The proportion of patients who achieved a response to the study drug, based on a reduction of DAS28-CRP of ≥1.2, by week 24 was 88.5 % (54/61 patients) in the 10 mg/kg abatacept group, 68.7 % (46/67 patients) in the 2 mg/kg abatacept group and 30.3 % (20/66 patients) in the placebo group (Fig. 4a). The proportions of patients with low disease activity (i.e., DAS28-CRP ≤3.2) were 41.0, 25.4, and 7.6 %, respectively, while the proportions of patients with remission (i.e., DAS28-CRP <2.6) were 24.6, 14.9, and 1.5 %, respectively (Fig. 4b). The rates of remission and low disease activity were greatest in the 10 mg/kg abatacept group (Fig. 4b).

The proportion of patients who showed an improvement in daily activities, defined as a reduction in HAQ score of ≥0.3 points, was greater in the 10 mg/kg abatacept group (60.7 %; 37/61 patients) than in the 2 mg/kg abatacept group (49.3 %; 33/67 patients), and the placebo group (24.2 %; 16/66 patients) (Fig. 5).

Safety

All of the patients ($n = 194$) who received at least one dose of study drug (61 in the 10 mg/kg abatacept group, 67 in the 2 mg/kg abatacept group, and 66 in the placebo group) were included in the safety evaluation.

SAEs were reported in 8.2 % (5/61), 3.0 % (2/67), and 9.1 % (6/66) of patients in the 10 mg/kg abatacept, 2 mg/kg abatacept, and placebo groups, respectively, (Table 3), and study drug-related SAEs were reported in 3.3 % (2/61), 0 % (0/67), and 1.5 % (1/66) of patients, respectively. Regarding SAEs, in the 10 mg/kg abatacept group, pure red cell aplasia, parvovirus infection and upper respiratory tract infection were reported in one patient, while abdominal pain and vomiting in a second. These SAEs resolved without treatment or with appropriate treatment. Discontinuation of the study drug because of AEs or SAEs occurred in the placebo group only. No deaths occurred during the study.

AEs were reported in 72.1 % (44/61), 73.1 % (49/67), and 62.1 % (41/66) of patients in the 10 mg/kg abatacept, 2 mg/kg abatacept and placebo groups, respectively, and study drug-related AEs were reported in 49.2 % (30/61), 59.7 % (40/67), and 34.8 % (23/66) of patients, respectively. The incidences of AEs and study drug-related AEs were similar in both abatacept groups, but were higher these groups compared with the placebo group. The most common AE was nasopharyngitis in each of the three treatment groups (Table 4). Most AEs were mild to moderate in intensity.

Table 2 Disease activity at baseline and at week 24

	Abatacept (10 mg/kg)		Abatacept (2 mg/kg)		Placebo	
	n = 61		*n* = 67		*n* = 66	
	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24
Tender joint count	21.8 ± 9.3	8.2 ± 9.5	21.0 ± 8.2	8.8 ± 7.2	21.6 ± 8.2	15.8 ± 12.6
Swollen joint count	16.6 ± 6.7	5.2 ± 4.5	17.6 ± 6.5	6.6 ± 5.5	17.5 ± 6.1	13.7 ± 10.0
Patient global VAS	63.5 ± 20.0	33.4 ± 20.8	59.6 ± 19.5	37.4 ± 22.6	67.2 ± 17.5	54.9 ± 21.2
HAQ physical function	1.4 ± 0.6	0.8 ± 0.6	1.3 ± 0.6	0.9 ± 0.7	1.6 ± 0.7	1.4 ± 0.7
CRP (mg/dL)	3.4 ± 2.7	0.9 ± 1.5	3.0 ± 2.4	1.3 ± 1.4	3.4 ± 2.3	3.4 ± 2.7
DAS28-CRP	6.0 ± 0.7	3.5 ± 1.3	5.8 ± 0.7	4.0 ± 1.2	6.0 ± 0.7	5.3 ± 1.2

Values are mean ± standard deviation

CRP C-reactive protein, *DAS28* Disease Activity Score 28, *HAQ* Health Assessment Questionnaire

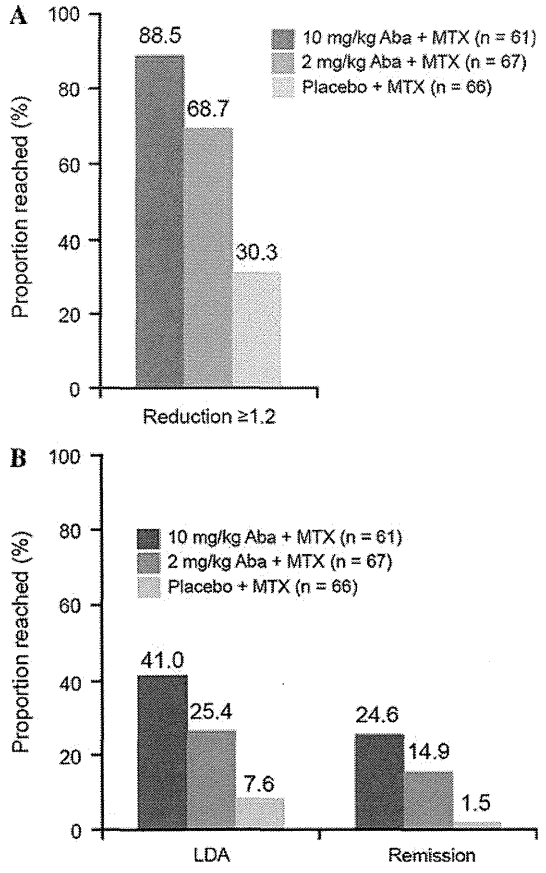

Fig. 4 Efficacy and disease status upon intravenous infusion of abatacept. The proportion of patients who improved based on a reduction of DAS28-CRP of ≥1.2 at week 24 is indicated in (**a**) and the proportion of patients with low disease activity and remission at week 24 are indicated in (**b**). Improved, DAS28-CRP change ≥1.2; LDA, low disease activity; DAS28-CRP ≤3.2; remission, DAS28-CRP <2.6. *Aba* abatacept, *CRP* C-reactive protein, *DAS28* Disease Activity Score 28, *LDAS* low disease activity, *MTX* methotrexate

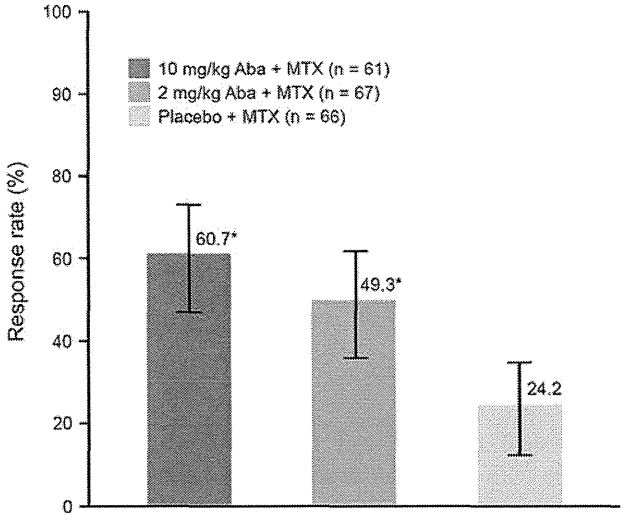

Fig. 5 HAQ response rates at week 24. The 95 % confidence interval versus placebo did not include zero (*asterisk*). *Aba* abatacept, *HAQ* Health Assessment Questionnaire, *MTX* methotrexate

Immunogenicity

The immunogenicity of abatacept was measured in 128 patients who received abatacept (61 in the 10 mg/kg abatacept group and 67 in the 2 mg/kg abatacept). None of these patients developed anti-abatacept or anti-CTLA4-T antibodies following administration of abatacept [26].

Discussion

The introduction of DMARDs and anti-TNF-α and anti-IL-6 agents has substantially revolutionized RA therapy. However, several limitations remain, including secondary failure of these drugs and discontinuation of treatment because of AEs, particularly in patients with RA with an inadequate response to conventional therapy. Abatacept is the first in a new class of RA treatments that selectively modulate the co-stimulatory signal required for full T cell activation. Phase II studies in Western populations have shown that treatment with abatacept is associated with significant reductions in disease activity and improvements

Table 3 Incidence of serious adverse events and adverse events

	Abatacept (10 mg/kg) $n = 61$	Abatacept (2 mg/kg) $n = 67$	Placebo $n = 66$
Deaths	0	0	0
Patients with SAEs	5 (8.2)	2 (3.0)	6 (9.1)
Patients with study drug-related SAEs	2 (3.3)	0	1 (1.5)
Patients who discontinued because of SAEs	0	0	2 (3.0)
Patients who discontinued because of AEs	0	0	2 (3.0)
Patients with AEs	44 (72.1)	49 (73.1)	41 (62.1)
Patients with study drug-related AEs	30 (49.2)	40 (59.7)	23 (34.8)

Values are *n* (%)

AE adverse event, *SAE* serious adverse event

Table 4 Adverse events occurring in ≥5 % of patients in any treatment group

System organ class and preferred term	Abatacept (10 mg/kg) $n = 61$	Abatacept (2 mg/kg) $n = 67$	Placebo $n = 66$
Gastrointestinal disorders	15 (24.6)	15 (22.4)	13 (19.7)
Stomatitis	5 (8.2)	2 (3.0)	3 (4.5)
Constipation	1 (1.6)	1 (1.5)	4 (6.1)
Infections and infestations	20 (32.8)	28 (41.8)	16 (24.2)
Nasopharyngitis	13 (21.3)	18 (26.9)	8 (12.1)
Cystitis	0	4 (6.0)	0
Investigations	7 (11.5)	7 (10.4)	5 (7.6)
Blood pressure increased	2 (3.3)	5 (7.5)	1 (1.5)
Nervous system disorders	5 (8.2)	8 (11.9)	6 (9.1)
Headaches	2 (3.3)	4 (6.0)	3 (4.5)
Respiratory, thoracic, and mediastinal disorders	7 (11.5)	8 (11.9)	8 (12.1)
Upper respiratory tract inflammation	5 (8.2)	3 (4.5)	3 (4.5)

in physical function over the course of 12 months in patients with active RA despite MTX treatment [17]. The efficacy and dose response, based on ACR20 response rates, and the safety of abatacept in the present study were similar to those reported in Western patients [10], suggesting that the results of global Phase III studies of abatacept [14, 18, 21] can be extrapolated to Japanese patients.

This study showed that the efficacy of 10 mg/kg abatacept was significantly greater than that of placebo in Japanese patients with active RA despite MTX therapy, based on the differences in ACR20, ACR50, and ACR70 response rates. These results in Japanese patients differ from those of the global Phase II study [10]. At week 24, the ACR20 response rates in the global Phase II study were 60.0, 41.9, and 35.3 % in the 10 mg/kg abatacept, 2 mg/kg abatacept, and placebo groups, respectively [10], compared to 77.0, 62.7, and 21.2 %, respectively, in the present study.

The high rate of response to 2 mg/kg abatacept among Japanese patients may be due to differences in baseline characteristics between patients in the global Phase II study [10] and the Japanese patients in our study. The Japanese patients enrolled in our study had a shorter duration of disease compared to those in the global study (mean duration 7.3–8.5 vs. 8.9–9.7 years, respectively), and fewer tender and swollen joints (mean number of tender joints 21.0–21.8 vs. 28.2–30.8, respectively; mean number of swollen joints 16.6–17.6 vs. 20.2–21.8, respectively). In addition, the patients in our study were treated with a lower dose of MTX than were patients in the global study (mean dose 7.1–7.3 mg/week vs. 15.0–15.8 mg/week, respectively) but had a higher mean CRP concentration (mean concentration 3.0–3.4 vs. 2.9–3.2 mg/dL, respectively).

Although the 2 mg/kg abatacept dose achieved high ACR response rates, 10 mg/kg abatacept had more rapid effects, with significant improvements in ACR20 and ACR50 response rates compared with placebo at week 4 in the 10 mg/kg group versus weeks 8 and 12, respectively, in the 2 mg/kg abatacept group. Based on these data, the 10 mg/kg dose was identified as the optimal dosage to rapidly achieve remission in Japanese patients.

Changes in disease activity were also assessed using the DAS28-CRP, which has been used in several pivotal studies [14, 18]. Generally, the European League Against Rheumatism (EULAR) response rates were greater when assessed using the DAS28-CRP than with the DAS28-ESR. A retrospective clinical study of infliximab identified a new

threshold for the definition of high and low disease activity states [27]. Both the DAS28-CRP and DAS28-ESR were shown to be valid and comparable measures of disease activity in patients with RA treated with abatacept [28]. In the present study, 24.6 % of patients treated with 10 mg/kg abatacept achieved remission, defined as DAS28-CRP <2.6, by week 24.

Abatacept demonstrated a good risk-to-benefit profile in the present Japanese patients with active RA; it was generally well tolerated, and the most common AEs, such as nasopharyngitis and upper respiratory tract inflammation, were similar to those reported with other biological agents [29–32]. Of note, no tuberculosis or infusion reactions were observed in this study. These findings are supported by the results of other studies in different patient populations, which have also shown abatacept to be well tolerated and to have a well-characterized safety profile [10, 13, 19]. The lack of immunogenicity observed in patients treated with abatacept in this study suggests that the development of resistance to this treatment is unlikely. Further studies, including post-marketing surveillance studies, are required to further evaluate the safety of abatacept.

The findings of this Phase II bridging study, and those of previous studies, support the role of T cell activation in RA and confirm the validity of inhibiting T cell activation as a therapeutic target in this disease.

RA is a major cause of chronic inflammation in patients worldwide and has a complex etiology, which includes both environmental and genetic factors. Several genes that confer susceptibility for the development of RA have been identified; some of these interact with environmental factors, while others are restricted to particular populations. Furthermore, some of the genes present in particular ethnic groups are present in Asian and European populations [33, 34]. Here, we demonstrated that abatacept was effective in Japanese patients, with outcomes equivalent to those seen in global studies, which included European patients.

In conclusion, abatacept demonstrated good efficacy at the 10 mg/kg dose compared with placebo, and was well tolerated with a good benefit-to-risk profile in Japanese patients with active RA despite MTX therapy. These findings indicate that 10 mg/kg is an appropriate clinical dose and is expected to be clinically useful in Japanese patients with active RA. Taken together, abatacept is suitable for the treatment of patients with active RA despite MTX therapy, regardless of ethnicity.

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Conflict of interest TT has received lecture fees from Abbott, Astellas Pharma, Brystol-Meyers, Chugai Pharma, Eisai Pharma, Mitsubishi-Tanabe Pharma, Pfizer, Takeda Pharmaceutical. AY is employee of Bristol-Myers K.K. NM has received research grants, consultant fees, and/or speakers' bureau honoraria from Chugai Pharmaceutical Co., Tanabe-Mitsubishi Pharmaceutical Co., Takeda Pharmaceutical Co., Pfizer Japan, Abbott Japan, Eisai Pharmaceutical Co., Astellas Pharmaceutical Co., and Bristol-Myers Squibb.

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EXTENDED REPORT

Golimumab monotherapy in Japanese patients with active rheumatoid arthritis despite prior treatment with disease-modifying antirheumatic drugs: results of the phase 2/3, multicentre, randomised, double-blind, placebo-controlled GO-MONO study through 24 weeks

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ABSTRACT

Objective To evaluate the efficacy and safety of golimumab 50 and 100 mg monotherapy in Japanese patients with active rheumatoid arthritis (RA) despite treatment with disease-modifying antirheumatic drugs (DMARDs).

Methods A total of 316 patients were randomised to receive subcutaneous injections every 4 weeks of placebo (group 1), golimumab 50 mg (group 2) or golimumab 100 mg (group 3); group 1 crossed over to golimumab 50 mg at week 16. The primary end point was the proportion of patients achieving ≥20% improvement in the American College of Rheumatology criteria (ACR20) at week 14. ACR50 and ACR70 response rates were also measured. Adverse events (AEs) were monitored throughout the study.

Results Demographics were similar across groups; the mean age was 52 years and 81.8% of patients (252/308) were female. Week 14 ACR20 response rates were significantly greater in groups 2 (51/101 (50.5%)) and 3 (60/102 (58.8%)) than in group 1 (20/105 (19.0%); $p<0.0001$ for both), as were ACR50 and ACR70 response rates. After placebo crossover at week 16, week 24 ACR response rates were similar in groups 1 and 2. Through week 16, 63.8% of patients in group 1, 62.4% in group 2 and 60.8% in group 3 had AEs and 1.9%, 1.0% and 2.0% had serious AEs. After week 16, one malignancy was reported (breast cancer, group 3). Infections were the most common AEs. No deaths or cases of tuberculosis were reported through week 24.

Conclusions Golimumab monotherapy (50 and 100 mg) was effective in reducing the signs and symptoms of RA in Japanese patients with active disease despite DMARD treatment.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by dysregulation of several cytokines, including tumour necrosis factor (TNF).[1 2] The bone and cartilage damage in the joints can significantly affect physical function[3] and the chronic inflammation of RA is associated with significant morbidity and mortality.[4] In observational studies, the anti-TNF agents infliximab[5] and etanercept[6] reduced disease activity in Japanese patients with RA.

Golimumab is a monoclonal antibody that binds with high affinity and specificity to TNF.[7] In large, phase 3, randomised, placebo-controlled trials, golimumab demonstrated efficacy in methotrexate (MTX)-naïve[8] and MTX-experienced patients with RA.[9] In these studies, many patients were treated with concomitant MTX. Some patients cannot tolerate MTX treatment[10]; therefore, it is clinically relevant to evaluate the safety and efficacy of golimumab monotherapy in Japanese patients with active RA who were previously treated with disease-modifying antirheumatic drugs (DMARDs).

PATIENTS AND METHODS

Patients

Patients (20–75 years) had to have a diagnosis of RA according to the American College of Rheumatology (ACR) criteria[11] for ≥3 months and active disease, despite previous DMARD treatment, defined as six or more swollen joints and six or more tender joints and two or more of the following: C-reactive protein (CRP) ≥2.0 mg/dl or erythrocyte sedimentation rate ≥28 mm/h using the Westergren method, morning stiffness ≥30 min, investigator-documented evidence of bone erosion on radiographs, or positive for anti-cyclic citrullinated peptide antibodies or rheumatoid factor. Patients were screened for latent and active tuberculosis (see also online supplementary text). All DMARDs were discontinued ≥4 weeks before the first study agent administration. Concomitant oral corticosteroids (stable dose ≤10 mg of prednisolone/day or equivalent) were permitted.

Study design

This was a phase 2/3 multicentre, randomised, double-blind, placebo-controlled trial carried out at 102 sites in Japan. Patients were randomly assigned (1:1:1) to receive subcutaneous injections every 4 weeks of placebo (group 1), golimumab 50 mg (group 2) or golimumab 100 mg (group 3). Concomitant DMARD treatment, including MTX, was prohibited in all treatment groups (a 4-week washout period was required). At week 16, all patients in group 1 crossed over to receive golimumab 50 mg in a double-blinded fashion.

The study was conducted according to the Declaration of Helsinki and in compliance with good clinical practice guidelines. The protocol was reviewed and approved by the institutional review board at each site. All patients provided written informed consent before any study-related procedures.

Study end points

Response to treatment was evaluated using the ACR criteria, the 28-joint count disease activity score (DAS28) using erythrocyte sedimentation rate and the ACR index of improvement in disease activity (ACR-N); physical function was evaluated with the Health Assessment Questionnaire-Disability Index (HAQ-DI). The primary end point was the proportion of patients achieving ≥20% improvement in ACR criteria (ACR20) at week 14. Due to ethical concerns about the potential for an inadequate response to placebo, week 14 was chosen for the primary efficacy assessment. Secondary end points included ACR50/70/90 response rates at weeks 14 and 24, changes from baseline at weeks 14 and 24 in DAS28 and HAQ-DI scores, ACR-N scores at weeks 14 and 24 and changes from baseline to week 24 in van der Heijde/Sharp (vdH–S) scores. Also the proportions of patients achieving a good or moderate DAS28 score[12 13] or DAS28 remission (score<2.6) were determined at weeks 14 and 24.

Radiographs of the hands and feet were obtained at baseline and week 24 or at the time of study discontinuation, if applicable, and scored by two independent readers (see online supplementary text). Radiographic progression was evaluated as changes from baseline to week 24 in the vdH–S score.[14] Erosion, joint space narrowing and total vdH–S scores are reported. All radiographs were scored by BioClinica Corporation (Newtown, Pennsylvania, USA) and readers were blinded to patient identity, treatment group and time point.

Patients were monitored for adverse events (AEs), including injection-site reactions and abnormal routine laboratory values.

Pharmacokinetic analyses and immunogenicity

Blood samples for the measurement of serum golimumab concentrations were obtained at weeks 0, 4, 8, 12, 14, 16, 20 and 24, with one additional sample between weeks 4 and 12. Blood samples for evaluation of antibodies to golimumab were obtained at weeks 0, 12 and 24. Antibodies to golimumab were detected using a previously described validated antigen bridging enzyme immunoassay.[15] Blood samples were drawn before administration of the study agent.

A post hoc analysis evaluated week 24 ACR20, ACR50 and ACR70 response rates for patients stratified according to the following serum golimumab concentration quartiles: <0.24 μg/ml, ≥0.24–<0.63 μg/ml, ≥0.63–<1.29 μg/ml and ≥1.29 μg/ml.

Statistical analyses

All patients who received at least one study agent injection and had efficacy data available were included in the efficacy analysis. All patients who received at least one study agent injection were included in the safety analysis. Patients who received one or more golimumab injection and had pharmacokinetic data available were included in the pharmacokinetic analysis. Descriptive statistics are reported. Differences between the treatment groups in ACR and DAS28 response rates were assessed using a χ^2 test. Type I error at the 0.05 level of significance was preserved with a hierarchical approach to control for multiplicity, in which a comparison between groups 3 and 1 was performed first and a comparison between groups 2 and 1 was performed only if the difference between groups 3 and 1 was significant. For changes in continuous variables, treatment group differences were assessed using analysis of covariance (ANCOVA) for HAQ-DI, DAS28 and vdH–S scores or analysis of variance (ANOVA) for ACR-N scores. Least-squares means and 95% CIs are reported. ACR response rates, ACR-N and HAQ-DI were calculated using the last observation carried forward method for the week 14 and week 24 time points. In the analysis of DAS28 response at weeks 14 and 24, observed data were used with no imputation for missing data, with the exception of the DAS28 remission analysis, in which patients with missing data were counted as non-responders. Observed data were used in the pharmacokinetic analysis.

Changes from baseline in vdH–S scores were compared between each golimumab group and placebo using two methods. ANCOVA was the prespecified method in the protocol and was chosen for consistency with the analyses of other continuous variables. A post hoc ANOVA based on van der Waerden normal scores was undertaken to account for the non-normal data distribution due to one patient in group 3 with an atypically large change in vdH–S score. Additionally, a cumulative probability plot of the changes in vdH–S scores from baseline to week 24 for each treatment group was constructed.

Assuming that 5% of patients would be excluded from the efficacy analysis owing to study discontinuation, the target total sample size of 300 patients provided >90% power to detect a difference between groups 2 and 3 and group 1 in ACR20 response rates at week 14 (α=0.05).

RESULTS

Patient disposition and baseline characteristics

A total of 316 patients were randomised; eight withdrew consent before administration of any study agents (figure 1). Therefore, 308 patients received one or more study agent administration (group 1, n=105; group 2, n=101; group 3, n=102). Patient demographics and baseline disease characteristics were well balanced across all groups (table 1). Among all patients, 82% were female, the mean age was 52 years, the mean disease duration was 8.9 years and the mean CRP level was 2.5 mg/dl. Most (73.7%) patients received prior MTX treatment.

Efficacy results

Clinical response and physical function

At week 14, significantly greater proportions of patients in groups 2 (50.5%) and 3 (58.8%) achieved an ACR20 response in comparison with group 1 (19.0%; p<0.0001 for both) (table 2). Likewise, significantly higher ACR50 and ACR70 response rates were seen in groups 2 and 3 than in group 1. While no patient in group 1 had an ACR90 response at week 14, three patients in group 2 and two in group 3 achieved an ACR90 response; however, statistical significance from placebo was not attained.

At week 24, after placebo crossover to golimumab 50 mg at week 16, patients in group 1 generally had ACR response rates

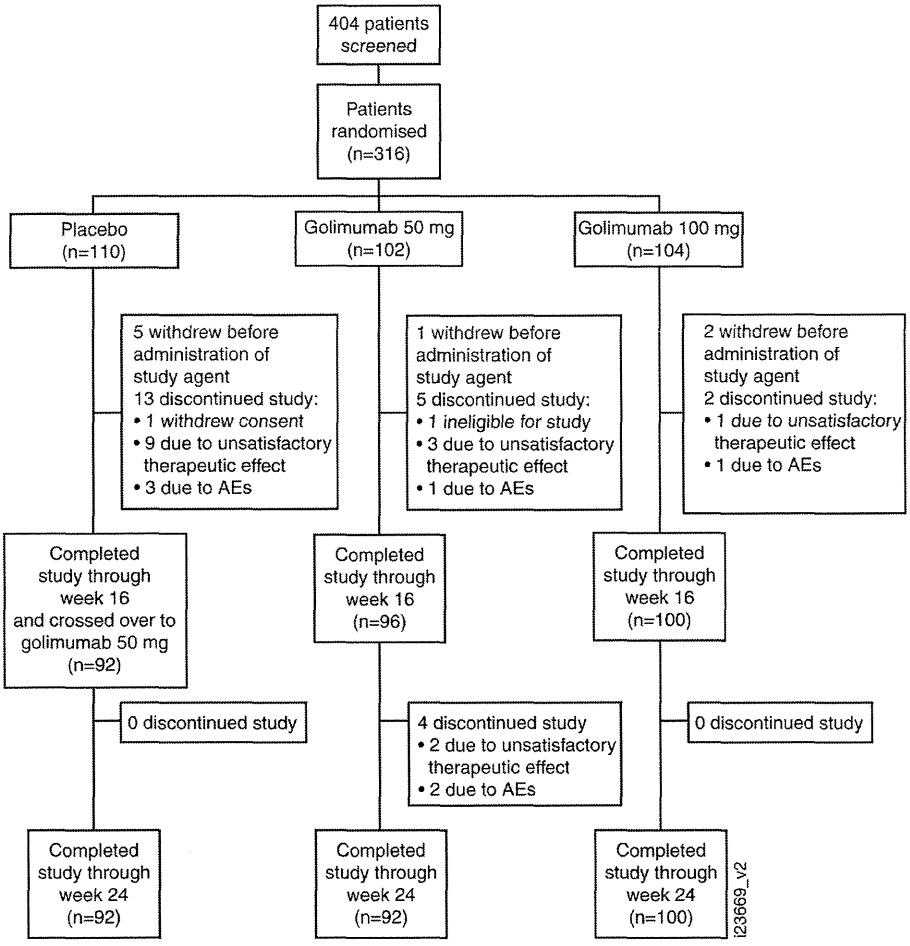

Figure 1 Patient disposition through week 24. AE, adverse event.

similar to those for patients who were initially assigned to group 2 from baseline (table 2). In group 3, week 14 ACR response rates were maintained at week 24.

Mean ACR-N scores at week 14 were significantly greater in groups 2 (30.5) and 3 (33.0) than in group 1 (9.1; $p<0.0001$ for both) (table 2). Mean improvements from baseline to week 14 in DAS28 scores were also significantly greater in groups 2 and 3 than in group 1 and significantly greater proportions of patients in groups 2 and 3 achieved a moderate or good DAS28 response or DAS28 remission. Improvements from baseline in physical function (HAQ-DI) were also significantly greater in groups 2 and 3 than in group 1.

Patients in group 1 had ACR-N scores at week 24 and mean improvements in DAS28 and HAQ-DI scores from baseline to week 24 that were similar to those seen in patients who were initially randomised to group 2. In group 3, week 14 ACR-N, DAS28 and HAQ-DI responses were maintained at week 24.

Radiographic progression

Two patients did not have complete radiographic data available (missing baseline data for one patient in group 3 and missing week 24 data for one patient in group 2) and changes from baseline in vdH–S score for these patients were substituted with the median change for all patients. Agreement between the two primary readers was good, with intraclass correlation coefficients of 0.98 at baseline and week 24 and 0.80 for the change at week 24. The proportion of patients with a change in total vdH–S score greater than the smallest detectable change was 22.1% (group 1, n=27; group 2, n=21; group 3, n=20).

At week 24, increases in erosion, joint space narrowing and total vdH–S scores were seen in all three groups (table 2), with smaller changes in erosion and total scores in groups 2 and 3, indicating less radiographic progression than in group 1, as shown in the probability plot (figure 2). In the a priori analysis (ANCOVA), no significant differences were seen in mean changes between groups 2 and 3 and group 1 at week 24. In the post hoc ANOVA using normalised scores, no significant differences were seen between groups 2 and 1. Although increases from baseline were observed in both groups 3 and 1, the mean changes in erosion and total vdH–S scores in group 3 were statistically significantly smaller than those in group 1 (1.1 vs 1.3, p=0.0316 and 2.1 vs 2.6, p=0.0043, respectively). Also, the median changes in total vdH–S scores followed a trend, showing less radiographic progression in groups 2 and 3 than in group 1 (0.5 and 0.0, respectively, vs 1.0).

Golimumab pharmacokinetics and antibodies to golimumab

Through week 16, serum golimumab levels increased in a dose-proportional manner; steady state was reached at week 12. Median serum golimumab concentrations for groups 2 and 3, respectively, were 0.52 μg/ml and 1.17 μg/ml at week 12 and

Table 1 Baseline patient demographics and disease characteristics

Characteristics	Group 1: Placebo	Group 2: Golimumab 50 mg	Group 3: Golimumab 100 mg	Total
Patients, n	105	101	102	308
Female, n (%)	86 (81.9)	81 (80.2)	85 (83.3)	252 (81.8)
Age, years	52.4 (11.1)	52.9 (11.3)	51.6 (11.9)	52.3 (11.4)
Body weight, kg	54.4 (10.4)	56.2 (12.4)	53.9 (9.8)	54.8 (10.9)
Duration of RA, years	9.2 (8.6)	8.1 (8.4)	9.4 (8.5)	8.9 (8.5)
Swollen joint count (0–66)	13.1 (6.9)	12.6 (5.8)	12.9 (6.7)	12.9 (6.5)
Tender joint count (0–68)	14.9 (8.5)	15.5 (9.0)	16.6 (10.2)	15.7 (9.3)
Patient's assessment of pain (VAS; 0–100 mm)	55.2 (24.5)	55.6 (22.3)	57.5 (23.1)	56.1 (23.3)
Patient's global assessment (VAS; 0–100 mm)	54.3 (25.4)	54.3 (23.7)	53.9 (24.5)	54.2 (24.5)
Physician's global assessment (VAS; 0–100 mm)	58.8 (17.8)	58.4 (18.1)	59.6 (18.3)	58.9 (18.0)
CRP, mg/dl	2.5 (2.5)	2.2 (2.5)	2.6 (2.8)	2.5 (2.6)
DAS28-ESR	5.9 (1.0)	5.8 (1.1)	6.0 (1.0)	5.9 (1.0)
HAQ-DI (0-3)	1.0 (0.6)	1.1 (0.6)	1.0 (0.6)	1.0 (0.6)

Data are presented as mean (SD) unless otherwise noted.
Results include data for all randomised patients who received at least one administration of the study agent and had available efficacy data.
CRP, C-reactive protein; DAS28-ESR, 28-joint Disease Activity Score using erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; RA, rheumatoid arthritis; VAS, visual analogue scale.

0.46 μg/ml and 1.04 μg/ml at week 16. Median serum concentrations at week 24 were 0.35 μg/ml in group 1, 0.43 μg/ml in group 2 and 0.99 μg/ml in group 3. Week 24 ACR20, ACR50 and ACR70 response rates were evaluated according to serum golimumab concentration, with patients stratified by the following quartiles: <0.24 μg/ml (n=45), ≥0.24–<0.63 μg/ml (n=50), ≥0.63–<1.29 μg/ml (n=49) and ≥1.29 μg/ml (n=48). Overall, response rates were lowest in patients with serum golimumab concentrations <0.24 μg/ml and increased with increasing serum golimumab concentration (figure 3).

At week 12, two patients (2.0%) each in groups 2 and 3 tested positive for antibodies to golimumab. At week 24, three patients each in group 1 (3.3%) and group 2 (3.2%) and four patients (4.0%) in group 3 tested positive for antibodies to golimumab. No antibody-positive patient demonstrated an ACR response.

Adverse events

Through week 16 (placebo-controlled period), AEs occurred in 63.8% of patients in group 1, 62.4% in group 2 and 60.8% in group 3 (table 3). Most AEs were mild. The most common AEs were infections (group 1 (23.8%); group 2 (26.7%); group 3 (28.4%)). The most common infections among all golimumab-treated patients were nasopharyngitis (16.3%), pharyngitis (3.4%) and gastroenteritis (2.0%). Three patients (2.9%) in group 1 (herpes zoster, atypical mycobacterial infection and abnormal liver function test), two patients (2.0%) in group 2 (liver disorder and cataract) and one patient (1.0%) in group 3 (transient cerebral ischaemic attack) discontinued the study agent owing to AEs. Serious AEs (SAEs) through week 16 were herpes zoster and organising pneumonia (n=1 each) in group 1, hydrocele (n=1) in group 2 and cellulitis and transient ischaemic attack (n=1 each) in group 3. When assessed by length of follow-up, the incidences (95% CI) of serious infection at week 24 were 3.30 (0.08 to 18.38), 1.69 (0.04 to 9.40) and 2.16 (0.05 to 12.01) for groups 1, 2 and 3, respectively.

After the placebo crossover at week 16, AEs occurred in 31 (33.7%) patients in group 1, 34 (35.4%) in group 2 and 33 (33.0%) in group 3 through week 24 (table 3). Infections were the most common AEs during this time period, consistent with results seen during the placebo-controlled period. AEs leading to discontinuation of the study agent after week 16 were ovarian neoplasm (non-malignant; n=1) and RA (n=1) in group 2 and breast cancer (n=1) in group 3. After week 16, SAEs occurred in three patients in group 2 (non-malignant ovarian neoplasm and dental pulpitis, each in one patient; paroxysmal tachycardia and RA in one patient) and in two patients in group 3 (breast cancer, between weeks 20 and 24 and organising pneumonia, one patient each); no SAEs were reported in group 1 during this period.

The incidence of injection-site reactions through week 16 was similar among all groups (group 1, 7/105 (6.7%); group 2, 8/101 (7.9%); group 3, 8/102 (7.8%)). From week 16 through week 24, the rates of injection-site reactions were 3.3% (3/92) in group 1, 6.3% (6/96) in group 2 and 5.0% (5/100) in group 3. All injection-site reactions were mild.

There were no reports of anaphylactic reactions, serum sickness-like reactions, or deaths through week 24. No cases of tuberculosis were reported through week 24; however, one case of atypical mycobacterial infection occurred in group 1 before week 16.

DISCUSSION

In this phase 2/3 study of golimumab 50 mg and 100 mg in Japanese patients with active RA despite DMARD treatment, those treated with golimumab monotherapy had significant improvements from baseline to week 14 in clinical measures of efficacy, including ACR20, ACR50 and ACR70 response rates and DAS28 and ACR-N scores, in comparison with those who received placebo. Physical function was also significantly improved from baseline in the golimumab groups compared with placebo. These significant improvements were seen despite the overall study population displaying relatively mild disease at study outset (mean swollen/tender joint counts of 13/16). However, clinical response to golimumab monotherapy was relatively modest in comparison with golimumab+MTX treatment in another Japanese population.[16]

Patients with active RA despite previous MTX treatment were evaluated previously in the large phase 3 GO-FORWARD trial.[9] While concomitant MTX was included in GO-FORWARD golimumab 100 mg monotherapy was also evaluated. ACR responses were also evaluated at week 14 in both trials and while significantly greater ACR response rates were achieved in group 3 in this study in comparison with placebo,

Table 2 Clinical efficacy and radiographic results† through week 24

	Placebo-controlled period			Placebo crossover period		
	Week 14			Week 24		
	Group 1: Placebo (n=105)	Group 2: Golimumab 50 mg (n=101)	Group 3: Golimumab 100 mg (n=102)	Group 1: Placebo→Golimumab 50 mg (n=105)	Group 2: Golimumab 50 mg (n=101‡)	Group 3: Golimumab 100 mg (n=102)
Clinical efficacy results						
ACR20 response	20 (19.0)	51 (50.5) p<0.0001	60 (58.8) p<0.0001	18 (17.1)	47 (46.5) p<0.0001	71 (69.6) p<0.0001
ACR50 response	6 (5.7)	29 (28.7) p<0.0001	33 (32.4) p<0.0001	8 (7.6)	28 (27.7) p=0.0001	43 (42.2) p<0.0001
ACR70 response	1 (1.0)	13 (12.9) p=0.0007	12 (11.8) p=0.0013	2 (1.9)	17 (16.8) p=0.0002	22 (21.6) p<0.0001
ACR90 response	0 (0.0)	3 (3.0) p=0.0752	2 (2.0) p=0.1493	0	5 (5.0) p=0.021	3 (2.9) p=0.0767
ACR-N	9.1 (4.3 to 14.0)	30.5 (25.6, 35.5) p<0.0001	33.0 (28.1, 38.0) p<0.0001	9.3 (3.9, 14.7)	30.9 (25.4, 36.4) p<0.0001	40.0 (34.6, 45.5) p<0.0001
DAS28-ESR						
Change from baseline	n=94 −0.3 (−0.6 to −0.1)	n=97 −1.5 (−1.8, −1.3) p<0.0001	n=100 −1.9 (−2.1 to −1.7) p<0.0001	n=91 −1.5 (−1.8, −1.2)	n=93 −1.6 (−1.9 to −1.4)	n=100 −1.9 (−2.1, −1.6)
Moderate response	n=93 27 (29.0)	n=97 69 (71.1) p<0.0001	n=100 74 (74.0) p<0.0001	n=91 56 (61.5)	n=93 65 (69.9)	n=100 78 (78.0)
Good response	n=93 4 (4.3)	n=97 23 (23.7) p=0.0001	n=100 32 (32.0) p<0.0001	n=91 21 (23.1)	n=93 21 (22.6)	n=100 31 (31.0)
Remission	n=94 2 (2.1)	n=97 13 (13.4) p=0.0025	n=100 23 (23.0) p<0.0001	n=92 8 (8.7)	n=93 16 (17.2)	n=100 19 (19.0)
HAQ-DI						
Change from baseline	−0.03 (−0.12 to 0.06)	0.24 (0.15 to 0.34) p<0.0001	0.33 (0.24 to 0.42) p<0.0001	−0.03 (−0.13 to 0.07)	0.23 (0.13 to 0.33) p=0.0003	0.33 (0.23 to 0.43) p<0.0001
Radiographic results						
vdH–S score, baseline						
Total	–	–	–	56.1 (62.2)	43.8 (50.6)	56.9 (57.0)
Joint space narrowing	–	–	–	25.9 (30.2)	19.9 (24.0)	25.3 (26.2)
Erosion	–	–	–	30.2 (33.8)	23.9 (28.3)	31.7 (33.0)
vdH–S score, change from baseline to week 24						
Total				n=105 2.6 (4.7) 1.0 (−2.5 to 29.8)	n=100 1.9 (4.1) 0.5 (−1.8 to 23.0) p=0.5091* p=0.1802**	n=102 2.1 (10.4) 0.0 (−2.5 to 102.5) p=0.6573* p=0.0043**
Joint space narrowing				n=92 0.9 (1.9) 0.0 (−1.0 to 9.5)	n=93 1.0 (2.8) 0.0 (−1.5 to 17.5) p=0.7530* p=0.3373**	n=99 1.0 (5.1) 0.0 (−2.0 to 48.5) p=0.9353* p=0.0832**

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	n=92	n=93	n=99
	1.3 (2.5)	1.0 (2.1)	1.1 (5.7)
	0.5 (−2.5 to 14.5)	0.5 (−1.5 to 11.5)	0.0 (−2.5 to 54.0)
		p=0.6272*	p=0.7614*
		p=0.5895**	p=0.0316**
Erosion			

*p Values based on analysis of covariance on least-squares mean and two-sided 95% CIs with treatment and baseline value as covariates.
**p Values based on analysis of variance on van der Waerden normal scores.
†Clinical efficacy data are presented as n (%) or least-squares mean (95% CI). Radiographic data are presented as mean (SD) and median (range).
‡Data from one patient who discontinued the study before week 24 were included in these analyses because the timing of the study termination visit fell within the prespecified time period for week 24 data collection.
ACR20/50/70/90, 20%/50%/70%/90% improvement in the American College of Rheumatology criteria; ACR-N, American College of Rheumatology index of improvement; DAS28-ESR, 28-joint Disease Activity Score using erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; vdH–S, van der Heijde/Sharp.

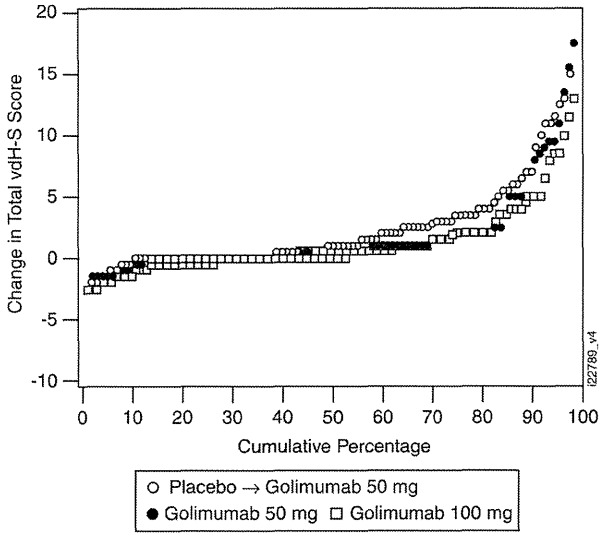

Figure 2 Cumulative probability plot of changes in van der Heijde-Sharp (vdH–S) scores from baseline to week 24 Data from one patient in the golimumab 100 mg group who had an atypically large change in vdH–S score were excluded.

the primary end point was not achieved in the golimumab 100 mg monotherapy group in the GO-FORWARD trial. Possible explanations for the non-statistically significant response in the GO-FORWARD 100 mg monotherapy group were previously described (eg, the relatively low disease activity in the trial population and the high response rate in the MTX monotherapy group).[9] However, factors such as patient body weight, which is known to affect the pharmacokinetic properties of monoclonal antibodies,[17–19] may also account for the difference in response seen in the two trials. While a previous study found no apparent differences in the pharmacokinetic parameters of golimumab in healthy body-weight-matched Caucasian and Japanese male subjects,[20] it is possible that the body weights of patients in 100 mg monotherapy groups in

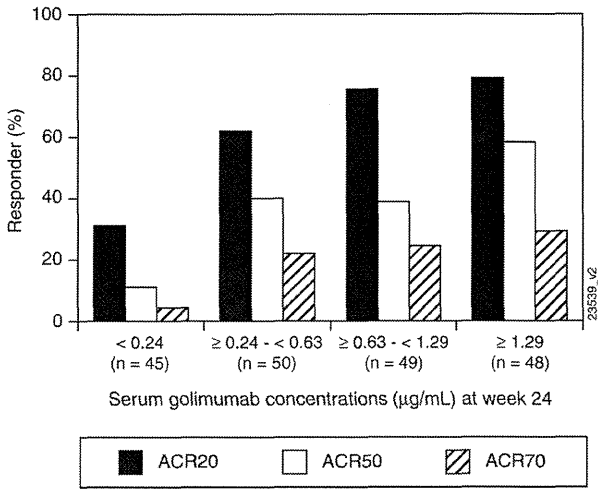

Figure 3 The proportions of patients achieving an ACR20, ACR50 and ACR70 responses stratified by serum golimumab concentration quartiles (μg/ml) at week 24. ACR20/50/70, 20%/50%/70% improvement in the ACR criteria.

Table 3 Week 16 and week 24 safety results

	Placebo-controlled period			Placebo crossover period			Cumulative	
	Weeks 0–16			Weeks 16–24			Weeks 0–24	
	Group 1: Placebo	Group 2: Golimumab 50 mg	Group 3: Golimumab 100 mg	Group 1: Placebo→Golimumab 50 mg	Group 2: Golimumab 50 mg	Group 3: Golimumab 100 mg	Group 2: Golimumab 50 mg	Group 3: Golimumab 100 mg
Patients, n	105	101	102	92	96	100	101	102
Patients with AEs	67 (63.8)	63 (62.4)	62 (60.8)	31 (33.7)	34 (35.4)	33 (33.0)	72 (71.3)	72 (70.6)
Patients with SAEs	2 (1.9)	1 (1.0)	2 (2.0)	0 (0)	3 (3.1)	2 (2.0)	4 (4.0)	4 (3.9)
Patients with AEs leading to discontinuation of study agent	3 (2.9)	2 (2.0)	1 (1.0)	0 (0)	2 (2.1)	1 (1.0)	4 (4.0)	2 (2.0)
Patients with infections	25 (23.8)	27 (26.7)	29 (28.4)	5 (5.4)	11 (11.5)	7 (7.0)	33 (32.7)	34 (33.3)
Patients with serious infections	1 (1.0)	0 (0)	1 (1.0)	0 (0)	1 (1.0)	0 (0)	1 (1.0)	1 (1.0)
Patients with abnormal LFTs	3 (2.9)	0 (0)	4 (3.9)	0 (0)	0 (0)	0 (0)	0 (0)	4 (3.9)
Patients with injection-site reactions	7 (6.7)	8 (7.9)	8 (7.8)	3 (3.3)	6 (6.3)	5 (5.0)	12 (11.9)	10 (9.8)
Patients with neoplasms (benign, malignant and unspecified)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2.1)	1 (1.0)	2 (2.0)	1 (1.0)
Breast cancer	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.0)	0 (0)	1 (1.0)
Skin papilloma	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.0)	0 (0)	1 (1.0)	0 (0)
Ovarian neoplasm	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.0)	0 (0)	1 (1.0)	0 (0)

Data are presented as n (%) unless otherwise noted.
AEs, adverse events; LFT, liver function test; SAEs, serious adverse events.

this trial and in GO-FORWARD might have varied considerably[21] given that Japanese patients are generally more slight, and the resulting dose per unit mass would be higher than in other populations. Indeed, treatment effects on radiographic progression appear to be related to serum golimumab concentrations, as patients receiving golimumab 50 mg+MTX in the GO-FORTH trial in Japanese patients with RA (week 16 median serum golimumab concentration=0.73 μg/ml) demonstrated significantly less radiographic progression than placebo-treated patients,[16] while such a difference was not seen in this study, in which patients receiving golimumab 50 mg had a week 16 median serum golimumab concentration of 0.46 μg/ml.

Radiographic progression was evaluated at week 24, at which point patients randomised to group 1 had been receiving golimumab 50 mg since week 16. The a priori ANCOVA did not show significant differences in radiographic progression between either groups 2 or 3 and group 1; however, in a post hoc analysis using normalised data, significantly smaller changes from baseline in erosion and total vdH–S scores were seen in group 3 than in group 1. This significant difference was confirmed by an additional ANCOVA that excluded a single group 3 patient with an atypically large change in vdH–S score (p=0.01; data not shown). Biological monotherapy with the anti-interleukin 6 agent tocilizumab has also demonstrated radiographic benefit in patients with RA with inadequate response to DMARD treatment.[22] In this study, the mean baseline CRP level, which is a good predictor of radiographic progression,[23] was moderately raised and 22.1% of patients had a change in total vdH–S that exceeded the smallest detectable change. In contrast, only 4.3% of patients in GO-FORWARD had such a change in total vdH–S score.[24] Thus, patients in our study probably had higher disease activity than patients in GO-FORWARD. This may account for the observation that radiographic progression in this study was greater than expected based on the clinical response seen at similar time points in earlier golimumab trials, including GO-FORWARD.[24] Our results suggest that golimumab 100 mg monotherapy may prevent further joint damage in Japanese patients with active radiographic progression, which is consistent with the golimumab package insert approved by the Japanese Pharmaceuticals and Medical Devices Agency.[25]

Golimumab was generally well tolerated. Infections were the most common AEs. Serious infections were reported in two patients through week 16 and one patient between weeks 16 and 24; the week 24 incidences per 100 patient-years of follow-up indicated no increase in serious infection versus placebo. Most AEs were mild and few patients discontinued due to AEs. Rates of SAEs, serious infections and malignancies were low. No deaths and one malignancy (breast cancer) occurred through week 24. Of note, this study was not powered to detect rare events and these findings are limited also by the short-term nature of the analysis.

This was the first golimumab monotherapy study to demonstrate that Japanese patients with active RA despite prior DMARD treatment had significantly improved signs and symptoms of RA after 14 weeks of treatment with 50 or 100 mg golimumab in comparison with placebo. Group 3 had significantly less radiographic progression than group 1 when analysed post hoc using normalised scores, and median changes in total vdH–S scores suggested a dose-dependent trend. Additional long-term analyses are needed to further explore the effect of golimumab monotherapy on joint destruction and fully assess its safety profile in Japanese patients with RA.

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Golimumab monotherapy in Japanese patients with active rheumatoid arthritis despite prior treatment with disease-modifying antirheumatic drugs: results of the phase 2/3, multicentre, randomised, double-blind, placebo-controlled GO-MONO study through 24 weeks

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ORIGINAL ARTICLE

A phase 3 randomized, double-blind, multicenter comparative study evaluating the effect of etanercept versus methotrexate on radiographic outcomes, disease activity, and safety in Japanese subjects with active rheumatoid arthritis

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Abstract
Objectives The aim of this phase 3, double-blind study was to compare the radiographic and clinical effects of etanercept (ETN) versus methotrexate (MTX) over 52 weeks in Japanese subjects with active rheumatoid arthritis.
Methods The study population comprised 550 subjects with inadequate response to ≥1 disease-modifying anti-rheumatic drugs who were randomized to treatment groups of ETN 25 mg twice weekly (BIW; $n = 182$), ETN 10 mg BIW ($n = 192$), or MTX (≤8.0 mg/week; $n = 176$).
Results Of the 550 subjects initially enrolled in the three treatment groups, 21.6 % discontinued the study; a significantly higher proportion of those who withdrew from the study due to lack of efficacy were in the MTX (21.6 %) group compared with the ETN 25 mg (3.3 %) and ETN 10 mg (6.8 %) groups ($P < 0.001$). Mean change from baseline in the modified total Sharp score at week 52 (primary endpoint) was significantly lower in the ETN 25 mg [3.33; standard error (SE), 0.73] and ETN 10 mg (5.19; SE 0.93) groups than in the MTX group (9.82; SE 1.16; $P < 0.0001$ vs. either ETN group). Compared with subjects receiving MTX, significantly higher percentages of subjects treated with ETN 25 and 10 mg achieved American College of Rheumatology (ACR) ACR20 and ACR50 response rates at all time points ($P < 0.01$). ETN was well-tolerated, with no unexpected safety findings.
Conclusions ETN 25 mg BIW and ETN 10 mg BIW slowed radiographic progression and improved clinical outcomes more effectively than MTX in this Japanese population.

Keywords Etanercept · Methotrexate · Randomized controlled trial · Rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is a chronic, systemic disease that is characterized by joint inflammation that often leads to bone destruction. The resulting structural damage to bones can severely affect the functional ability of patients with RA [1, 2]. Regardless of the disease duration, radiographic progression tends to occur at a constant rate [3] and can continue to progress even in patients whose disease activity seems to be under control [4, 5].

Therapeutic targets for patients with RA are increasingly being defined by improvements in both clinical and radiographic outcomes; therefore, new treatment strategies are needed that aim to achieve these goals [6]. Although conventional disease-modifying anti-rheumatic drugs (DMARDs) may show improvements in clinical and functional outcomes of subjects with active RA, they may not be sufficiently efficacious in slowing joint destruction [7–9]. Previous studies have demonstrated that tumor necrosis factor inhibitors (TNFi) improve outcomes in terms of both clinical disease activity and radiographic