Table 4 | Number of patients with nonsteroidal anti-inflammatory drug-associated gastrointestinal symptoms after 24 weeks' treatment with esomeprazole 20 mg once daily or placebo, stratified by baseline severity of symptoms (full analysis set)

		Esomeprazole 20 mg once daily		Placebo	
		Baseline		Baseline	
Symptom	Study end	None	Mild–Severe	None	Mild–Severe
Epigastric pain	None	130	20	124	11
	Mild–Severe	11	10	22	11
Stomach discomfort	None	140	14	132	11
	Mild–Severe	5	12	13	12
Feeling of abdominal fullness	None	132	20	131	12
	Mild–Severe	12	7	11	14
Nausea/ vomiting	None	149	12	146	9
	Mild–Severe	6	4	9	4
Heartburn	None	145	18	138	10
	Mild–Severe	5	3	15	5
Anorexia	None	147	14	147	2
	Mild–Severe	7	3	12	7

Table 5 | Summary of adverse event (AE) findings (safety analysis set*)

	Esomeprazole 20 mg once daily (n = 173)	Placebo (n = 168)
Any AE	134 (77.5)	124 (73.8)
Severe AEs	2 (1.2)	3 (1.9)
Serious nonfatal AEs	12 (6.9)	5 (3.0)
AEs leading to discontinuation	18 (10.4)	21 (12.5)
Drug-related AEs†	24 (13.9)	27 (16.1)
Constipation	2 (1.2)	2 (1.2)
Diarrhoea	2 (1.2)	2 (1.2)
Upper abdominal pain	2 (1.2)	1 (0.6)
Abnormal hepatic function	2 (1.2)	0
Vomiting	2 (1.2)	0
Reflux oesophagitis	0	4 (2.4)
Pruritus	0	2 (1.2)
Blood creatine phosphokinase increased	0	2 (1.2)

All values are presented as n (%) patients.

* Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each category.

† Drug-related AEs are those for which there was a possible relationship to study medication, as judged by the investigator. Only drug-related AEs reported by at least 1% of patients in either treatment group are listed, by preferred term.

Overall, treatment with esomeprazole was well tolerated and prevented peptic ulcer recurrence in this at-risk population, the gastroprotective effect being apparent from week 4 onwards. Such results add to experience with other PPIs in Japanese NSAID users.[22]

The findings of the present study are consistent with studies of esomeprazole for prevention of NSAID-related peptic ulcers in Western populations. In the pooled results of the Verification of Esomeprazole for NSAID Ulcers and Symptoms (VENUS) and Prevention of Latent Ulceration Treatment Options (PLUTO) studies that were conducted in Western NSAID users at increased GI risk, for example, the estimated 6-month rate of peptic ulcer development was 5.2% in patients receiving esomeprazole 20 mg od, while the placebo group had an ulcer incidence of 17.0% ($P < 0.001$).[14] Although the peptic ulcer development rate is similar among esomeprazole recipients in these pooled results to that observed in the current study, the incidence of ulcers in placebo recipients in our sample of Japanese patients is more than two times greater than that observed in patients who received placebo in the VENUS and PLUTO studies. Differences in study populations, particularly in terms of the higher prevalence of *H. pylori* infection, may explain the higher rate of ulcer recurrence among placebo recipients in the present study.

At the time of the present study, no drug was indicated for the prevention of NSAID-induced ulcer in Japanese patients and therefore mucosal protectants were widely used in combination with a NSAID.[11] In the present study, however, use of concomitant mucosal protectant medications did not appear to protect placebo-treated patients from recurrent ulcer. These data imply that mucosal protection is not optimal in the Japanese patient population studied, and patients remain at increased risk of ulcer recurrence unless treated with a PPI.

A number of subgroup analyses based on patients' baseline characteristics were conducted. Similar to patterns seen in Western populations,[23, 24] patients aged $\geq$75 years were at the highest risk of recurrence of NSAID-associated peptic ulcer, and treatment with esomeprazole 20 mg od prevented ulcers in this elderly population relative to placebo. Esomeprazole also seemed to be associated with high ulcer-free rates irrespective of

H. pylori status, whereas *H. pylori*-positive patients had lower ulcer-free rates than *H. pylori*-negative patients in the placebo group. This finding adds to the evidence that *H. pylori* infection and NSAID use increase upper GI risk synergistically, and that appropriate gastroprotection with a PPI is needed in NSAID users with GI risk irrespective of *H. pylori* status.[25, 26]

Esomeprazole provided high ulcer-free rates (approximately 96%) irrespective of CYP2C19 genotype. This finding is in line with previous data showing that patients' CYP2C19 genotype has a minimal effect on the acid-inhibitory effect of esomeprazole.[27, 28]

Cyclo-oxygenase-2 selective inhibitors have been proven to be associated with a lower risk of GI injury among Japanese patients than traditional, nonselective NSAIDs.[29] However, in this study, similar ulcer recurrence rates were seen in patients in the placebo group whether COX-2 selective or nonselective NSAIDs were used. Indeed, the ulcer recurrence rate was high even in recipients of the COX-2 selective inhibitor celecoxib, although patient numbers are too small to draw valid conclusions. Esomeprazole 20 mg od improved the ulcer-free rates relative to placebo in patients who used either type of NSAID. These results are similar to those of the pooled VENUS and PLUTO studies, in which ulcer development was significantly reduced with esomeprazole vs. placebo regardless of whether patients were taking COX-2 selective inhibitors or traditional, nonselective NSAIDs.[14]

Long-term treatment with esomeprazole was well tolerated in the present study and there were no safety concerns. While there have been recent reports of the possible association between long-term PPI therapy and risk of osteoporotic fracture (hip, spine and wrist)[30] and pneumonia,[31] few patients (<1%) experienced such events in the present study [fracture: three patients (two esomepazole); pneumonia: three patients (two esomeprazole)]. Moreover, all cases of fracture and pneumonia were not considered to be related to the study drug.

A major strength of this study lies in its randomised, controlled design; this, along with the inclusion of adequate patient numbers to maintain statistical power, means that the results can be generalised to the general population of Japanese patients who are at risk of peptic ulcer recurrence and who are also taking long-term, daily, oral NSAIDs for the management of inflammatory and rheumatic conditions. Another strength of this study was objective endoscopic visualisation, rather than the use of surrogate markers (e.g. symptoms), of peptic ulcer recurrence. Indeed, only around half of patients with ulcer recurrence in the present study were symptomatic, which outlines the importance of using an objective endoscopic end point. The subgroup analyses conducted in this study provide interesting data, but it should be noted that the number of patients in each subgroup was small in some instances. Thus, no statistical comparisons were undertaken for these exploratory subgroup analyses, and generalisations to these patient subgroups (such as older patients, *H. pylori*-negative and -positive patients, and users of COX-2 selective and traditional, nonselective NSAIDs) should be made cautiously. Finally, we did not evaluate clinically important end points such as GI bleeding in this trial. Further large-scale studies in the real-world Japanese clinical setting will be required to address this important point.

In conclusion, esomeprazole 20 mg od provides effective long-term protection against peptic ulcers in Japanese patients with a confirmed history of peptic ulcers and who require chronic NSAID therapy, confirming previously reported data from Western populations. In addition, esomeprazole 20 mg od is well tolerated in combination with continuous long-term, oral NSAID use in Japanese patients.

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ORIGINAL ARTICLE

Structural damages disturb functional improvement in patients with rheumatoid arthritis treated with etanercept

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Abstract Tumor necrosis factor (TNF) inhibitors have produced improvements in clinical, radiographic, and functional outcomes in rheumatoid arthritis (RA) patients. However, it remains unclear whether factors affecting physical functions remain following TNF therapy. The objective of our study was to assess factors affecting improvement of physical functions and to shed light on relations to disease activity and structural changes in patients with RA treated with etanercept. The study enrolled 208 patients, all of whose composite measures regarding clinical, radiographic, and functional estimation both at 0 and 52 weeks after etanercept therapy were completed. Mean disease duration of 208 patients was 9.6 years, mean Disease Activity Score for 28 joints (DAS28) was 5.4, and mean van der Heijde modified total Sharp score (mTSS) was 94.6. Mean Health Assessment Questionnaire Disability Index (HAQ-DI) improved from 1.4 at 0 weeks to 1.0 at 52 weeks after etanercept therapy, a 31% reduction, which was much less than changes in DAS28 and mTSS. By multivariate analysis, HAQ-DI and mTSS at baseline were significantly correlated HAQ remission. Median HAQ-DI improved in 100 versus 20% of the HAQ-DI $\leq$0.6 versus $\geq$2.0 groups, respectively. The mTSS cutoff point at baseline to obtain HAQ remission was 55.5. During etanercept treatment in the mTSS <55.5 versus >55.5 groups, median HAQ-DI improved in 70 versus 39%; remission was achieved in 59 versus 33%; and there was no improvement in14 versus 30%, respectively. HAQ-DI improvement was significantly correlated with that of DAS28 but not of mTSS. In conclusion, higher HAQ and mTSS at baseline inhibits HAQ-DI improvement within 1 year of etanercept treatment, and the cutoff point necessary for mTSS to improve physical functions in patients with RA was 55.5.

Keywords Rheumatoid arthritis · Anti-TNF · Treatment · Disease activity · Physical function

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Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease that causes significant morbidity and mortality. Tumor necrosis factor (TNF) plays a pivotal role in the pathological processes of RA through accumulation of inflammatory cells and self-perpetuation of inflammation, leading to joint destruction. The combined use of biologics targeting TNF and methotrexate (MTX) has revolutionized RA treatment, producing significant improvements in clinical, radiographic, and functional outcomes that were not previously observed, as well as producing the emerging outcome of clinical, structural, and functional remission [1–5]. Among them, the most important endpoint is

improvement and maintenance of physical functions and functional remission, but the relevance of clinical and structural factors affecting physical functions and limiting improvement of physical functions remain unclear.

The safety and efficacy of the representative TNF inhibitor etanercept, a fully human TNF soluble receptor Fc fusion protein, have been reported in patients with active RA regardless of treatment with MTX [6–10]. One of the most important reports regarding long-term safety, maintenance, and efficacy of etanercept for RA was reported by Weinblatt et al. [11–13]. In their studies, the Health Assessment Questionnaire Disability Index (HAQ-DI) score assessing physical functions decreased rapidly, and the HAQ-DI reductions were clinically significant and maintained for >10 years in all RA patients treated with etanercept. Also, greater median reductions in HAQ-DI scores occurred in patients with early (mean duration 1 year) compared with longstanding (mean duration 12 years) RA, and that difference was sustained at each observation point for 10 years, implying that HAQ-DI improvement is limited in longstanding RA patients. Furthermore, HAQ-DI decreased rapidly within 1 year, and the reduction maintained for 10 years and median HAQ-DI responses at year 11 were 0.4 for the early and 0.9 for longstanding RA patients, suggesting that HAQ-DI score at 10 years after initiation of etanercept therapy depends on HAQ-DI changes at during the first year of treatment [11]. Hence, it appears that physical function after a decade of etanercept therapy depends on the degree of HAQ-DI reduction within the first year of treatment initiation.

However, factors affecting reduced physical function at the initial 1 year remain unclear. Based on this background, the multicenter study reported here was undertaken to assess factors at baseline affecting improvement of physical functions, shedding light on not only disease activity but also on structural values to evaluate progression of articular destruction.

Materials and methods

Patients and methods

Data and information on RA patients that fulfilled the diagnostic criteria of the American College of Rheumatology (ACR) [14] were collected from the major rheumatology centers in Japan, including the First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health Japan, Kitakyushu; the Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, Saitama Medical Center, Saitama Medical University, Saitama; Department of Rheumatology and Clinical Immunology, School of Medicine, Keio University; and the Institute of Rheumatology, Tokyo Women's Medical University. This retrospective study (the ENRICH study) enrolled 208 patients with RA, all of whose information collection regarding composite disease activities, functional ability, and physical functions both at 0 and 52 weeks after initiation of etanercept therapy was completed. All patients who received etanercept treatment (25 mg twice a week in 203 patients and 25 mg once a week in five patients) by March 2009 were registered. The study design was approved by each institution, and informed consent was obtained from each patient before etanercept treatment was undertaken. Demographic data, including disease duration and concomitant therapy, were collected from medical charts. The following parameters were evaluated before and at 52 weeks after the initial etanercept therapy: tender joint count (TJC) 28, swollen joint count (SJC) 28, patient's global assessment of disease activity (PGA), and C-reactive protein (CRP). Disease activity of individual patients was assessed by the Disease Activity Score for 28 joints (DAS28) erythrocyte sedimentation rate (ESR) or DAS28-CRP, calculated according to the authorized formula (http://www.das-score.nl/). Concomitant use of MTX was instituted in all patients, although dose was determined by each attending physician. Joint damage was assessed by van der Heijde modified total Sharp score (mTSS). X-ray images of hands and feet at baseline, study entry, and 1 year after the study were available and evaluable for 120 patients due to loss of radiographs and/or low-quality of X-ray images. Two expert readers independently scored articular damage and progression in a blinded fashion according to the mTSS scoring method. Difference of the two readers' scores for each patient's radiographs was <1% of the maximum mTSS score—that is, 448 [15–17]. Patient demographic indicators and baseline disease characteristics are summarized in Table 1.

Statistical analysis

Patient's baseline characteristics are summarized in Table 1 using the mean values for continuous variables. All multivariate analyses were conducted using the variables of gender, age, disease duration, DAS28-ESR score, DAS28-CRP score, tender joint count (TJC) (0–28), swollen joint count (SJC) (0–28), PGA (0–100 mm, visual analogue scale), ESR, CRP, HAQ-DI, rheumatoid factor (RF), MTX dose, and prednisolone (PSL) dose at baseline. Spearman's correlation analyses were performed to evaluate the association between multivariables at baseline and at 52 weeks after initiation of etanercept therapy (last observation carried forward) of 208 patients. Logistic regression analysis was carried out to estimate HAQ-DI at 52 weeks as dependent variables (probability), and by mTSS at 0 weeks

Table 1 Demographic indicators and baseline disease characteristics

	Mean	Standard deviation	Maximum	Median	Minimum
Age	54.6	13.4	84.0	56.0	18.0
Sex	$f = 83.1\%$				
Duration (year)	9.6	8.2	41.0	8.0	1.0
MTX	w/= 65%				
CS	w/= 68%				
Prior biologics	w/= 20%				
RF	210	346	3510	116	0
MMP-3	278	311	2400	178	8
SJC	7.5	5.2	28.0	6.5	0.0
TJC	7.5	6.3	28.0	6.0	0.0
CRP (mg/dl)	2.9	3.1	23.4	1.9	0.0
ESR (mm/1 h)	51.9	25.6	140.0	49.0	2.3
GH (mm/100 mm)	56	23	100	60	1
DAS28-ESR	5.5	1.1	8.2	5.6	2.9
DAS28-CRP	4.9	1.2	7.8	4.9	2.2
HAQ-DI	1.4	0.8	3.0	1.4	0.0
mTSS	94.6	79.6	378.0	74.0	6.0
EJ	47.9	47.5	233.0	37.5	0.0
JSN	46.7	33.9	145.0	38.6	0.0
ΔmTSS	15.2	16.1	133.8	11.3	0.5

Data are number of patients (%) for categorical data and means for continuous data. Statistical difference was assessed by nonparametric Wilcoxon t test and P (Prob > ChiSq) values are shown. Data supplied for 208 patients with RA

HAQ-DI Health Assessment Questionnaire Disability Index, *DAS28* Disease Activity Score for 28 tender and 28 swollen joints, *CS* corticosteroid, *RF* rheumatoid factor, *MMP-3* matrix metalloprotease-3, *SJC* swollen-joint count, *TJC* tender-joint count, *GH* Global Health Assessment, *CRP* C-reactive protein, ESR erythrocyte sedimentation rate, *EJ* erosive joint, *JSN* joint-space narrowing, *mTSS* van der Heijde modified total Sharp score, Δ estimated yearly progression

as independent variables. A receiver operating characteristic (ROC) curve was developed based on logistic analysis, and the significant cutoff point was determined from the curve. For categorical response parameters, group comparisons were made using a nonparametric Wilcoxon t test. Statistical analyses were performed using JMP software version 8 (SAS Institute, Cary, NC, USA). All reported P values are two sided; $P < 0.05$ was considered significant.

Results

Changes in DAS28, ΔmTSS, and HAQ-DI in patients with RA before and after etanercept treatment

Demographic indicators and baseline characteristics of the 208 patients were: mean age 54.6 years; mean disease duration 9.6 years; mean HAQ-DI 1.4; mean DAS28-ESR 5.5, implying that most patients had highly active disease; and mean mTSS 94.6, indicating that the population included patients with long-established RA (Table 1). Mean DAS28-CRP was 4.9 at baseline, but DAS28-CRP at 52 weeks after initiation of etanercept treatment was 2.6 ($P < 0.0001$ by nonparametric Wilcoxon t test), producing a 46% reduction in DAS (Fig. 1a). Furthermore, as shown in the probability plot, score improvement was observed in the majority of patients, and 55% reached DAS remission, showing values of DAS28 < 2.6 (Fig. 1d). Estimated yearly mTSS progression (ΔmTSS) at 0 weeks was 15.3, whereas that at 52 weeks after etanercept therapy was 2.0 ($P < 0.0001$ by nonparametric Wilcoxon t test), producing a 87% reduction rate in joint destruction (Fig. 1b). In addition, progression was completely inhibited in 48% of patients (Fig. 1e). In contrast, after initiation of etanercept treatment, the HAQ-DI at 52 weeks was not markedly improved, and patients who showed higher HAQ-DI appeared to remain unchanged (Fig. 1c), although the mean HAQ-DI improved from 1.4 at 0 weeks to 1.0 at 52 weeks. The reduction in HAQ-DI from 0 to 52 weeks was 31%, which was much less than changes of DAS28-CRP and ΔmTSS; a similar probability curve was observed before and after initiation of etanercept treatment (Fig. 1f).

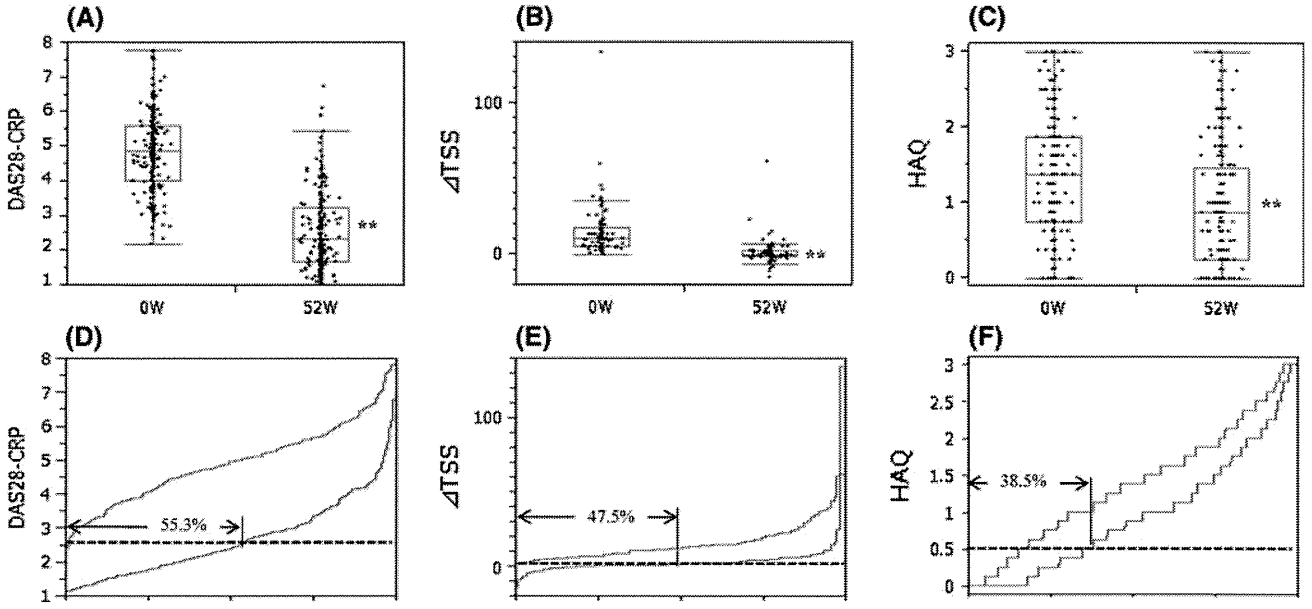

Fig. 1 Disease Activity Score for 28 joints (DAS28) values (**a**, **d**), yearly progression of modified total Sharp score (mTSS) (**b**, **e**), and Health Assessment Questionnaire Disability Index (HAQ-DI) values (**c**, **f**) in patients with rheumatoid arthritis (RA) at 0 and 54 weeks after the start of etanercept therapy. *Upper panels* show distribution of values, mean ± standard deviation (SD), and median, with the 25th and 75th percentiles of DAS28 values (**a**), yearly mTSS progression (**b**), and HAQ (**c**) at 0 and 52 weeks after initiation of etanercept treatment. *Lower panels* are probability plots of DAS28 values (**d**), yearly progression of mTSS (**e**), and HAQ values (**f**) at 0 (*red lines*) and 54 (*blue lines*) weeks after initiation of etanercept treatment. Statistical difference was assessed by nonparametric Wilcoxon t test (*$P < 0.05$, **$P < 0.01$)

Effects of HAQ-DI at baseline on HAQ-DI improvement in RA patients treated with etanercept

To clarify background factors related to HAQ-DI improvement with etanercept therapy, we assessed the relationship between achievement of HAQ-remission (<0.5) at 52 weeks of the treatment and a series of clinical parameters at baseline using multivariate analysis after adjusting for confounding variables. Although no significant correlations between HAQ remission at 52 weeks and the majority of a series of clinical parameters were found, HAQ-DI ($P < 0.0001$) and mTSS ($P = 0.0138$) at baseline were significantly correlated with HAQ remission after initiation of etanercept therapy (Table 2).

Subsequently, changes in HAQ-DI were estimated in patients groups divided by upper quartile (HAQ-DI $\geq$ 2.0), lower quartile (HAQ-DI $\leq$ 0.6), and median values (0.6 < HAQ-DI < 2.0) at the baseline. Mean HAQ-DI at 0 weeks was 2.5 and median was 2.5 at baseline in patients in the upper quartile. Median HAQ-DI was changed from 2.5 to 2.0, producing only a 20% improvement in the upper group (Fig. 2a). Conversely, mean HAQ-DI improved from 0.3 at 0 weeks to 0.2 at 52 weeks and median HAQ-DI from 0.3 to 0, indicating a 100% improvement in median HAQ-DI in the lower-quartile group at baseline (Fig. 2c). We further assessed changes in HAQ-DI based on the difference of HAQ-DI values and mTSS value at baseline. The HAQ-DI significantly and similarly decreased in patients whose baseline HAQ-DI was $\geq$ 2.0 and >73.0, the upper half of mTSS values (Fig. 3a); or HAQ-DI $\geq$ 2.0 and mTSS < 73.0 (Fig. 3d).

Effects of mTSS at baseline on HAQ-DI improvement in RA patients treated with etanercept

Next, logistic regression analysis to estimate the probability of HAQ-DI $\leq$ 0.5 at 52 weeks after initiation of etanercept therapy as a dependent variable and by mTSS at 0 weeks as independent variable was performed. A significant logistic regression curve was drawn between the dependent and independent variables ($P < 0.001$). From the ROC curve based on the analysis, the cutoff point of mTSS at baseline was 55.5 to achieve HAQ remission. Subsequently, one-way analysis of HAQ-DI at week 52 by mTSS at 0 weeks for <55.5 versus >55.5 was performed. Mean HAQ-DI at 0 weeks was 1.6 at baseline in patient group mTSS > 55.5 at 0 weeks. The median HAQ-DI changed from 1.9 to 1.1, producing a 39% improvement of HAQ-DI in the mTSS > 55.5 patient group (Fig. 4a). Conversely, median HAQ-DI improved from 1.3 at 0 weeks to 0.4 at 52 weeks, indicating a 70% improvement of median HAQ-DI in patient group mTSS < 55.5 at

Table 2 Multivariant logistic analysis affecting Health Assessment Questionnaire (HAQ) at week 52 after initiation of etanercept treatment

	Estimated value	Standard error	*t* value	*P* value (Prob > |*t*|)
Duration	0.0050	0.0092	0.55	0.5817
MTX dose	−0.0243	0.0129	−1.88	0.0639
Corticosteroid	0.2099	0.1199	1.75	0.0840
RF	0.0000	0.0002	0.31	0.7571
DAS28-CRP	−0.0519	0.0722	−0.72	0.4748
ESR	0.0020	0.0026	0.76	0.4518
CRP	−0.0155	0.0322	−0.48	0.6309
HAQ	0.6472	0.0853	7.59	<0.0001*
mTSS	0.0025	0.0009	2.52	0.0138*

MTX methotrexate, *RF* rheumatoid factor, *DAS28-CRP* Disease Activity score for 28 joints C-reactive protein; *ESR* erythrocyte sedimentation rate, *HAQ* Health Assessment Questionnaire, *mTSS* modified total Sharp score

* *P* values <0.05 were considered significant. Data supplied for 208 patients with RA

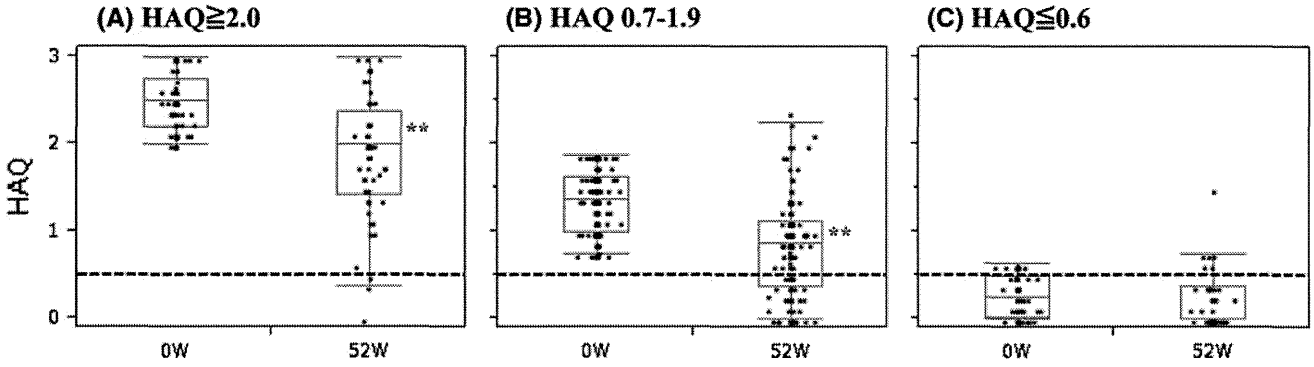

Fig. 2 Changes in Health Assessment Questionnaire (HAQ) values divided by baseline HAQ values before and after treatment with etanercept. One-way analysis of HAQ at 52 weeks after treatment by HAQ at 0 weeks, >2.0;upper 25th percentile of HAQ values (**a**); <0.6, lower 25th percentile (**c**); and between 0.7 and 1.9 between the 25th and 75th percentile (**b**) was performed. Statistical difference between the two groups was determined by nonparametric Wilcoxon *t* test (**P* < 0.05, ***P* < 0.01)

baseline. HAQ remission was observed in 59% of patients whose mTSS was <55.5 at 0 weeks, whereas only 33% of the mTSS > 55.5 group at 0 weeks reached HAQ remission after therapy (Fig. 4a, b).

Median $\Delta HAQ_{[0-52\ weeks]}$ of patients whose mTSS was <55.5 and >55.5 at baseline was −0.63 and −0.38, respectively; and 14 versus 30% of patients with mTSS < 55.5 and >55.5, respectively; revealed no improvement in HAQ-DI following etanercept therapy (Fig. 3c, d). Furthermore, $\Delta HAQ_{[0-52\ weeks]}$ was significantly correlated with $\Delta DAS28_{[0-52\ weeks]}$ ($r = -0.029$, $P < 0.0001$), whereas no correlation was found between $\Delta HAQ_{[0-52\ weeks]}$ and $\Delta mTSS_{[0-52\ weeks]}$ ($r = -0.527$, $P = 0.427$) during etanercept therapy (Fig. 5). These results indicate that higher mTSS at baseline appears to inhibit improvement in HAQ-DI and that improvement in DAS28 but not mTSS affects improvement in HAQ-DI in patients with RA treated with etanercept within the 1 year.

Discussion

The combined use of TNF inhibitors and MTX has produced significant improvements in clinical, radiographic, and functional outcomes that were not previously seen and has revolutionized the treatment goal of RA to clinical, structural, and functional remission [1–5]. In the study population reported here, whose mean disease duration was 9.6 years and mean DAS28-ESR was 5.5, 55% reached clinical remission and 48% achieved structural remission at 52 weeks after initiation of etanercept treatment. However, the HAQ-DI, a marker of physical function, at 52 weeks was not markedly improved, and patients who showed higher HAQ-DI appeared to remain unchanged by etanercept therapy. Probability plot analysis also showed inferior improvement in HAQ-DI than that in DAS28, a marker of clinical disease activity; and ΔmTSS, a marker of radiographic change; and probability curve of HAQ-DI was

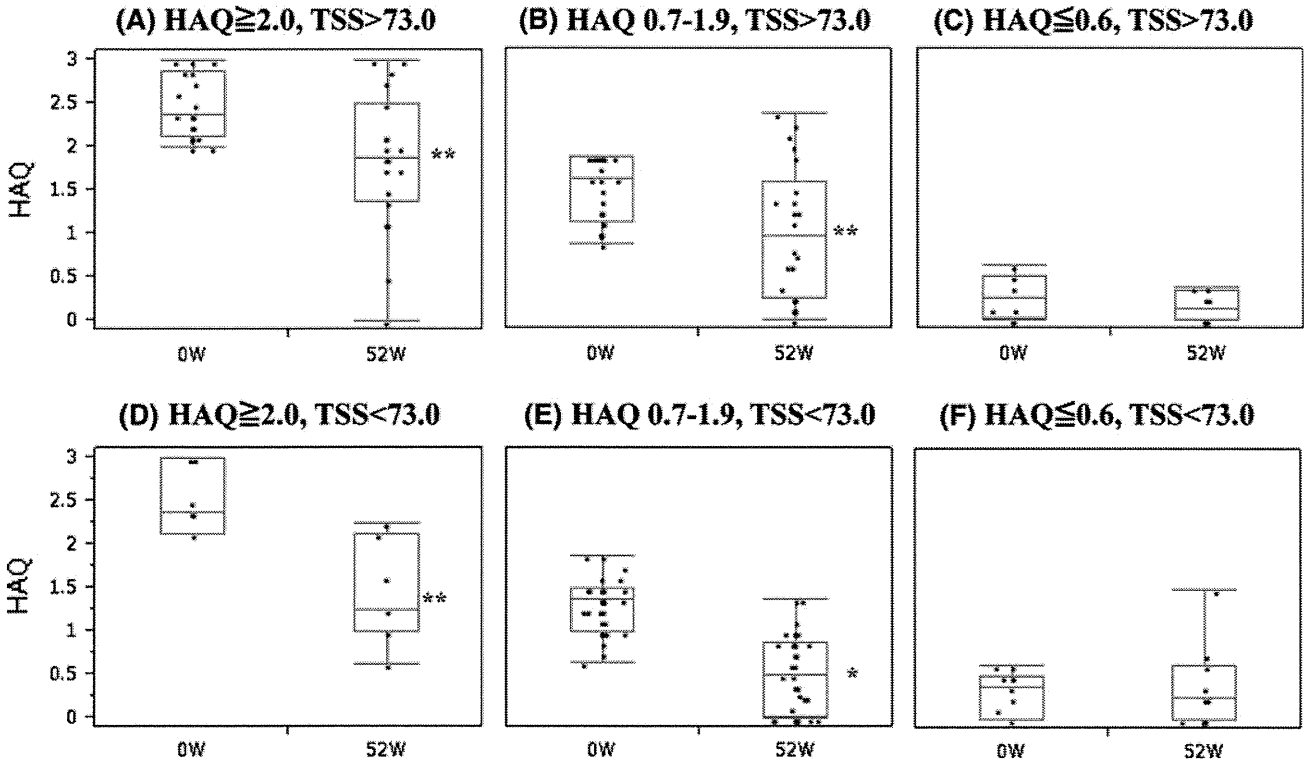

Fig. 3 Changes in Health Assessment Questionnaire (HAQ) values divided by baseline HAQ values and modified total Sharp score (mTSS) values before and after etanercept treatment; one-way analysis of HAQ at 52 weeks after treatment, at 0 weeks, >2.0; upper 25th percentile of HAQ values and >73.0; upper half of mTSS values (**a**) or <73.0; lower half or mTSS (**d**) <0.6; lower 25th percentile of HAQ and mTSS > 73.0 (**c**), or mTSS < 73.0 (**f**), and between 0.7 and 1.9 between the 25th and 75th percentile of HAQ and mTSS > 73.0 (**b**) or mTSS < 7.3 (**e**). Statistical difference of the two groups was determined by nonparametric Wilcoxon *t* test (*$P < 0.05$, **$P < 0.01$)

similar before and after etanercept therapy. Accordingly, we assessed the background factor affecting HAQ-DI improvement using multivariate analysis and found that HAQ-DI and mTSS at baseline were significantly correlated with HAQ remission after the etanercept therapy. Actually, median HAQ-DI improved within 1 year from 2.5 to 2.0, producing only a 20% improvement, in patients whose HAQ-DI at baseline was categorized at the upper quartile (HAQ-DI $\geq$ 2.0). Median HAQ-DI improved from 0.3 to 0, producing a 100% improvement in patients whose HAQ-DI at baseline was in the lower quartile (HAQ-DI $\leq$ 0.6). Thus, higher HAQ at baseline appears to inhibit HAQ-DI improvement with etanercept therapy.

Another important background factor affecting HAQ-DI improvement with the etanercept therapy was mTSS at baseline. The ROC curve based on logistic regression analysis and the cutoff point of mTSS at baseline was determined to be 55.5 for the probability of HAQ-DI $\leq$ 0.5 at 52 weeks after the therapy. Actually, within 1 year, median HAQ-DI improved from 1.9 to 1.1, a 39% improvement, in patients whose mTSS was >55.5 at baseline. Median HAQ-DI improved from 1.3 to 0.4, a 70% improvement of median HAQ-DI, in patients whose mTSS was <55.5 at baseline; also, HAQ remission was observed in 33 and 59% of patients, respectively at 0 weeks. HAQ-DI was not improved by etanercept therapy in 30 and 14% of patients whose mTSS was >55.5 and <55.5 at the baseline, respectively. Furthermore, although improvement in HAQ was significantly correlated with that of DAS28 within a year of etanercept therapy initiation, it was not related to changes in mTSS. From these results, higher mTSS (>55.5) at baseline appears to interfere with HAQ-DI improvement, implying that functional improvement cannot be easily obtained in patients whose mTSS is >55.5. Although this explanation may be too simple, it seems that calculations using our data indicate that the mean ΔmTSS of our study population at baseline was 15.2 and that mTSS could reach 55.5 within 4 years. Physical function, thereby, cannot improve unless patients are treated with MTX and TNF inhibitors within 4 years of disease onset. Therefore the first 4 years may be a "window of opportunity" to prevent disease progression to functional disability.

Impaired physical function in patients with RA is governed by various factors, but Smolen et al. [18, 19] reported

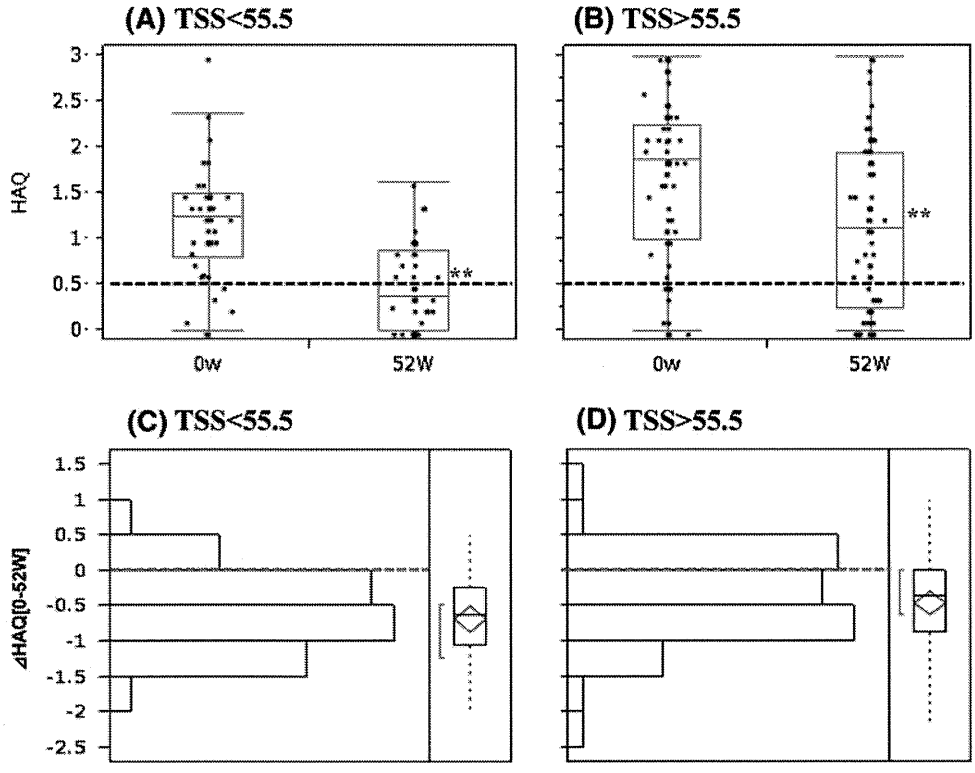

Fig. 4 Changes of Health Assessment Questionnaire (HAQ) values, divided by baseline modified total Sharp score (mTSS) values before and after initiation of etanercept treatment. From receiver operating characteristic (ROC) curve based on logistic regression analysis, the cutoff point of mTSS before treatment was 55.5. Subsequently, one-way analysis of HAQ at 0 and 52 weeks after treatment according to mTSS <55.5 group at baseline (**a**) and >55.5 group at baseline (**b**) was performed, and the statistical difference of the two groups was sought by nonparametric Wilcoxon *t* test (*$P < 0.05$, **$P < 0.01$). Histogram of estimated yearly progression in Health Assessment Questionnaire $(\Delta HAQ)_{[0-52\ weeks]}$, distribution of values, mean ± standard deviation (SD), and median, with the 25th and 75th percentiles of the values divided by mTSS at baseline for the <55.5 (**c**) and >55.5 (**d**) groups are shown

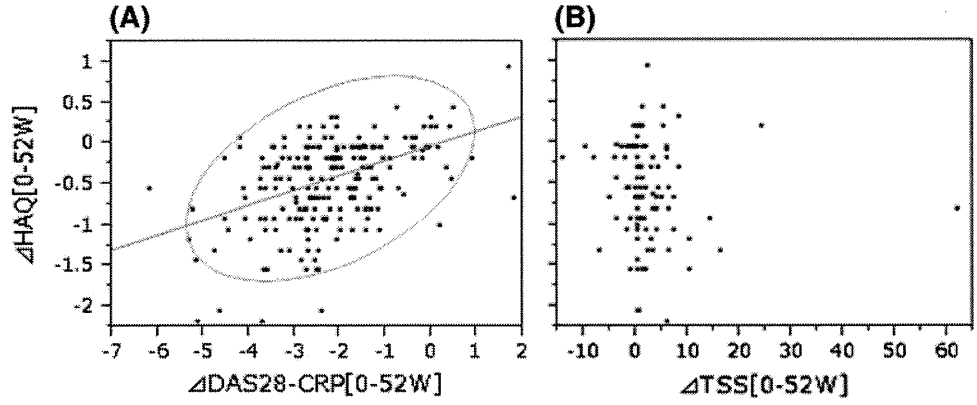

Fig. 5 Correlation between estimated yearly progression in Health Assessment Questionnaire Disease Index (ΔHAQ-DI) and Disease activity Score for 28 joints (ΔDAS28) (**a**) and between ΔHAQ-DI and modified total Sharp score (ΔmTSS) (**b**). *Dot plot* represents an individual value, and the *circle* represents the 95% confidence interval (95% CI). Correlation between $\Delta HAQ_{[0-52\ weeks]}$ and $\Delta DAS28_{[0-52\ weeks]}$ (**a**) and between $\Delta HAQ_{[0-52\ weeks]}$ and $\Delta mTSS_{[0-52\ weeks]}$ (**b**) during etanercept therapy

that HAQ is composed of disease-activity-related HAQ and damage-related HAQ; changes in activity HAQ were mainly due to changes in disease activity, although there was little damage during a short-term therapeutic intervention, whereas HAQ would worsen with increasing damage. Actually, HAQ-DI similarly decreased in a group of patients whose baseline mTSS was >73.0 and in another group with mTSS <73.0, indicating that HAQ

improvement did not depend on baseline mTSS and that etanercept improved activity-related HAQ. Those authors also reported that for every 10 mTSS units, HAQ increase by 1/10th of a unit. Their description is similar to results of our study, in which the cutoff point of mTSS at baseline was 55.5 and a critical HAQ-DI was 0.6 in order to obtain significant improvement or functional remission of HAQ-DI with etanercept therapy. Furthermore, as a recent report indicated that physical disability in RA was associated with cartilage damage rather than bone erosion, further analysis regarding the relevance of joint-space narrowing or bone erosion to changes in HAQ-DI are warranted [20]. Beyond these points, mTSS $>$ 55.5 and/or HAQ-DI $\geq$ 0.6, HAQ-DI would be highly indicative of damage-related HAQ, and these may be critical levels at which structural damage becomes irreversible, even with etanercept and MTX treatment.

We analyzed the relationship between absolute values and changes in DAS28, mTSS, and HAQ-DI simultaneously and found that physical functions cannot improve if joint destruction has progressed beyond the critical level of mTSS $>$ 55.5. Thus, appropriate intervention using TNF inhibitors is strongly recommended during the window of opportunity, when RA patients are treated by addressing the upcoming endpoint for treatment: improvement and maintenance of physical functions.

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Conflict of interest Y. Tanaka has received consulting fees, speaking fees, and/or honoraria from Mitsubishi-Tanabe, Chugai, Eisai, Takeda, Astellas, and Abbott and has received research grant support from Mitsubishi-Tanabe, Takeda, MSD, Pfizer, Astellas, Chugai, Abbott, and Eisai. H Yamanaka has received Research grant from Chugai Pharmaceutical, Astellas Pharma Inc., Wyeth K. K., Daiichi Sankyo, Banyu Pharmaceutical, Mitsubishi Tanabe Pharma, Abbott Japan, Eisai, Santen Pharmaceutical, Taishotoyama Pharmaceutical, Takeda Pharmaceutical Company Limited, Kissei Pharmaceutical, Janssen Pharmaceutical K.K. and lecture fee and/or consulting fee from Abbott, Eisai, Takeda Pharmaceutical, Mitsubishi Tanabe Pharma, Janssen Pharmaceutical, Hoffmann-La Roche, Chugai Pharmaceutical, Pfizer. S Momohara has received speaking fees from Mitsubishi Tanabe Pharma Corporationfrom, Abbott Japan Co., Ltd., and Santen Pharmaceutical Co., Ltd. H. Kameda has received honoraria from Abbott, Centocor Ortho Biotech, Chugai Pharma, Eisai Pharmaceuticals, Mitsubishi Tanabe Pharma, Takeda Pharmaceuticals, Wyeth Japan. K. Amano has received honoraria from Abbott, Chugai Pharmaceutical, Eisai Pharmaceuticals, Mitsubishi Tanabe Pharma, Takeda Pharmaceuticals, Wyeth Japan. T. Takeuchi has received honoraria from the following companies: Abbott, Bristol-Myers Squibb, Chugai Pharmaceutical, Eisai Pharmaceuticals, Janssen Pharmaceutica, Mitsubishi Tanabe Pharma, Novartis, Takeda Pharmaceuticals, Wyeth Japan.

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ORIGINAL ARTICLE

Effectiveness and safety of adalimumab in Japanese patients with rheumatoid arthritis: retrospective analyses of data collected during the first year of adalimumab treatment in routine clinical practice (HARMONY study)

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Abstract We retrospectively investigated the ability of adalimumab (ADA) to reduce disease activity, improve physical function, and retard the progression of structural damage in 167 patients with rheumatoid arthritis. Clinical and functional outcomes were compared between patients with or without prior biologic treatment and those with or without concomitant methotrexate (MTX) treatment. At week 52, 38.3% achieved clinical remission: 42.4 and 28.6% of patients achieved remission in those without and with previous biologics, respectively, while 42.7 and 12.5% of patients achieved remission in those with and without concomitant MTX, respectively. ADA treatment significantly reduced the rate of radiographic progression from 27.1 ± 46.0 (median 13.6; 25th–75th percentiles 8.3 to 28.9) at baseline to 0.8 ± 5.0 (median 0.0; 25th–75th percentiles −0.9 to 2.0) at week 52 ($P < 0.0001$). Radiographic progression was absent in 59.8% of patients. Sixty adverse events (34.21/100 patient-years) were reported, 16 of which were serious (9.12/100 patient-years). ADA therapy is highly effective for reducing disease activity, improving physical function, and limiting radiographic progression. It is generally safe and well tolerated by Japanese RA patients in routine clinical practice.

Keywords Adalimumab · Japanese · Retrospective study · Radiographic outcome · Rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is characterized by progressive inflammatory synovitis and subsequent articular matrix degradation, which may result in joint destruction [1]. Disability and premature death result if the aggressive form of the disease goes untreated [2]. Over the last decade, management of RA has evolved radically because of the development of aggressive therapies for early stages of the disease and the advent of molecular targeted therapies [3, 4]. Although the pathophysiology of RA is not completely understood, tumor necrosis factor (TNF) plays a critical role in mediating the inflammatory synovitis, articular matrix degradation, and bony erosions in RA. Hence, TNF is recognized to be an important molecular target for directed biologic intervention [5].

Adalimumab (ADA) is a fully human immunoglobulin G_1 (IgG_1) monoclonal antibody with a high specificity for TNF-α [6]. ADA's efficacy and safety are well established both with and without concomitant methotrexate (MTX) treatment, based on randomized controlled clinical trials with RA patients conducted in Western countries [7–11]. In Japan, ADA was approved in 2008, making it the third TNF blocker to earn approval. Infliximab (a chimeric

monoclonal antibody to TNFα) [12] and etanercept (a recombinant human TNF receptor-Fc fusion protein) [13] were the first two TNF blockers to be approved. Recently, these biological agents have been reported to be effective and safe for Japanese RA patients encountered during routine clinical practice [14–17]. For ADA, the CHANGE study served as the bridging study for extrapolating data obtained for patients of Western origin to Japanese patients, in whom only the effects of monotherapy had previously been investigated [18]. However, the overseas clinical data obtained so far suggest that ADA monotherapy has only limited effectiveness compared to combination therapies with DMARDs, and in particular MTX.

Therefore, it is of clinical importance to further investigate the effects of ADA, particularly when it is administered concomitantly with MTX to Japanese RA patients. This study aimed to retrospectively investigate the clinical, functional, and radiographic responses to ADA as well as safety in Japanese RA patients encountered in routine clinical practice. This is the first study to evaluate the radiographic response to ADA in Japanese RA patients.

Patients and methods

Patients

Patients with available baseline components for the 28-joint Disease Activity Score based on erythrocyte sedimentation rate (DAS28-ESR) who started treatment with ADA between July 15, 2008 and June 15, 2009 at the following 4 medical institutions were enrolled in this study: (1) the Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, Saitama Medical Center, Saitama Medical University, Saitama; (2) the Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Keio University, Tokyo; (3) the First Department of Internal Medicine of the School of Medicine, University of Occupational and Environmental Health, Kitakyushu; and (4) the Institute of Rheumatology, Tokyo Women's Medical University, Tokyo. All of the patients satisfied the classification criteria of the American College of Rheumatology [19]. Information on patient characteristics was obtained from medical records and pooled for retrospective analyses; the demographic data included age, gender, disease duration, concomitant medications, co-morbidity, and other variables. For subanalyses, patients were divided into subsets based on whether they had or had not received the following: (1) previous biologic treatment; (2) concomitant MTX treatment at baseline.

This study was a retrospective observational study using anonymized information, and it conformed to the standard anti-TNF treatment guideline proposed by the Japan College of Rheumatology (JCR). Written consent was obtained from the patients according to the Declaration of Helsinki.

ADA treatment

ADA treatment was started in accordance with the Japan College of Rheumatology guidelines for adalimumab therapy [20]. We administered 40 mg ADA every other week, in keeping with the dosage instructions on the Japanese drug label. Concomitant use of MTX, disease-modifying antirheumatic drugs (DMARDs) other than MTX, and/or oral steroids was at the discretion of the attending physician. Dose adjustment was carried out according to standard medical practice for controlling disease activity.

Clinical efficacy

Disease activity was assessed using the DAS28-ESR [21]. Functional disability was assessed using the disability index of the Health Assessment Questionnaire (HAQ-DI) [22]. Radiographs of the hands/wrists and feet at baseline and at week 52 were available for 71 patients. The images were scored using van der Heijde's modified Sharp method [23] independently by 2 readers.

Safety

Safety was assessed based on the adverse events reported by patients as well as on the findings of physical examinations and standard clinical laboratory tests recorded from the start of July 15, 2008 through to the data cut-off date of June 15, 2010. All adverse events were summarized according to the Medical Dictionary for Regulatory Activities system organ class (MedDRA SOC) and reported as events per 100 patient-years. Adverse events judged to be serious by the attending physicians were individually listed.

Retention rate

Kaplan–Meier analysis was used to estimate retention rates during the first 52 weeks; 2 patients were excluded because their exact discontinuation dates were unknown. Reasons for discontinuation were categorized for all patients who withdrew at any time, even after 52 weeks.

Statistical analysis

Patient baseline characteristics were summarized using mean (standard deviation), median (interquartile range), or n (%), as appropriate, for the entire patient population and for patient subgroups stratified by previous use of biological agents (previous biologics + or −) and

concomitant use of MTX (concomitant MTX + or −). Demographic and baseline characteristics were analyzed using the Mann–Whitney *U* test for continuous variables and Pearson's chi-square test for discrete variables for the previous biologics (+) versus (−) and the concomitant MTX (+) versus (−) groups. For patients who withdrew before week 52, the last observation carried forward (LOCF) method, including baseline values, was employed to evaluate all efficacy parameters other than the radiographic endpoint. Missing radiographic values at week 52 were determined by linear extrapolation using data at baseline and at the last observation point (where available) if the patients had received ADA treatment for at least 180 days. Patients who withdrew before the 180th day of treatment were not considered in the calculation. The Wilcoxon signed rank test was used to detect statistically significant differences in disease activity and functional outcomes between baseline and week 52. The impact of previous biologic treatment or concomitant MTX treatment on the patient's response to ADA was examined using Pearson's chi-square test. Kaplan–Meier analysis was used to estimate retention rates during the first 52 weeks, and the difference in retention curves was examined by means of a log-rank test. All reported *P* values are two-sided and not adjusted for multiple testing. *P* values <0.05 were considered significant. Data were analyzed with StatView for Windows Version 5.0 (SAS Institute Inc., Cary, NC, USA).

Endpoints

Co-primary endpoints were the percentages of patients achieving remission, as defined by a DAS28-ESR of <2.6 at week 52, and of patients with no radiographic progression, as defined by a change in the total Sharp score (TSS) ≤0.5 from baseline to week 52. Other endpoints include the proportion of patients achieving functional remission (HAQ score ≤0.5) and safety.

Results

Baseline characteristics of the patients

A total of 167 patients for whom ADA therapy was initiated between June 2008 and June 2009 at the 4 medical institutions had all of the DAS28-ESR components at baseline. Baseline demographic and disease characteristics are summarized in Table 1. The mean age of all 167 patients included in this study was 58.4 years, and the majority of the subjects were women (82.6%). The mean duration of disease was 9.0 ± 9.5 years. The baseline mean DAS28-ESR and HAQ scores were 5.3 ± 1.3 ($n = 167$) and 1.24 ± 0.78 ($n = 149$), respectively. The initial mean TSS was 89.7 ± 83.1 (median 65.5; 25th–75th percentiles 36.0–115.0) ($n = 87$), and yearly progression before the initiation of ADA therapy was estimated to be 27.1 ± 46.0 (median 13.6; 25th–75th percentiles 8.3–28.9) ($n = 87$). Among the 167 patients, 118 (70.7%) were naïve to biologic treatment, whereas 49 (29.3%) had been treated with biologics prior to ADA. In total, 143 (85.6%) received concomitant MTX and 69 (41.3%) received concomitant oral steroid, with mean doses of 8.5 ± 2.9 mg/week and 4.8 ± 2.7 mg/day (prednisolone equivalents), respectively, at the beginning of ADA treatment. A comparison of the baseline demographics for different patient subgroups is provided in Table 1. When compared within subsets, patients who had received previous biologic therapy (+) were younger ($P < 0.05$) and had a more severe disease by stage ($P < 0.05$), a longer duration of disease ($P < 0.05$), and a higher rate and dose of concomitant prednisolone ($P < 0.05$ for both) than patients who had not received previous biologic therapy (−). The duration of disease was longer in the concomitant MTX (−) group than in the concomitant MTX (+) group ($P < 0.05$). Moreover, a higher proportion of the patients received concomitant prednisolone in the concomitant MTX (−) group than in the concomitant MTX (+) group ($P < 0.05$). The baseline yearly radiographic progression was greater in the previous biologics (−) group (28.9 ± 50.2) (median 13.2; 25th–75th percentiles 7.9–31.0) than in the previous biologics (+) group (18.3 ± 10.7) (median 14.0; 25th–75th percentiles 11.2–26.5), while it was greater in the concomitant MTX (+) group (28.7 ± 48.0) (median 14.0; 25th–75th percentiles 8.5–30.9) than in the concomitant MTX (−) group (11.1 ± 7.1) (median 10.2; 25th–75th percentiles 7.1–14.4). There were no differences in other baseline demographic and disease characteristics between the previous biologics (+) and (−) groups and between the concomitant MTX (+) and (−) groups.

Clinical efficacy of ADA

DAS28-ESR

Overall, the mean DAS28-ESR score decreased from 5.3 ± 1.3 at baseline to 3.5 ± 1.5 at week 52 ($P < 0.0001$ vs. baseline) (Fig. 1). In the previous biologics (+) and (−) groups, the mean DAS28-ESR scores decreased from 5.3 ± 1.2 to 4.0 ± 1.7 and from 5.3 ± 1.3 to 3.3 ± 1.4, respectively. Although the decreases were statistically significant in both previous biologics (+) and (−) groups, it was more substantial in the previous biologics (−) group ($P < 0.0001$ vs. baseline) than the previous biologics (+) group ($P < 0.05$ vs. baseline). Similarly, in the concomitant MTX (+) and (−) groups, the DAS28-ESR scores decreased from 5.3 ± 1.3 to 3.3 ± 1.4 ($P < 0.0001$ vs.

Table 1 Baseline characteristics of patients

Variables	Total ($n = 167$)	Previous biologics			Concomitant MTX		
		(+) ($n = 49$)	(−) ($n = 118$)	P value	(+) ($n = 143$)	(−) ($n = 24$)	P value
Age (years)	58.4 ± 13.0	55.1 ± 11.5	59.7 ± 13.4	<0.05	58.2 ± 12.9	59.1 ± 14.1	0.5560
Gender, n (% female)	138 (82.6)	43 (87.8)	95 (80.5)	0.2603	118 (82.5)	20 (83.3)	0.9222
Disease duration (years)	9.0 ± 9.5	9.9 ± 8.1	8.7 ± 10.0	<0.05	8.6 ± 9.5	11.8 ± 8.9	<0.05
Stage (I/II/III/IV %)	(15.0/33.5/ 18.6/32.9)	(10.2/24.5/ 16.3/49.0)	(16.9/37.3/ 19.5/26.3)	<0.05	(16.1/34.3/ 18.9/30.8)	(8.3/29.2/ 16.7/45.8)	0.4836
Class (I/II/III/IV %)	(11.4/74.3/ 14.4/0.0)	(12.2/69.4/ 18.4/0.0)	(11.0/76.3/ 12.7/0.0)	0.5953	(11.2/72.7/ 16.1/0.0)	(12.5/83.3/ 4.2/0.0)	0.3052
Prior use of biologics, n (%)	49 (29.3)	49 (100.0)	0 (0.0)	–	39 (27.3)	10 (41.7)	0.1518
RF positive, n (%)	158 (94.6)	46 (93.9)	112 (94.9)	0.7868	136 (95.1)	22 (91.7)	0.4900
MTX use, n (%)	143 (85.6)	39 (79.6)	104 (88.1)	0.1518	143 (100.0)	0 (0.0)	–
MTX dose (mg/week)	8.5 ± 2.9	9.9 ± 8.1	8.1 ± 3.0	0.2153	8.5 ± 2.9	0.0 ± 0.0	–
Oral steroid use, n (%)	69 (41.3)	26 (53.1)	43 (36.4)	<0.05	54 (37.8)	15 (62.5)	<0.05
Oral steroid dose (mg/day[a])	4.8 ± 2.7	5.7 ± 2.6	4.2 ± 2.6	<0.05	4.7 ± 2.6	4.9 ± 3.1	0.9590
MMP-3 (ng/mL[b])	297.6 ± 344.3	292.4 ± 250.7	299.8 ± 377.5	0.2757	312.3 ± 366.1	208.1 ± 127.9	0.7895
SJC, 0-28	6.5 ± 5.6	6.2 ± 6.2	6.6 ± 5.4	0.2307	6.3 ± 4.9	7.6 ± 8.8	0.6004
TJC, 0-28	7.3 ± 6.9	6.7 ± 6.8	7.6 ± 6.9	0.3585	7.4 ± 6.5	7.2 ± 9.1	0.1809
ESR (mm/h)	54.0 ± 31.3	54.4 ± 28.8	53.8 ± 32.4	0.7544	54.0 ± 31.4	53.6 ± 31.2	0.9582
CRP (mg/dL)	2.8 ± 3.9	2.9 ± 3.4	2.8 ± 4.1	0.4068	2.9 ± 4.1	2.3 ± 2.5	0.7391
GH, VAS 0–100 mm	50.7 ± 25.1	56.2 ± 24.5	48.4 ± 25.1	0.0932	49.6 ± 25.1	57.3 ± 25.1	0.1192
DAS28-ESR	5.3 ± 1.3	5.3 ± 1.2	5.3 ± 1.3	0.8398	5.3 ± 1.3	5.2 ± 1.5	0.6598
HAQ-DI[c]	1.24 ± 0.78	1.24 ± 0.85	1.25 ± 0.76	0.8833	1.24 ± 0.78	1.27 ± 0.84	0.8360
TSS[d]	89.7 ± 83.1	98.8 ± 66.0	87.9 ± 86.6	0.2757	88.9 ± 80.5	98.3 ± 112.5	0.6648
Median (IQR)	65.5 (36.0–115.0)	73.5 (52.5–141.5)	65.3 (32.6–109.6)		66.5 (39.8–113.3)	44.3 (22.0–153.5)	
Estimated YP (ΔTSS)[d]	27.1 ± 46.0	18.3 ± 10.7	28.9 ± 50.2	0.2795	28.7 ± 48.0	11.1 ± 7.1	0.1542
Median (IQR)	13.6 (8.3–28.9)	14.0 (11.2–26.5)	13.2 (7.9–31.0)		14.0 (8.5–30.9)	10.2 (7.1–14.4)	

Mean ± SD unless otherwise indicated

Demographic and baseline characteristics were analyzed by the Mann–Whitney U test for continuous variables and Pearson's chi-square test for discrete variables for previous biologics (+) versus (−) and concomitant MTX (+) versus (−)

RF rheumatoid factor, *MTX*, methotrexate, *MMP-3* matrix metalloproteinase 3, *SJC* swollen joint count, *TJC* tender joint count, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *GH* patient's global assessment of disease activity, *VAS* visual analogue scale, *DAS* disease activity score, *HAQ-DI* health assessment questionnaire disability index, *TSS* total Sharp score, *YP* yearly progression, *IQR* interquartile range

[a] Prednisolone equivalents

[b] Total $n = 163$; previous biologics (+) $n = 48$; previous biologics (−) $n = 115$; concomitant MTX (+) $n = 140$; concomitant MTX (−) $n = 23$

[c] Total $n = 149$; previous biologics (+) $n = 41$; previous biologics (−) $n = 108$; concomitant MTX (+) $n = 131$; concomitant MTX (−) $n = 18$

[d] Total $n = 87$; previous biologics (+) $n = 15$; previous biologics (−) $n = 72$; concomitant MTX (+) $n = 79$; concomitant MTX (−) $n = 8$

baseline) and from 5.2 ± 1.5 to 4.6 ± 1.5 ($P < 0.05$ vs. baseline), respectively. In all groups, rapid improvement was achieved during the first 4 weeks of ADA treatment.

Figure 2 shows the percentages of patients who achieved different disease statuses (high, DAS28 > 5.1; moderate, 3.2 ≤ DAS28 ≤ 5.1; low, 2.6 ≤ DAS28 < 3.2; and remission, DAS28 < 2.6) over the time course of treatment. The percentages of patients who achieved clinical remission using the criterion of DAS28 < 2.6 were 31.7% at week 24 and 38.3% at week 52. At week 52, 28.6 and 42.4% of patients in the previous biologics (+) and (−) groups, respectively, achieved remission. The difference in the remission rate was more pronounced between the concomitant MTX (+) and (−) groups ($P < 0.01$) than between the previous biologics (+) and (−) groups ($P = 0.0948$) at week 52. In the concomitant MTX (+) group, the proportion of patients who achieved remission increased over time and reached 42.7% at week 52, while

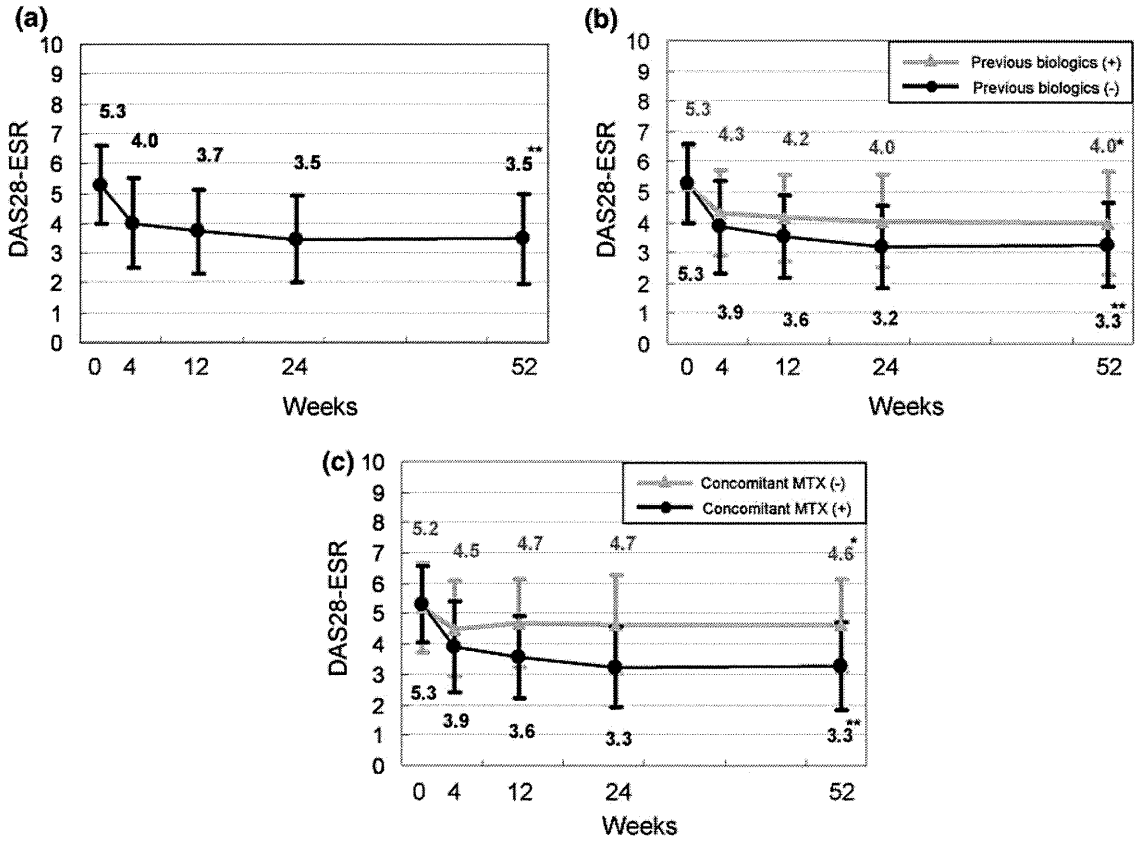

Fig. 1 Time course of the disease activity score over 52 weeks following the initiation of adalimumab treatment. Data were analyzed by the last observation carried forward (LOCF) method. *Points* and *bars* represent means and standard deviations, respectively. **a** All patients ($n = 167$), **b** previous biologics (+) ($n = 49$) and (−) ($n = 118$), **c** concomitant MTX (+) ($n = 143$) and (−) ($n = 24$). $^*P < 0.05$ and $^{**}P < 0.0001$ versus baseline by the Wilcoxon signed rank test

in the concomitant MTX (−) group, the baseline value shifted steadily around 12.5% after 4 weeks.

HAQ

The mean HAQ score of 1.24 ± 0.78 at baseline decreased to 0.92 ± 0.77 at week 52 (Fig. 3). The improvement was moderate but significant ($P < 0.0001$ vs. baseline). At week 4, the mean change was −0.22, which has been associated with meaningful clinical improvements and can be considered to represent the minimum clinically important difference (MCID) [24]. Although the baseline HAQ scores were comparable between the previous biologics (+) and (−) groups on average (1.24 ± 0.85 vs. 1.25 ± 0.76), patients without previous biologic therapy (−) showed a greater improvement than those with previous biologic treatment (+) (0.83 ± 0.72 vs. 1.16 ± 0.86) at week 52. In addition, the difference at week 52 was even more striking between the concomitant MTX treatment (+) and (−) groups (0.87 ± 0.75 vs. 1.29 ± 0.85). A significant improvement in the HAQ score as compared to baseline was detected only in the previous biologics (−) and concomitant MTX (+) groups ($P < 0.0001$ for both groups).

Figure 4 shows the time course of HAQ-DI categorized by increments of 0.5 units from 0.0 to 3.0. At baseline, 23.5% of all patients had HAQ scores ≤0.5, suggesting that about a quarter of the patients had normal function at the time of entry. At week 52, the percentage increased to 43.0%. Although in general the functional profile was consistently better in the previous biologics (−) group at all the time points, there was no difference in the percentage of patients with a HAQ score of ≤0.5 from the previous biologic (+) group at week 52 (44.4 vs. 39.0%, $P = 0.5506$). In the concomitant MTX (+) group, the proportion of patients with a HAQ score of ≤0.5 at baseline (22.9%) increased steadily and almost doubled to 45.0% at week 52. In contrast, there was no increase in the proportion of patients who did not receive concomitant MTX (−) at week 52 when compared to the baseline, though it was not significantly different from the concomitant MTX (+) group ($P = 0.1654$) at week 52.

Radiographic outcomes

Radiographic data at both the baseline and week 52 were available for 71 patients. Linear imputation was employed

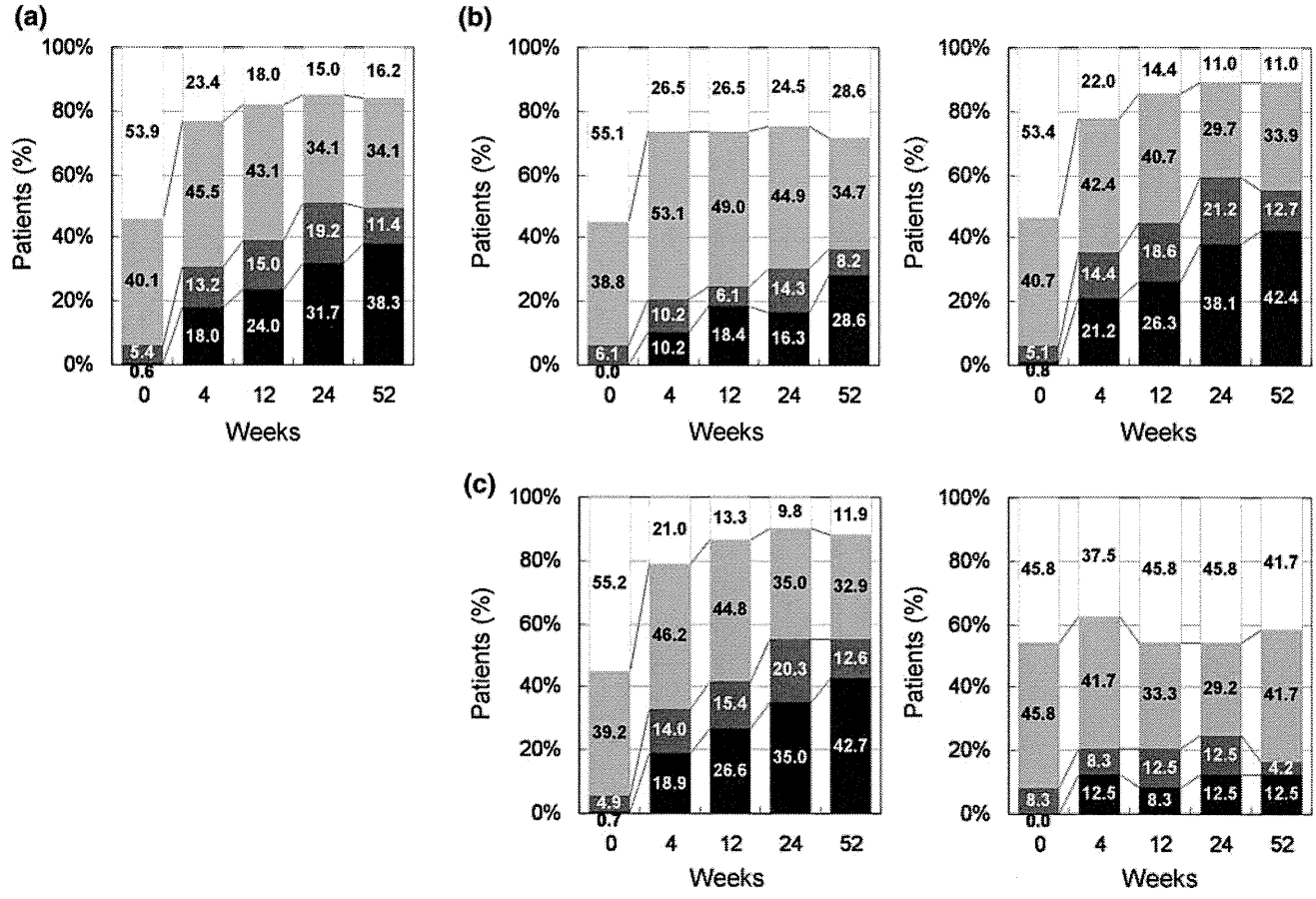

Fig. 2 Time course of disease activity over 52 weeks following initiation of adalimumab treatment. Data were analyzed by the last observation carried forward (LOCF) method. **a** All patients ($n = 167$), **b** previous biologics (+, *left*) ($n = 49$) and (−, *right*) ($n = 118$), and **c** concomitant MTX (+, *left*) ($n = 143$) and (−, *right*) ($n = 24$). Disease activity was categorized as follows

to determine missing data at week 52 for 16 patients who received ADA treatment for at least 180 days. A total of 87 patients were, therefore, subject to an evaluation of radiographic response to ADA. The mean estimated yearly progression was 27.1 ± 46.0 (median 13.6; 25th–75th percentiles 8.3–28.9) at baseline (Fig. 5), which is indicative of a great risk of further joint damage. After 52 weeks of ADA treatment, the mean change was significantly reduced to 0.8 ± 5.0 (median 0.0; 25th–75th percentiles −0.9 to 2.0) ($P < 0.0001$) (Fig. 5). It is particularly worth noting that ADA also suppressed the most aggressive progression in individuals with baseline changes of >100 TSS units/year. The results clearly indicate the ability of ADA to prevent further joint damage as assessed by a reduction in the rate of radiographic disease progression. A cumulative probability plot of changes in TSS was used to illustrate these findings (Fig. 6) [29]. The percentage of patients with no radiographic progression (as defined by a change in TSS of ≤0.5 units) over 52 weeks was 59.8%. However, there were 4 patients with a change in TSS of >10 despite ADA treatment (range 11.0–26.5), 2 of whom discontinued treatment before 52 weeks, and their radiographic data were therefore imputed.

Safety

The overall exposure time to ADA used for the safety evaluation was conservatively estimated to be 175.4 patient-years (as of June 15, 2010), using the last visit records for the 2 patients whose exact discontinuation dates were unknown. ADA was generally well tolerated. A total of 60 adverse events (34.21/100 patient-years) were reported (Table 2).

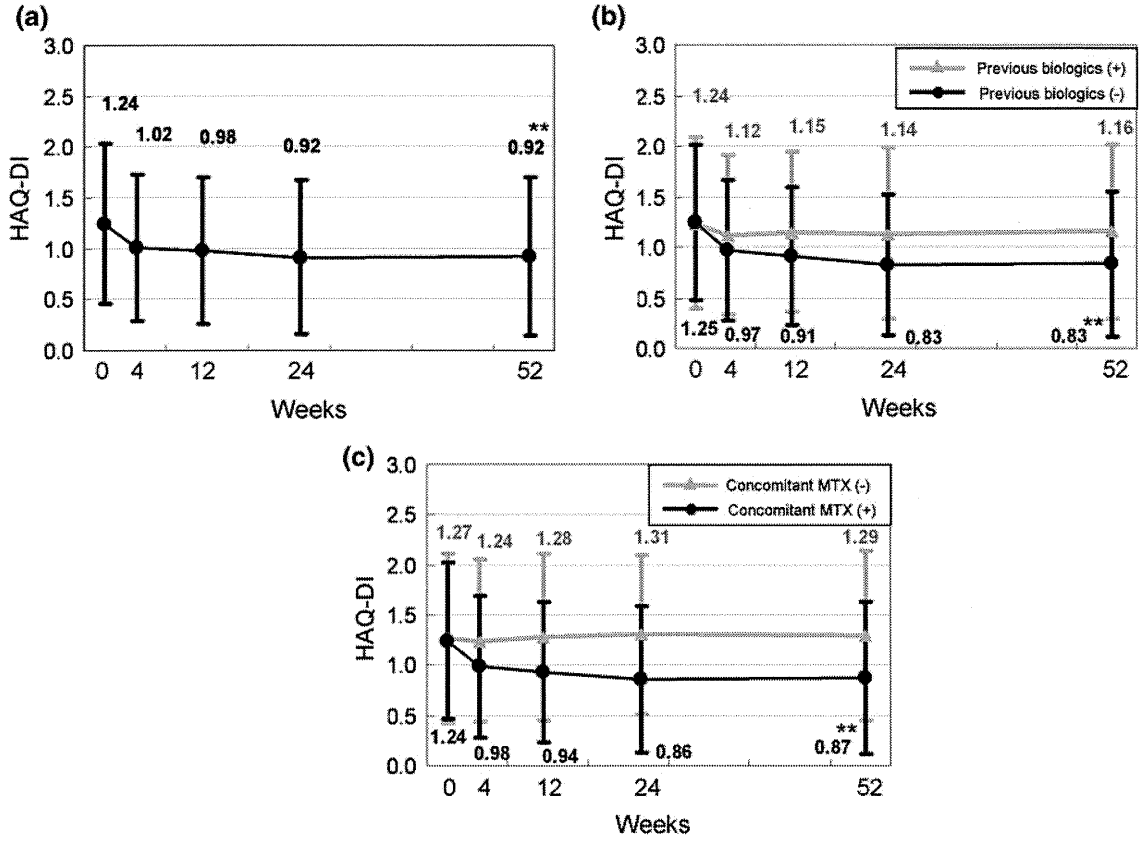

Fig. 3 Time course of Health Assessment Questionnaire—Disability Index (HAQ-DI) over 52 weeks following the initiation of adalimumab treatment. Data were analyzed by the last observation carried forward (LOCF) method. *Points* and *bars* represent the mean and standard deviation, respectively. **a** All patients ($n = 149$), **b** previous biologics (+) ($n = 41$) and (−) ($n = 108$), **c** concomitant MTX (+) ($n = 131$) and (−) ($n = 18$). $^{**}P < 0.0001$ versus baseline by the Wilcoxon signed rank test

The most frequently reported adverse event (SOC) was general disorders and administration site conditions, which were observed at a frequency of 11.40/100 patient-years. ADA therapy was also associated with incidences of infections and infestations at a rate of 10.26/100 patient-years.

Serious adverse events are individually depicted in Table 3. A total of 16 serious adverse events were observed at a rate of 9.12/100 patient-years. Other than the injection site reactions, infections such as *Pneumocystis jiroveci* pneumonia, tuberculosis, nontuberculous mycobacteriosis, and cellulitis were the most frequent serious adverse events. In one patient, perforated colon diverticulum was detected. In another patient, malignant lymphoma was diagnosed. There were no deaths in this study.

Retention rate

In this study, the median duration of ADA treatment was estimated to be 55.9 weeks, with a minimum of 2 weeks and a maximum of 100 weeks ($n = 167$). At week 52, 69.7% of the 165 patients were still undergoing ADA therapy (Fig. 7). A greater percentage of patients in the previous biologics (−) group adhered to the treatment (77.6%) than patients in the previous biologics (+) group (51.0%) during the 52-week period ($P < 0.0001$). Similarly, the retention rate in the concomitant MTX (+) group (73.0%) was significantly higher than that in the concomitant MTX (−) group (50.0%) ($P < 0.05$).

Reasons for withdrawals, including those that occurred after 52 weeks of ADA treatment, are summarized in Table 4. The most common reason for discontinuation was lack of efficacy ($n = 24$), followed by adverse events ($n = 16$). Adverse events that led to discontinuation were *Pneumocystis jiroveci* pneumonia ($n = 1$), miliary tuberculosis ($n = 1$), interstitial pneumonitis ($n = 2$), interstitial pneumonitis/common colds ($n = 1$), generalized rash/nontuberculous mycobacteriosis/upper respiratory inflammation ($n = 1$), cellulitis/injection site reaction ($n = 1$), lymphoproliferative disorder ($n = 1$), perforated colon diverticulum/injection site reaction ($n = 1$), pancytopenia ($n = 1$), malignant lymphoma ($n = 1$), gastrointestinal disorder/injection site reaction ($n = 1$), generalized urticaria/injection site reaction ($n = 1$), and injection site reaction ($n = 3$). Note that 5 patients withdrew after