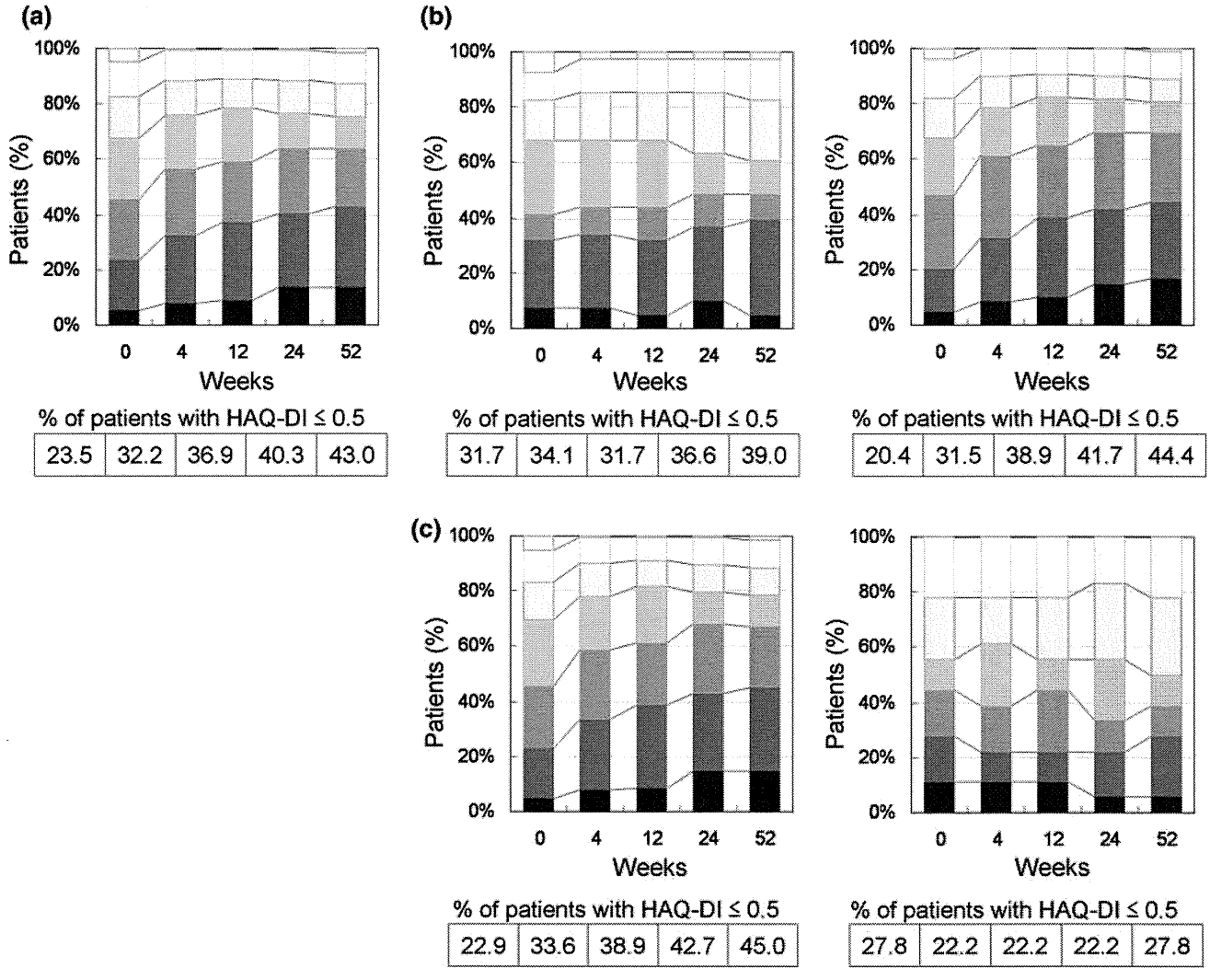

Fig. 4 Time course of the Health Assessment Questionnaire—Disability Index (HAQ-DI) over 52 weeks following the initiation of adalimumab treatment. Data were analyzed by the last observation carried forward (LOCF) method. **a** All patients ($n = 149$), **b** previous biologics (+, *left*) ($n = 41$) and (−, *right*) ($n = 108$), and **c** concomitant MTX (+, *left*) ($n = 131$) and (−, *right*) ($n = 18$). HAQ-DI was categorized as follows

maintaining remission status (DAS28-ESR < 2.6) for more than 24 weeks. The median ADA treatment duration in those 5 patients was 38 weeks (range 28–52 weeks).

Discussion

The present study was carried out to retrospectively analyze the efficacy and safety of ADA in Japanese patients with RA. The study included 167 patients with all individual DAS28-ESR components at baseline. Further, 149 of these had baseline HAQ-DI, and 87 had evaluable radiographic data. For our subjects, ADA therapy provided significant clinical, functional, and radiographic benefits during routine clinical care while also demonstrating generally acceptable safety and tolerability.

The PREMIER study showed that when combination treatment with ADA and MTX is initiated early, it leads to superior clinical, functional, and radiographic outcomes as compared with treatment with MTX alone or ADA alone;

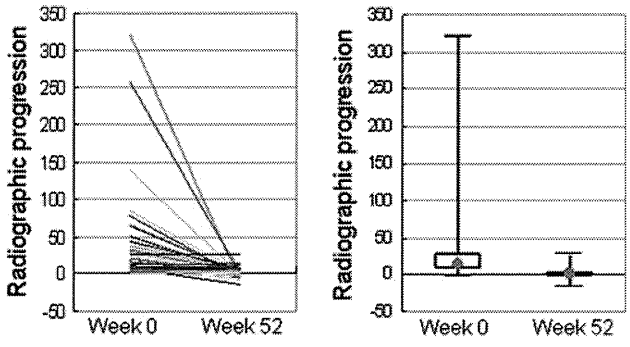

Fig. 5 Yearly progression of TSS in individual patients at weeks 0 and 52 of adalimumab treatment ($n = 87$). Radiographic images were available for 71 of 167 patients at weeks 0 and 52. Linear imputation was used for missing data at week 52 for 16 patients who received adalimumab treatment for at least 180 days. *Right points* and *boxes* represent the median (13.6 at week 0 and 0.0 at week 52) and the interquartile range (8.3–28.9 at week 0 and −0.9 to 2.0 at week 52), respectively. Median reduction in the yearly radiographic progression was 100%. The reduction was statistically significant by the Wilcoxon signed rank test ($P < 0.0001$)

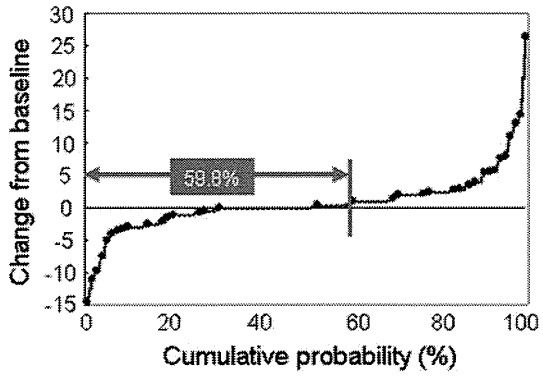

Fig. 6 Cumulative probability plot of change in the total modified Sharp score from baseline to week 52 ($n = 87$). Radiographic images were available for 71 of 167 patients at baseline and week 52. Linear imputation was used for missing data at week 52 for 16 patients who received adalimumab treatment for at least 180 days. In 52 out of the 87 patients (59.8%), the yearly radiographic progression was ≤0.5

adverse event profiles were comparable in all 3 arms [11]. The efficacy confirmed in the CHANGE study should be seen as such [18], since all the ADA-treated patients received ADA monotherapy. The results compared well to those of the DE011 monotherapy study conducted overseas [8]. The present HARMONY study is the first study to demonstrate the efficacy and safety of ADA therapy in combination with MTX in Japanese RA patients. An average of 8.5 mg/week MTX was used at baseline. This study clearly confirmed the superior effectiveness of combination therapy with MTX over ADA monotherapy. Indeed, the impact of concomitant MTX use was greater than that of a lack of history of biologic therapy in terms of both clinical and functional improvement (42.7% DAS28 remission and 45.0% normal function at week 52). Although a rapid

Table 2 Adverse events

MedDRA SOC	Number of events	Events/100 patient-years
Total	60	34.21
Infections and infestations	18	10.26
Respiratory, thoracic, and mediastinal disorders	5	2.85
General disorders and administration site conditions	20	11.40
Hepatobiliary disorders	3	1.71
Gastrointestinal disorders	5	2.85
Skin and subcutaneous tissue disorders	2	1.14
Blood and lymphatic system disorders	1	0.57
Eye disorders	1	0.57
Neoplasms (benign, malignant, and unspecified)	1	0.57
Injury, poisoning, and procedural complications	1	0.57
Investigations	3	1.71

MedDRA SOC Medical Dictionary for Regulatory Activities system organ class

Table 3 Serious adverse events

Adverse events	Number of events	Events/100 patient-years
Total	16	9.12
Injection site reactions[a]	3	1.71
Interstitial pneumonitis	2	1.14
Pneumocystis jiroveci pneumonia	1	0.57
Pneumonia	1	0.57
Miliary tuberculosis	1	0.57
Nontuberculous mycobacteriosis	1	0.57
Cellulitis	1	0.57
Malignant lymphoma	1	0.57
Lymphoproliferative disorder	1	0.57
Perforated colon diverticulum	1	0.57
Generalized rash	1	0.57
Generalized urticaria	1	0.57
Left fibula fracture	1	0.57

Serious adverse events as judged by the attending physicians

[a] Injection site reactions include erythema, itching, hemorrhage, pain, and swelling

response was evident in terms of both HAQ and DAS28 by week 4, the corresponding remission rates tended to increase even after week 24 until week 52, from 35.0 to 42.7%

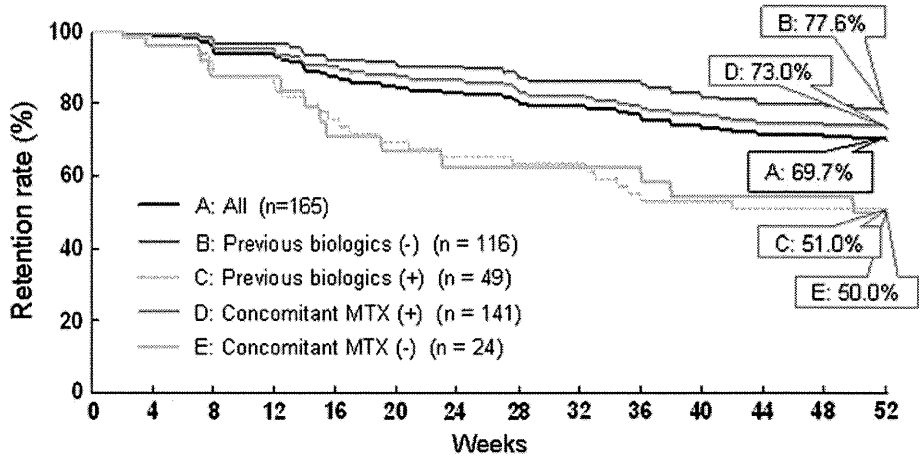

Fig. 7 Retention rates of adalimumab treatment over 52 weeks (Kaplan–Meier plots). Two patients were excluded from the plots because of an unknown date of discontinuation. $P < 0.0001$ between previous biologics (+) versus (−), and $P = 0.0109$ between concomitant MTX (+) versus (−) by the log-rank test

Table 4 Reasons for discontinuation

Two drop-outs with unknown discontinuation date were included. Those who discontinued after 52 weeks of treatment were also included

[a] Other reasons include patient's choice and eye surgery

Variables	All (n = 167)	Previous biologics		Concomitant MTX	
		(+) (n = 49)	(−) (n = 119)	(+) (n = 144)	(−) (n = 24)
Total	55	25	30	42	13
Lack of efficacy	24	14	10	16	8
Adverse events	16	9	7	13	3
Efficacy	5	0	5	4	1
Other reasons[a]	10	2	8	9	1

(DAS28-ESR < 2.6) and from 42.7 to 45.0% (HAQ-DI ≤0.5). Thus, it may be prudent to wait a further 24 weeks to see whether ADA can induce remission in a small portion of patients who responded to ADA at early time points. MTX reduced apparent ADA clearance after multiple dosing in 44% of patients with RA, thereby increasing systemic ADA trough levels [25]. This is because concomitant MTX use is considered to suppress levels of anti-ADA antibodies due to its immunosuppressive effect.

The radiographic outcome presented here is the first evidence of the ability of ADA to significantly limit radiographic progression in Japanese RA patients. Approximately 60% of patients exhibited no radiographic progression in HARMONY, which compares well with the results obtained in the PREMIER study (64 and 51% in the ADA + MTX and ADA monotherapy groups, respectively) [11]. Note that 26 out of the 87 evaluable patients (29.9%) exhibited ΔTSS ≤−0.5, indicating possible radiographic repair.

ADA treatment was generally well tolerated. No anaphylactoid reaction was reported, while injection site reactions occurred at a rate of 11.9% (20/167). This rate was far lower than that reported in the CHANGE study (30.8% in the 40 mg arm). The observed difference may possibly be due to the immunosuppressive effects of the concomitant use of MTX in favor of combination therapy.

Serious infections occurred at a rate of 2.85/100 patient-years (one event of each: *Pneumocystis jiroveci* pneumonia, pneumonia, military tuberculosis, cellulitis, and nontuberculous mycobacteriosis). Recently, the effectiveness and safety of biologic agents in Japanese patients were reviewed, and pneumonia, tuberculosis, *Pneumocystis jiroveci* pneumonia and interstitial pneumonitis were identified as important adverse reactions [26]; these were also observed in our study. Komano et al. [27] reported serious infections at a rate of 6.24/100 patient-years in Japanese patients treated with either infliximab or etanercept for up to 1 year. Although direct comparisons cannot be made among different studies, this may suggest that ADA therapy does not carry an increased risk for serious infections when compared to another anti-TNF therapy.

The overall retention rate observed in the present study (82.4% at 26 weeks and 69.7% at 52 weeks) falls within the range reported for infliximab (75.6% at 54 weeks) [15], etanercept (85.1% at 6 months) [17], and tocilizumab (79.5% at 24 weeks) [28] in daily clinical practice. However, it is not surprising that the retention rate varies among different biologics, as it is believed to be influenced by numerous factors other than efficacy and safety, such as co-morbidity, concomitant therapy, costs, launch timing, and availability of other therapies [29]. In the literature, it was indicated that the drug survival time of a second TNF inhibitor is shorter than a prior TNF inhibitor, while the survival of anti-TNF treatment was shown to be prolonged with concomitant use of MTX [30–32]. Our own findings in HARMONY resemble these published data, as shown by

week 52 retention rates in the previous biologic (−) and concomitant MTX (+) groups of 77.6 and 73.0%, respectively.

In conclusion, this retrospective study has demonstrated that ADA therapy is highly efficacious at reducing disease activity, improving physical function, and limiting radiographic progression, and is generally safe and tolerable in Japanese RA patients encountered during routine clinical practice. Furthermore, the results of this study demonstrate that ADA in combination with MTX is associated with substantial improvements in clinical, functional, and radiographic responses and retention rate, meaning that this could potentially serve as a first-line treatment.

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References

1. Lee DM, Weinblatt ME. Rheumatoid arthritis. Lancet. 2001;358:903–11.
2. Hakoda M, Oiwa H, Kasagi F, Masunari N, Yamada M, Suzuki G, et al. Mortality of rheumatoid arthritis in Japan: a longitudinal cohort study. Ann Rheum Dis. 2005;64:1451–5.
3. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 update. Arthritis Rheum. 2002;46:328–46.
4. Smolen JS, Aletaha D, Koeller M, Weisman MH, Emery P. New therapies for treatment of rheumatoid arthritis. Lancet. 2007;370:1861–74.
5. Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. N Engl J Med. 2001;344:907–16.
6. Salfeld J, Kaymakçalan Z, Tracey D, Roberts A, Kamen R. Generation of fully human anti-TNF antibody D2E7 [abstract]. Arthritis Rheum. 1998;41(Suppl 9):S57.
7. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti-tumor necrosis factor α monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum. 2003;48:35–45.
8. van de Putte LB, Atkins C, Malaise M, Sany J, Russell AS, van Riel PL, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis. 2004;63:508–16.
9. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum. 2004;50:1400–11.
10. Furst DE, Schiff MH, Fleischmann RM, Strand V, Birbara CA, Compagnone D, et al. Adalimumab, a fully human anti-tumor necrosis factor-α monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (safety trial of adalimumab in rheumatoid arthritis). J Rheumatol. 2003;30:2563–71.
11. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum. 2006;54:26–37.
12. Miyasaka N, Takeuchi T, Eguchi K. Proposed [corrected] Japanese Guidelines for the use of infliximab for rheumatoid arthritis. Mod Rheumatol. 2005;15:4–8.
13. Miyasaka N, Takeuchi T, Eguchi K. Guidelines for the proper use of etanercept in Japan. Mod Rheumatol. 2006;16:63–7.
14. Yamanaka H, Tanaka Y, Sekiguchi N, Inoue E, Saito K, Kameda H, et al. Retrospective clinical study on the notable efficacy and related factors of infliximab therapy in a rheumatoid arthritis management group in Japan (RECONFIRM). Mod Rheumatol. 2007;17:28–32.
15. Tanaka Y, Takeuchi T, Inoue E, Saito K, Sekiguchi N, Sato E, et al. Retrospective clinical study on the notable efficacy and related factors of infliximab therapy in a rheumatoid arthritis management group in Japan: one-year clinical outcomes (RECONFIRM-2). Mod Rheumatol. 2008;18:146–52.
16. Takeuchi T, Yamanaka H, Inoue E, Nagasawa H, Nawata M, Ikari K, et al. Retrospective clinical study on the notable efficacy and related factors of infliximab therapy in a rheumatoid arthritis management group in Japan: one-year outcome of joint destruction (RECONFIRM-2J). Mod Rheumatol. 2008;18:447–54.
17. Iwamoto N, Kawakami A, Fujikuwa K, Aramaki T, Kawashiri S, Tamai M, et al. Prediction of DAS28-ESR remission at 6 months by baseline variables in patients with rheumatoid arthritis treated with etanercept in Japanese population. Mod Rheumatol. 2009;19:488–92.

18. Miyasaka N, the CHANGE Study Investigators. Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: the CHANGE study. Mod Rheumatol. 2008;18:252–62.
19. Arnett FC, Edworthy SM, Bloch DA, Mcshane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315–24.
20. Japan College of Rheumatology. Guidelines for adalimumab (in Japanese). 2008. http://www.ryumachi-jp.com/info/guideline_ADA.pdf
21. Prevoo ML, van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995;38:44–8.
22. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980;23:137–45.
23. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol. 2000;27:261–3.
24. Goldsmith CH, Boers M, Bombardier C, Tugwell P. Criteria for clinically important changes in outcomes: development, scoring and evaluation of rheumatoid arthritis patient and trial profiles. OMERACT Committee. J Rheumatol. 1993;20:561–5.
25. Abbott Laboratories. Prescribing information for Humira® (adalimumab). Chicago: Abbott Laboratories; 2010.
26. Takeuchi T, Kameda H. The Japanese experience with biologic therapies for rheumatoid arthritis. Nat Rev Rheumatol. 2010;6:644–52.
27. Komano Y, Tanaka M, Nanki T, Koike R, Sakai R, Kameda H, et al. Incidence and risk factors for serious infection in patients with rheumatoid arthritis treated with tumor necrosis factor inhibitors: a report from the registry of Japanese rheumatoid arthritis patients for long-term safety. J Rheumatol. 2011. doi: 10.3899/jrheum.101009.
28. Yamanaka H, Tanaka Y, Inoue E, Hoshi D, Momohara S, Hanami K, et al. Efficacy and tolerability of tocilizumab in rheumatoid arthritis patients seen in daily clinical practice in Japan: results from a retrospective study (REACTION study). Mod Rheumatol. 2011;21:122–33.
29. Gomez-Reino JJ, Carmona L, BIOBADASER Group. Switching TNF antagonists in patients with chronic arthritis: an observational study of 488 patients over a four-year period. Arthritis Res Ther. 2006;8:R29.
30. Kristensen LE, Saxne T, Nilsson JA, Geborek P. Impact of concomitant DMARD therapy on adherence to treatment with etanercept and infliximab in rheumatoid arthritis. Results from a six-year observational study in southern Sweden. Arthritis Res Ther. 2006;8:R174.
31. Yazici Y, Krasnokutsky S, Barnes JP, Hines PL, Wang J, Rosenblatt L. Changing patterns of tumor necrosis factor inhibitor use in 9074 patients with rheumatoid arthritis. J Rheumatol. 2009;36:907–13.
32. Soliman MM, Ashcroft DM, Watson KD, Lunt M, Symmons DPM, Hyrich KL, et al. Impact of concomitant use of DMARDs on the persistence with anti-TNF therapies in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis. 2011;70:583–9.

EXTENDED REPORT

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

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

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ABSTRACT

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

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

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

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

INTRODUCTION

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

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

METHODS

Patients

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

Study design

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

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

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

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

Study endpoints

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

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

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

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

Statistical analyses

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

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

RESULTS

Patient disposition and baseline characteristics

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

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

Efficacy results

ACR response

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

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

Other clinical measures of RA and physical function

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

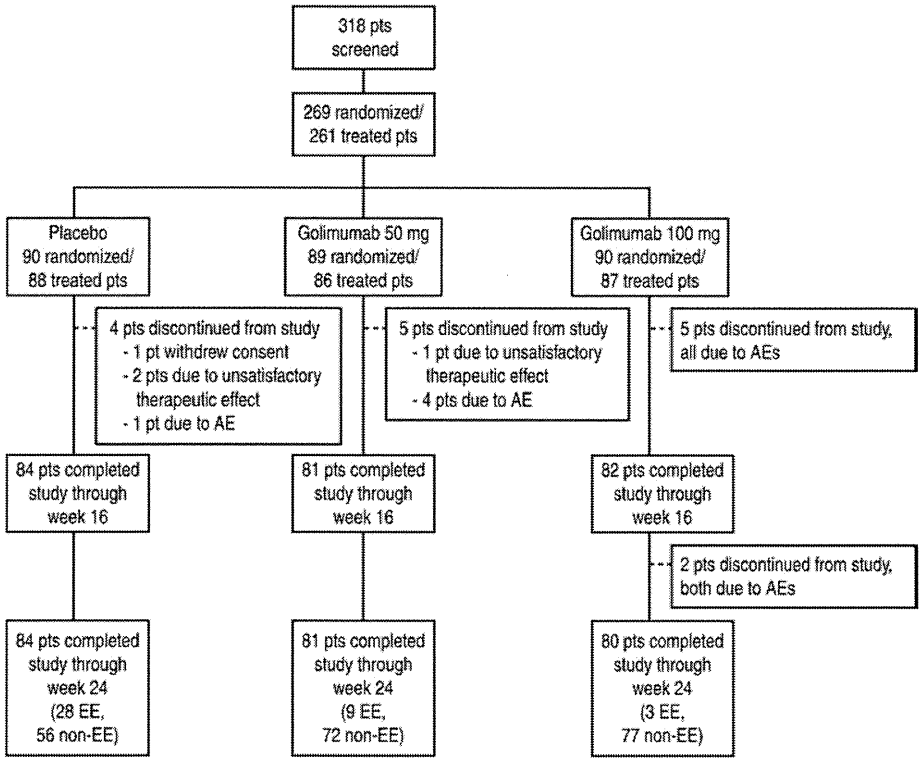

Figure 1 Patient disposition through week 24; randomised patients. Note that 'worsening of rheumatoid arthritis' is included in 'unsatisfactory therapeutic response' and not as an AE. AE, adverse event; EE, early escape; pts, patients.

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

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

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

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

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

	Week 14				Week 24			
	Group 1: Placebo+MTX	Group 2: Golimumab 50 mg+MTX	Group 3: Golimumab 100 mg+MTX	Combined groups 2 and 3	Group 1: Placebo+MTX	Group 2: Golimumab 50 mg+MTX	Group 3: Golimumab 100 mg+MTX	Combined groups 2 and 3
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.

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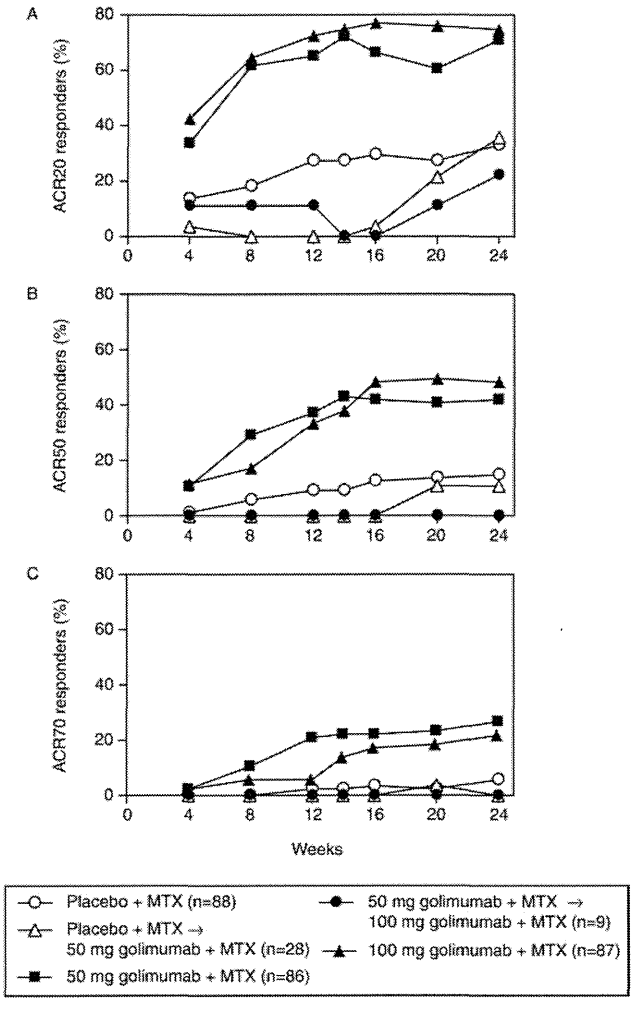

Figure 2 (A) American College of Rheumatology 20% (ACR20), (B) 50% (ACR50) and (C) 70% (ACR70) improvement from baseline through week 24. Note that patients who met the early escape criteria at week 16 and crossed over to golimumab 50 mg or dose escalated from golimumab 50 mg to 100 mg are shown with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

Radiographic progression

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

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

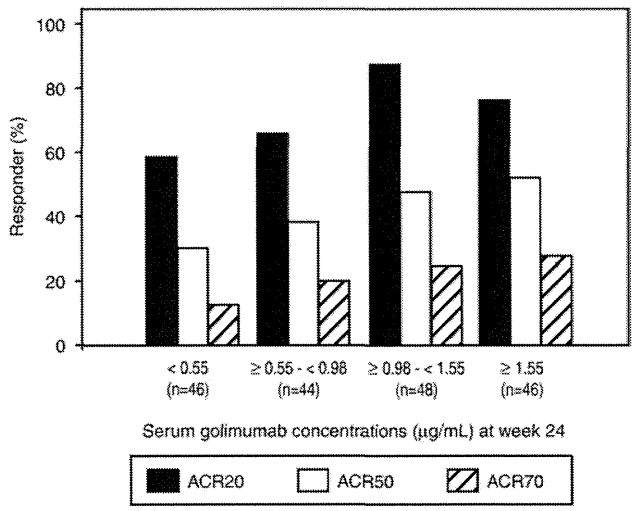

Figure 3 Proportions of patients achieving at least 20%, 50% and 70% improvement in the American College of Rheumatology (ACR20, ACR50, ACR70) response criteria by serum golimumab concentration quartiles (µg/ml) at week 24. The results are from a post hoc analysis of ACR responders in the combined Group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

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

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

Golimumab pharmacokinetics and antibodies to golimumab

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

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

Adverse events

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

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

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 (haemangoendothelioma) 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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REFERENCES

1. **Herman S**, Krönke G, Schett G. Molecular mechanisms of inflammatory bone damage: emerging targets for therapy. *Trends Mol Med* 2008;**14**:245–53.
2. **Smolen JS**, Aletaha D, Koeller M, *et al.* New therapies for treatment of rheumatoid arthritis. *Lancet* 2007;**370**:1861–74.
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5. **Keystone EC**, Genovese MC, Klareskog L, *et al.* Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. *Ann Rheum Dis* 2009;**68**:789–96.
6. **Keystone E**, Genovese MC, Klareskog L, *et al.* Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. *Ann Rheum Dis* 2010;**69**:1129–35.
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8. **Arnett FC**, Edworthy SM, Bloch DA, *et al.* The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;**31**:315–24.
9. **Felson DT**, Anderson JJ, Boers M, *et al.* American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995;**38**:727–35.
10. **Siegel JN**, Zhen B-G. Use of the American College of Rheumatology N (ACR-N) index of improvement in rheumatoid arthritis: argument in favor. *Arthritis Rheum* 2005;**52**:1637–41.
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12. **van Riel PL**, van Gestel AM, Scott DL. EULAR Handbook of Clinical Assessments in Rheumatoid Arthritis. Alphen Aan Den Rijn, The Netherlands: Van Zuiden Communications BV; 2000:1–55.
13. **Fries JF**, Spitz P, Kraines RG, *et al.* Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;**23**:137–45.
14. **van der Heijde DM**, van Leeuwen MA, van Riel PL, *et al.* Biannual radiographic assessments of hands and feet in a three-year prospective followup of patients with early rheumatoid arthritis. *Arthritis Rheum* 1992;**35**:26–34.
15. **Kay J**, Matteson EL, Dasgupta B, *et al.* Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. *Arthritis Rheum* 2008;**58**:964–75.
16. **Emery P**, Fleischmann R, van der Heijde D, *et al.* The effects of golimumab on radiographic progression in rheumatoid arthritis: results of randomized controlled studies of golimumab before methotrexate therapy and golimumab after methotrexate therapy. *Arthritis Rheum* 2011;**63**:1200–10.
17. **Visvanathan S**, Rahman MU, Keystone E, *et al.* Association of serum markers with improvement in clinical response measures after treatment with golimumab in patients with active rheumatoid arthritis despite receiving methotrexate: results from the GO-FORWARD study. *Arthritis Res Ther* 2010;**12**:R211.
18. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 update. *Arthritis Rheum* 2002; **46**:328–46.
19. **Seto Y**, Tanaka E, Inoue E, et al. Studies of the efficacy and safety of methotrexate at dosages over 8 mg/week using the IORRA cohort database. Mod Rheumatol. doi:10.1007/s10165-011-0445-4 (In Press).
20. **Scheinfeld N**. A comprehensive review and evaluation of the side effects of the tumor necrosis factor alpha blockers etanercept, infliximab and adalimumab. *J Dermatolog Treat* 2004;**15**:280–94.
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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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REFERENCES

1. **Herman S**, Krönke G, Schett G. Molecular mechanisms of inflammatory bone damage: emerging targets for therapy. *Trends Mol Med* 2008;**14**:245–53.
2. **Smolen JS**, Aletaha D, Koeller M, *et al.* New therapies for treatment of rheumatoid arthritis. *Lancet* 2007;**370**:1861–74.
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12. **van Riel PL**, van Gestel AM, Scott DL. EULAR Handbook of Clinical Assessments in Rheumatoid Arthritis. Alphen Aan Den Rijn, The Netherlands: Van Zuiden Communications BV; 2000:1–55.
13. **Fries JF**, Spitz P, Kraines RG, *et al.* Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;**23**:137–45.
14. **van der Heijde DM**, van Leeuwen MA, van Riel PL, *et al.* Biannual radiographic assessments of hands and feet in a three-year prospective followup of patients with early rheumatoid arthritis. *Arthritis Rheum* 1992;**35**:26–34.
15. **Kay J**, Matteson EL, Dasgupta B, *et al.* Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. *Arthritis Rheum* 2008;**58**:964–75.
16. **Emery P**, Fleischmann R, van der Heijde D, *et al.* The effects of golimumab on radiographic progression in rheumatoid arthritis: results of randomized controlled studies of golimumab before methotrexate therapy and golimumab after methotrexate therapy. *Arthritis Rheum* 2011;**63**:1200–10.
17. **Visvanathan S**, Rahman MU, Keystone E, *et al.* Association of serum markers with improvement in clinical response measures after treatment with golimumab in patients with active rheumatoid arthritis despite receiving methotrexate: results from the GO-FORWARD study. *Arthritis Res Ther* 2010;**12**:R211.
18. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 update. *Arthritis Rheum* 2002; **46**:328–46.
19. **Seto Y**, Tanaka E, Inoue E, et al. Studies of the efficacy and safety of methotrexate at dosages over 8 mg/week using the IORRA cohort database. Mod Rheumatol. doi:10.1007/s10165-011-0445-4 (In Press).
20. **Scheinfeld N**. A comprehensive review and evaluation of the side effects of the tumor necrosis factor alpha blockers etanercept, infliximab and adalimumab. *J Dermatolog Treat* 2004;**15**:280–94.
21. **Vila AT**, Puig L, Fernández-Figueras MT, *et al.* Adverse cutaneous reactions to anakinra in patients with rheumatoid arthritis: clinicopathological study of five patients. *Br J Dermatol* 2005;**153**:417–23.

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ORIGINAL ARTICLE

Safety and effectiveness of adalimumab in Japanese rheumatoid arthritis patients: postmarketing surveillance report of the first 3,000 patients

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Abstract This interim analysis of postmarketing surveillance data for adalimumab-treated rheumatoid arthritis (RA) patients summarizes safety and effectiveness during the first 24 weeks of therapy for the first 3,000 patients treated in Japan (June 2008–December 2009). Patient eligibility for antitumor necrosis factor therapy was based on the Japanese College of Rheumatology treatment guidelines and Japanese labeling. All patients were screened for tuberculosis. Approximately 50% of the population was biologic naïve, 66% received concomitant methotrexate (MTX), and 72% received concomitant glucocorticoids. The overall incidence rate of adverse events was 31% (5.5% serious) and that of adverse drug reactions (ADRs) was 27% (4.1% serious). Incidence rates of ADRs and serious ADRs were similar regardless of prior biologic therapy or concomitant MTX use but were significantly higher in patients receiving glucocorticoids compared with those not receiving glucocorticoids. Bacterial/bronchial pneumonia occurred in 1.2% of patients; interstitial pneumonia, 0.6%; *Pneumocystis jirovecii* pneumonia, 0.3%; tuberculosis, 0.13%; and administration-site reactions, 6.1%. Mean 28-joint Disease Activity Scores decreased significantly after 24 weeks from 5.29 to 3.91. All subgroups showed significant improvement, particularly the biologic-naïve patients receiving concomitant MTX. No new safety concerns were identified. ADR Incidence rates were similar to those of other biologic agents approved for RA.

Keywords Adalimumab · Effectiveness · Postmarketing surveillance · Rheumatoid arthritis · Safety

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Introduction

Adalimumab (HUMIRA®, Abbott Laboratories, Abbott Park, IL, USA) is a recombinant human monoclonal antibody specific to human tumor necrosis factor (TNF) approved in Japan for treating rheumatoid arthritis (RA) in patients showing an inadequate response to conventional therapy. Upon the drug's approval, Abbott Japan Co. Ltd. and Eisai Co. Ltd. initiated a mandatory regulatory registry to monitor safety and effectiveness during the first 6 months for all RA patients treated with adalimumab in

Japan. Similar postmarketing surveillance (PMS) studies for infliximab and etanercept have been published [1, 2]. Tocilizumab was more recently approved, and PMS is underway [3].

Worldwide prevalence of RA has been estimated at 0.5–1.0% of the adult population [4]. The burden of RA in Japan is substantial, with more than 700,000 patients affected. The morbidity rate is 0.5%, with many patients bedridden or requiring hospitalization [5, 6]. A longitudinal cohort study in Japan found that RA was an independent risk factor for mortality and that increased mortality rates in RA patients was associated with pneumonia, tuberculosis, and liver disease [7]. The safety and efficacy of adalimumab compared with a placebo in Japanese RA patients was demonstrated by the Clinical Investigation in Highly Disease-Affected Rheumatoid Arthritis Patients in Japan with Adalimumab Applying StaNdard and General Evaluation (CHANGE) study, which evaluated adalimumab monotherapy dosages of 20, 40, and 80 mg every other week [8].

The primary objective of the PMS study is to monitor the safety of adalimumab in the clinical setting by collecting adverse event (AE) and adverse drug reaction (ADR) data, focusing on events of particular interest with anti-TNF-agent therapy. These events include infections, tuberculosis, malignancies, administration-site reactions, congestive heart failure, and interstitial pneumonia. Monitoring the effectiveness of adalimumab is a secondary objective of the study. This report presents an interim analysis of the first 3,000 patients treated with adalimumab in Japan.

Methods

Participating centers

As of 27 December 2009, 1,107 medical institutions had treated patients under the registry's protocol (ClinicalTrials.gov identifier: NCT01076959). Patient enrollment was completed in October 2010, with approximately 7,800 patients enrolled, of whom the first 3,000 were analyzed for this interim report. To qualify for participation, medical centers were required to: (1) comply with the patient enrollment criteria specified in the protocol; (2) provide antirheumatic treatment by specialists [e.g., educational institutions certified by the Japan College of Rheumatology (JCR)]; (3) screen for and diagnose tuberculosis; and (4) diagnose and treat severe infections (e.g., opportunistic infections). All investigators had to be specialists certified by the JCR, rheumatologists certified by the Japanese Orthopaedic Association, or specialists registered by the Japan Rheumatism Foundation.

Patient eligibility

Every patient treated with adalimumab as of the April 2008 approval date in Japan was enrolled in a central registry. Patient eligibility for anti-TNF therapy was based on JCR treatment guidelines and Japanese labeling recommendations [9, 10]. The purpose of the surveillance was fully explained to and informed consent obtained from each patient prior to participation. Written informed consent for transition to self-injection of adalimumab was also obtained. Screening for tuberculosis was mandatory. Screening methods included purified protein derivative skin testing, chest X-ray, and/or computed tomography scan. The histories of tuberculosis infection and antituberculosis treatment were collected. For patients with a history of tuberculosis infection, the diagnostic method (e.g., diagnostic imaging, tuberculin skin reaction, bacteriological examination) was collected. If patients had a past history of tuberculosis or a diagnosis of latent tuberculosis, chemoprophylaxis was recommended following JCR guidelines; these patients could then be enrolled in the study. Other baseline laboratory evaluations for infection included serum β-D-glucan level, peripheral blood white blood cell count, peripheral blood lymphocyte count, serum immunoglobulin-G concentration, and serum creatinine concentration. Although patients had to have failed treatment with conventional therapy to be eligible for treatment with an anti-TNF agent, they were allowed to continue previous treatments such as other disease-modifying antirheumatic drugs (DMARDs), glucocorticoids, and nonsteroidal anti-inflammatory drugs.

Data recording

Internet-based electronic data capture was the preferred method for data collection. If this method was not feasible at a given medical center, paper forms were used. Baseline data collected included age, sex, pregnancy/lactation/gestation age (for women), weight, reason(s) for use of adalimumab, duration of RA, complications and comorbidities, past illnesses, allergies, smoking history, Steinbrocker's RA stage and functional class [11], prior and concomitant RA treatment, and concomitant medications other than for RA treatments.

Safety surveillance

The standard observation period was the first 24 weeks with a 4-week follow-up, or until the last administration of adalimumab if the patient discontinued use of the drug within 24 weeks, with a 4-week follow-up after the end of treatment. The dosage of adalimumab was 40 mg by subcutaneous injection every other week. However, in

accordance with the labeling in Japan, a dosage of 80 mg every other week was allowed for patients not receiving DMARDs. Adalimumab treatment was continued beyond 24 weeks for some patients at their physician's discretion. For patients who discontinued the surveillance, the date and reason(s) for discontinuation were recorded. All AEs, including those identified from abnormal laboratory findings, were collected. Specific information recorded included the type of AE, date of onset, level of seriousness, clinical course, outcome, causal relationship between the event and adalimumab, and measures taken related to adalimumab therapy and treatment of the AE. AEs were defined according to the International Conference on Harmonization guidelines [12], as any untoward or unintended signs (including abnormal laboratory findings), symptoms, or diseases temporally associated with the use of adalimumab, whether or not considered related to adalimumab. ADRs were defined as any noxious and unintended response for which causal relationship to adalimumab could not be excluded. The occurrence of infections, tuberculosis, malignancies, administration-site reactions, autoimmune diseases, pancytopenia, demyelinating diseases, congenital heart failure, and interstitial pneumonia were of particular interest. A sample size of 3,000 patients allowed detection of unknown AEs occurring at an incidence of 0.1% with 95% reliability.

Clinical course

Criteria used at baseline and week 24 to assess clinical course were morning stiffness, number of tender joints (28 joints), number of swollen joints (28 joints), Patient's Global Assessment of disease activity (10-cm visual analog scale), erythrocyte sedimentation rate (ESR; 1-h value), and C-reactive protein serum levels. The clinical course was also assessed at weeks 4 and 12, and at discontinuation when possible.

Data analysis

The overall incidence of AEs, ADRs, and serious events were coded using the *Medical Dictionary for Regulatory Activities* (MedDRA; version 12.1) and entered as the number and percentage of patients affected. ADRs, serious ADRs, infections, and serious infections were also stratified by concomitant methotrexate (MTX) and glucocorticoid use. Effectiveness was assessed using the 28-joint Disease Activity Score (DAS28); data entered were at the last observation. The DAS28-4 (ESR) was calculated using the standard formula incorporating the number of swollen and tender joints, ESR, and Patient's Global Assessment of disease activity. The DAS28-4 (ESR) scores range from 0 and 10, with lower scores indicating less active RA. A DAS28 >5.1 indicates high disease activity, a DAS28 <3.2 indicates low disease activity, and a DAS28 <2.6 indicates clinical remission corresponding to the American Rheumatology Association remission criteria [13]. The European League Against Rheumatism (EULAR) improvement criteria were calculated at weeks 4, 12, and 24, and at discontinuation when possible.

Statistical analysis

The safety analysis set was defined as all patients who received at least one injection of adalimumab. The effectiveness analysis set was defined as all patients who received at least one assessment of effectiveness under the treatment of adalimumab. Patients who were not diagnosed as having RA or who had a treatment period <2 weeks were excluded from the effectiveness analysis set. Chi-square tests were used to compare the rates of categorical variables. Risk factors for serious ADRs and serious infections were identified using multiple logistic regression models with the following explanatory variables: sex, age, past illnesses/comorbidities (e.g., diabetes mellitus, interstitial pneumonitis), histories of drug allergy and smoking, concomitant use of glucocorticoid, and Steinbrocker's functional RA class for serious ADRs; and sex, age, past illnesses/comorbidities (diabetes mellitus and interstitial pneumonitis), concomitant use of glucocorticoid, and Steinbrocker's functional RA class for serious infections. Changes in DAS28 from baseline (ΔDAS28), both overall and stratified by concomitant MTX and prior biologic use, at weeks 4, 12, and 24, were analyzed using Student's *t* test. Analysis of covariance (ANCOVA) models were used to analyze associations between ΔDAS28 and patient baseline characteristics, including sex, age, RA disease duration, history of illnesses/comorbidities, history of drug allergy, history of smoking, prior use of biologic DMARDs, concomitant glucocorticoid, concomitant MTX, concomitant DMARDs except MTX, disease activity at week 0, Steinbrocker's RA functional class and stage, and baseline disease activity. The Cochran–Armitage test for trend was used to analyze the association between rates of infection and glucocorticoid dosage.

Results

Patient demographics and clinical characteristics

Of the initial 3,000 adalimumab-treated patients, nine had diagnoses other than RA [3 malignant (RA with vasculitis), two adult Still's disease, one Behçet's disease, one polymyalgia rheumatica, one psoriasis, and one systemic lupus erythematosus]. Approximately 95% of patients

received adalimumab at a dosage of 40 mg every other week, and 94% had their therapy administered at a clinic rather than by self-injection. Baseline characteristics for the first 3,000 adalimumab-treated patients in Japan are summarized in Table 1. Eleven percent had a history of mycobacterial tuberculosis infection. Approximately 50% had previously received biologic therapy. Of the 1,491 biologic-experienced patients, 77.5% (1,156 patients) had received only one biologic therapy [700 (46.9%) etanercept; 428 (28.1%) infliximab, and 28 (1.9%) tocilizumab]. A total of 335 patients received more than one biologic therapy. Overall, 43.4% of the 3,000-patient cohort received infliximab, 63.4% etanercept, 8.0% tocilizumab, and 5.0% other biologic therapy. More than 90% had received prior DMARD therapy, and 82.0% were receiving at least 1 DMARD at study entry. Concomitant MTX use was reported for 66.1% of patients (mean dosage 6.8 ± 2.3 mg/week). According to the Japanese labeling at the time of the surveillance, the approved dosage of MTX is ≤8 mg/week. Sixty-eight percent of adalimumab-treated patients had a history of glucocorticoid therapy, and 71.7% were receiving concomitant glucocorticoid therapy (oral mean prednisolone-equivalent dosage 5.3 ± 3.4 mg/day).

Table 1 Baseline demographic and clinical characteristics

Background factors	Adalimumab (N = 3,000)[a]
Male/female (%)	16.5/83.5
Age (years), mean ± SD	60.1 ± 12.8
Age (years, %)	
<20	0.2
≥20 to <30	2.0
≥30 to <40	5.7
≥40 to <50	11.3
≥50 to <60	25.0
≥60 to <70	30.3
≥70 to <80	22.6
≥80	3.0
RA duration (years), mean ± SD	11.1 ± 9.5
Medical history (%)	
Concurrent illness[b]	63.7
Past illness[c]	34.5
Allergy	16.9
Smoking history	12.8
Steinbrocker's RA stage (%)	
I	8.7
II	24.7
III	30.9
IV	35.7
Steinbrocker's RA functional class (%)	
I	11.3
II	61.6
III	24.6
IV	2.4
Baseline DAS28, mean ± SD	5.27 ± 1.25
Prior medication (%)	
Biologic agent	49.7
DMARD[d]	92.1
Glucocorticoid	67.8
Concomitant medication (%)	
Methotrexate	66.1
>8 mg/week	11.5
Glucocorticoid	71.7

DAS28 28-joint Disease Activity Score, *DMARD* disease-modifying antirheumatic drug, *RA* rheumatoid arthritis, *SD* standard deviation

[a] 2,991 RA and nine with other diseases

[b] Most frequent concurrent illnesses were cardiovascular disease (22.6%) and respiratory disease (13.6%)

[c] Most frequent past illnesses were operations for RA (39.3%), tuberculosis (10.7%), and interstitial pneumonia (9.0%)

[d] Includes MTX

Postmarketing safety surveillance

All 3,000 cases were included in the safety analysis. In total, 33.2% of adalimumab-treated patients discontinued the study before their 6-month surveillance period was complete. Lack of efficacy (12.9%) and AEs (10.7%) were the most common reasons for discontinuation (Table S1). The overall incidence of AEs with adalimumab therapy was 31.0% (931 of 3,000 patients). Of these, 5.5% were serious. With total exposure in this study of 1,364 patient-years, the number of events per 100 patient-years was 120.4 for all AEs and 16.2 for serious AEs. Median time from the start of treatment to onset of the event was 86 days for all AEs and 126 days for serious AEs. ADRs were reported in 27.3% (818 of 3,000) and serious ADRs in 4.1% (124 of 3,000) of adalimumab-treated patients. The incidences of ADRs and serious ADRs were similar regardless of prior biologic therapy or concomitant DMARD use (Table S2). Skin disorders (8.5%), general disorders (8.0%), and infections (7.8%) were the most common ADRs (Table S2). The most common serious ADRs were infection (2.4%) and respiratory disorders (0.6%). A total of 42.9% of ADRs and 22.1% of serious ADRs occurred within the first 4 weeks of treatment. The mean duration from the start of treatment to ADR onset was 85 days overall and 127 days for serious ADRs. The median time to onset of infections was similar for all infections and for those infections considered to be ADRs (106 and 109 days, respectively), as well as those that were considered serious (129.5 and 127 days, respectively). The time to onset of ADRs was significantly longer for biologic-naïve patients compared with biologic-experienced

patients (92 vs. 82 days; $p = 0.05$, log-rank test). Patients receiving MTX had a longer interval from the start of treatment to occurrence of ADRs compared with patients not receiving MTX (94.5 vs. 57 days; $p = 0.002$, log-rank test).

Table 2 summarizes ADRs, serious ADRs, infections, and serious infections categorized by concomitant MTX and glucocorticoid treatment and dosages. Among patients receiving concomitant MTX, no observable dose-related pattern was found for ADRs or serious ADRs or for infection or serious infection. Patients receiving concomitant MTX had a significantly lower incidence rate of ADRs (26.0%) than did patients who were not receiving concomitant MTX (29.7%) ($p < 0.01$; chi-square test). Patients receiving concomitant glucocorticoids had a significantly greater incidence of ADRs (28.9%) and serious ADRs (4.8%) compared with patients who were not receiving concomitant glucocorticoids (23.2% and 2.5%, respectively) (both $p < 0.01$ vs. no glucocorticoid; chi-square test). The incidence of serious ADRs increased with glucocorticoid dosage increasing from the >7.5 mg/day prednisolone-equivalent dose. Rates for all infections and serious infections were significantly greater with increasing dosages of glucocorticoid ($p < 0.001$; Cochran–Armitage test for trend). Although the sample size was small, patients receiving glucocorticoid dosages >12.5 mg/day had the highest rates of ADRs (60%) and serious ADRs (26.7%) (both $p < 0.001$ vs. no glucocorticoids; chi-square test).

ADRs of interest included serious infections, pneumonia, tuberculosis, other opportunistic infections, interstitial pneumonia, skin reactions (local redness, itching and bleeding, etc.), administration-site reactions, and malignancies (Table 3). Of the 73 serious infections reported as ADRs by recording physicians, the most common were respiratory (42), followed by skin (10) (Table S2). There were 35 (1.2%) cases of bacterial/bronchial pneumonia, 20 of which were serious. Tuberculosis was reported in four patients (0.13%). Two of those patients experienced extrapulmonary tuberculosis: one with pleural tuberculosis; one with lymph node and peritoneal tuberculosis. Three patients used concomitant glucocorticoids at prednisolone-equivalent dosage ≤16 mg/day, and no patients received isoniazid for chemoprophylaxis. Three of these patients had used etanercept prior to adalimumab administration. Other opportunistic infections included nine (0.3%) cases of serious *Pneumocystis jirovecii* pneumonia (PCP), one of fungal infection (<0.1%), one of nontuberculous mycobacteriosis (<0.1%), and 28 of herpes zoster (0.9%). Interstitial pneumonia occurred in 0.6% of patients. Administration-site reactions were reported in 6.1% of patients, but none experienced a serious reaction to drug administration (i.e., anaphylactoid reaction or anaphylaxis) (Table 3). Patients receiving MTX had significantly fewer skin (6.7%) and administration-site reactions (5.3%) than patients not receiving MTX (11.5% and 7.5%, respectively, $p < 0.001$). The incidence of malignancy was 0.1% (two cases). Lymphoma was not observed.

Multiple logistic regression analyses identified the significant risk factors for serious ADRs: age ≥65 years [odds ratio (OR) (95% confidence interval; CI) 1.805

Table 2 Adverse drug reactions (ADRs), serious ADRs, infections, and serious infections in patients with and without methotrexate (MTX) and glucocorticoid therapy

	ADR		Serious ADR		Infection		Serious infection	
	N	%	*N*	%	*N*	%	*N*	%
MTX								
No ($n = 1{,}018$)	302	29.7	46	4.5	76	7.5	28	2.8
Yes ($n = 1{,}982$)	516	26.0[a]	78	3.9	157	7.9	45	2.3
≤4 mg/week ($n = 381$)	103	27.0	14	3.7	32	8.4	10	2.6
>4 to ≤6 mg/week ($n = 611$)	148	24.2[a]	15	2.5[a]	33	5.4	4	0.7
>6 to ≤8 mg/week ($n = 763$)	201	26.3	42	5.5	69	9.0	26	3.4
>8 to ≤10 mg/week ($n = 128$)	44	34.4	6	4.7	17	13.3	5	3.9
>10 to ≤12 mg/week ($n = 45$)	11	24.4	0	0	3	6.7	0	0
>12 mg/week ($n = 53$)	9	17.0[a]	1	1.9	3	5.7	0	0
Glucocorticoids								
No ($n = 849$)	197	23.2	21	2.5	51	6.0	12	1.4
Yes ($n = 2{,}151$)	621	28.9[a]	103	4.8[a]	182	8.5[b]	61	2.8[b]
≤2.5 mg/day ($n = 411$)	108	26.3	11	2.7	20	4.9	5	1.2
>2.5 to ≤5 mg/day ($n = 1{,}021$)	272	26.6	42	4.1	82	8.0	24	2.4
>5 to ≤7.5 mg/day ($n = 307$)	91	29.6[b]	14	4.6	37	12.1[c]	10	3.3[b]
>7.5 to ≤10 mg/day ($n = 244$)	55	24.6	12	5.4[b]	16	7.1	8	3.6[b]
>10 to ≤12.5 mg/day ($n = 27$)	6	22.2	3	11.1[a]	2	7.4	2	7.4[b]
>12.5 mg/day ($n = 45$)	27	60.0[c]	12	26.7[c]	11	24.4[c]	6	13.3[c]

Rates of all infections and serious infections were significantly greater with increasing dosages of glucocorticoid ($p < 0.001$; Cochran–Armitage test for trend)

[a] $p < 0.01$

[b] $p < 0.05$

[c] $p < 0.001$ (all compared with no MTX or no glucocorticoids; chi-square test)

Table 3 Adverse drug reactions (ADRs) of interest

	Adalimumab (%) ($N = 3,000$)[a]	
	N	%
ADR		
Total	818	27.3
Serious	124	4.1
ADRs of interest		
Serious infection	73	2.4
Pneumonia[b]	35 (22)[c]	1.2 (0.7)
Tuberculosis	4 (4)	0.1 (0.1)
PCP	9 (9)	0.3 (0.3)
Sepsis	5 (5)	0.2 (0.2)
Fungal infection	1 (0)	<0.1 (0.0)
Atypical mycobacteriosis	1 (1)	<0.1 (<0.1)
Herpes zoster	28 (7)	0.9 (0.2)
Interstitial pneumonia	17 (11)	0.6 (0.4)
Skin reaction	250 (3)	8.3 (0.1)
Administration-site reaction	182 (0)	6.1 (0.0)
Malignancy	2 (2)	0.1 (0.1)

PCP Pneumocystis jirovecii pneumonia

[a] 2,991 RA and nine other diseases

[b] Pneumonia, $n = 23$; bacterial pneumonia, $n = 7$; bronchial pneumonia, $n = 4$; pneumococcal pneumonia, $n = 1$

[c] Number of serious ADRs

(1.201–2.712); $p = 0.005$], diabetes mellitus history or as a comorbidity [2.132 (1.277–3.561), $p = 0.004$], interstitial pneumonitis history or comorbidity [1.899 (1.223–2.949), $p = 0.004$], and concomitant use of glucocorticoid [1.672 (1.003–2.790), $p = 0.049$]. Significant risk factors for serious infections were age ≥65 years [1.646 (1.012–2.676); $p = 0.045$], diabetes mellitus history or comorbidity [2.210 (1.221–4.001), $p = 0.009$], interstitial pneumonitis history or comorbidity [2.302 (1.381–3.837), $p < 0.001$], and advanced Steinbrocker's RA class [1.650 (1.013–2.689), $p = 0.044$].

Effectiveness

Of the 3,000 participants, effectiveness in patients with at least one DAS28/4 ESR ($n = 1,939$) was analyzed. Mean DAS28 scores and ΔDAS28 stratified by use of MTX and prior biologic treatment are shown in Fig. 1a. Mean DAS28 scores for all patients decreased from 5.3 at baseline to 3.9 at week 24. Mean ΔDAS28 of patients receiving concomitant MTX or who were biologic naïve were significantly greater than those of patients not receiving concomitant MTX or with prior biologic treatment, respectively ($p < 0.001$ at weeks 4, 12, and 24 for both comparisons; Student's *t* test).

Fig. 1 Change in 28-joint Disease Activity Score (DAS28)-4 [erythrocyte sedimentation rate (ESR)] over time. **a** Overall and stratified by concomitant methotrexate (MTX) and prior biologic use. $P < 0.001$ for concomitant use of MTX versus no MTX use at weeks 4, 12, and 24 (Student's *t* test). $P < 0.001$ for antitumor necrosis factor (anti-TNF)-naïve versus anti-TNF-experienced at weeks 4, 12, and 24 (Student's *t* test). **b** Stratified by MTX dosage. $P < 0.01$ for concomitant MTX (0 to ≤8 mg/week) versus no MTX use at week 4. $P < 0.001$ for concomitant MTX (>8 mg/week) versus no MTX use at week 4 (Student's *t* test). $P < 0.001$ for concomitant MTX at 0 to ≤8 or >8 mg/week versus no MTX use at week 12 and week 24 (Student's *t* test). **c** Stratified by specific prior biologic therapy. $P < 0.001$ for prior infliximab versus prior etanercept or prior infliximab plus etanercept at weeks 4, 12, and 24 (Student's *t* test)

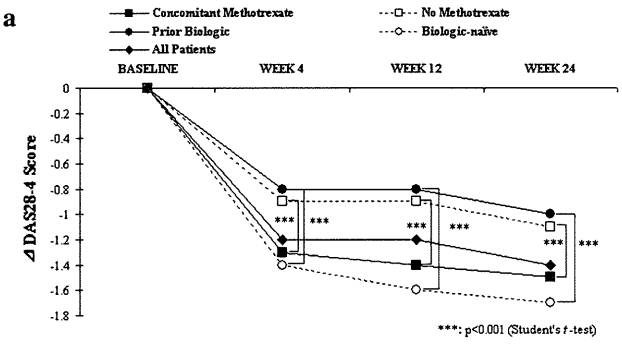
The majority of patients achieved moderate to good EULAR response by week 4, and the EULAR response rates remained stable through week 24 (Fig. S1). When the patients were stratified by mean MTX dosage during the 24 weeks (0, 0 to ≤8, and >8 mg/week), a significantly greater improvement was observed with MTX dosages of both 0 to ≤8 and >8 mg/week compared with patients who did not receive MTX ($p < 0.001$ at weeks 4, 12, and 24 for MTX at 0 to ≤8 mg/week, $p = 0.002$ at week 4, and $p < 0.001$ at weeks 12 and 24 for >8 mg/week) (Fig. 1b). Mean ΔDAS28 at weeks 4, 12, and 24 of patients who were switched from infliximab to adalimumab were significantly greater than those of patients who had received etanercept alone or both infliximab and etanercept previously ($p < 0.001$; Student's *t* test) (Fig. 1c). The mean ΔDAS28 of patients with and without concomitant MTX were further compared after stratification by Steinbrocker's RA stage and prior biologic treatment (Table 4) or by Steinbrocker's RA functional class and prior biologic treatment (Table S3).

To further clarify the association between prior use of biologic DMARDs, concomitant MTX use, and ΔDAS28 during treatment with adalimumab, we used ANCOVA analyses with various adjusting factors, as described in "Methods." Biologic DMARD naïve [estimated value (EV) (95% CI) −0.66 (−0.79 to −0.54); $p < 0.001$], concomitant MTX use [−0.47 (−0.62 to −0.33); $p < 0.001$], and baseline DAS28 [−0.44 (−0.49 to −0.38); $p < 0.001$] were significantly associated with ΔDAS28 during treatment with adalimumab.

Discussion

The incidences of serious ADRs in other PMS studies of anti-TNF therapies in Japanese patients with RA ranged from 4.6% for etanercept to 6.2% for infliximab [1, 2]. The incidence of serious ADRs for adalimumab-treated patients in the study reported here (4.1%) was at the lower end of this range. Overall, the safety profile of adalimumab in this PMS study was similar to that observed in clinical trials in both

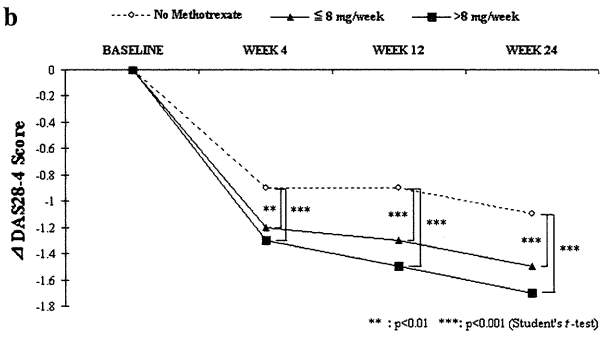
a



All Patients	5.3±1.3 (N=1939)	4.1±1.4 -1.2±1.1 (N=1401)	4.0±1.4 -1.2±1.3 (N=1662)	3.9±1.5 -1.4±1.4 (N=1915)
Concomitant Methotrexate	5.2±1.2 (N=1344)	4.0±1.3 -1.3±1.1 (N=993)	3.9±1.3 -1.4±1.2 (N=1170)	3.7±1.4 -1.5±1.3 (N=1342)
No Methotrexate	5.4±1.3 (N=595)	4.5±1.5 -0.9±1.2 (N=408)	4.4±1.5 -0.9±1.4 (N=492)	4.3±1.6 -1.1±1.4 (N=573)
Student's *t*-test (⊿DAS28-4 Score)		p<0.001	p<0.001	p<0.001
Biologic-naïve	5.3±1.2 (N=1027)	3.9±1.3 -1.4±1.0 (N=768)	3.7±1.3 -1.6±1.2 (N=885)	3.6±1.4 -1.7±1.2 (N=1021)
Prior Biologic	5.2±1.3 (N=912)	4.4±1.4 -0.8±1.1 (N=633)	4.4±1.5 -0.8±1.3 (N=777)	4.3±1.5 -1.0±1.4 (N=894)
Student's *t*-test (⊿DAS28-4 Score)		p<0.001	p<0.001	p<0.001

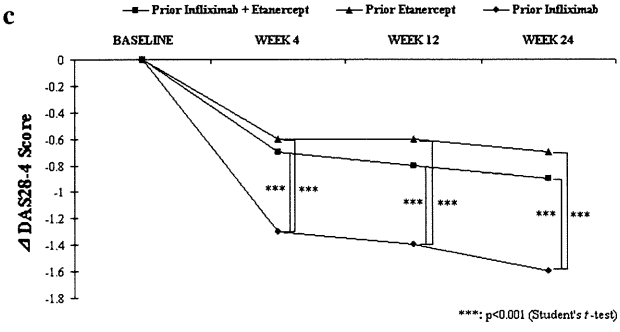
Mean DAS28-4 score, ⊿DAS28-4 Score, and the number of subjects are shown by each category and visit.

b



No Methotrexate	-0.9±1.2 (N=408)	-0.9±1.4 (N=492)	-1.1±1.4 (N=573)
≦8 mg/week	-1.2±1.1 (N=865)	-1.3±1.2 (N=1026)	-1.5±1.3 (N=1182)
>8 mg/week	-1.3±1.1 (N=127)	-1.5±1.3 (N=143)	-1.7±1.3 (N=159)
Student's *t*-test (No Methotrexate vs. ≦8 mg/week)	p<0.001	p<0.001	p<0.001
Student's *t*-test (No Methotrexate vs. >8 mg/week)	p=0.002	p<0.001	p<0.001

c



Prior Infliximab	-1.3±1.1 (N=182)	-1.4±1.3 (N=216)	-1.6±1.4 (N=249)
Prior Etanercept	-0.6±1.1 (N=278)	-0.6±1.2 (N=357)	-0.7±1.3 (N=418)
Prior Infliximab + Etanercept	-0.7±0.9 (N=88)	-0.8±1.1 (N=103)	-0.9±1.2 (N=114)
Student's *t*-test (Prior Infliximab vs. Prior Etanercept)	p<0.001	p<0.001	p<0.001
Student's *t*-test (Prior Infliximab vs. Prior Infliximab + Etanercept)	p<0.001	p<0.001	p<0.001

Japanese RA patients and RA patients in Western countries [8, 14, 15] and to those of infliximab and etanercept [1, 2]. No new ADRs of interest were identified in this analysis of the first 3,000 patients treated with adalimumab in Japan.

ADRs of particular interest to rheumatologists prescribing anti-TNF therapy include serious infections, particularly those of the respiratory system. A recent review of experience with biologic therapies in Japanese patients