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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

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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

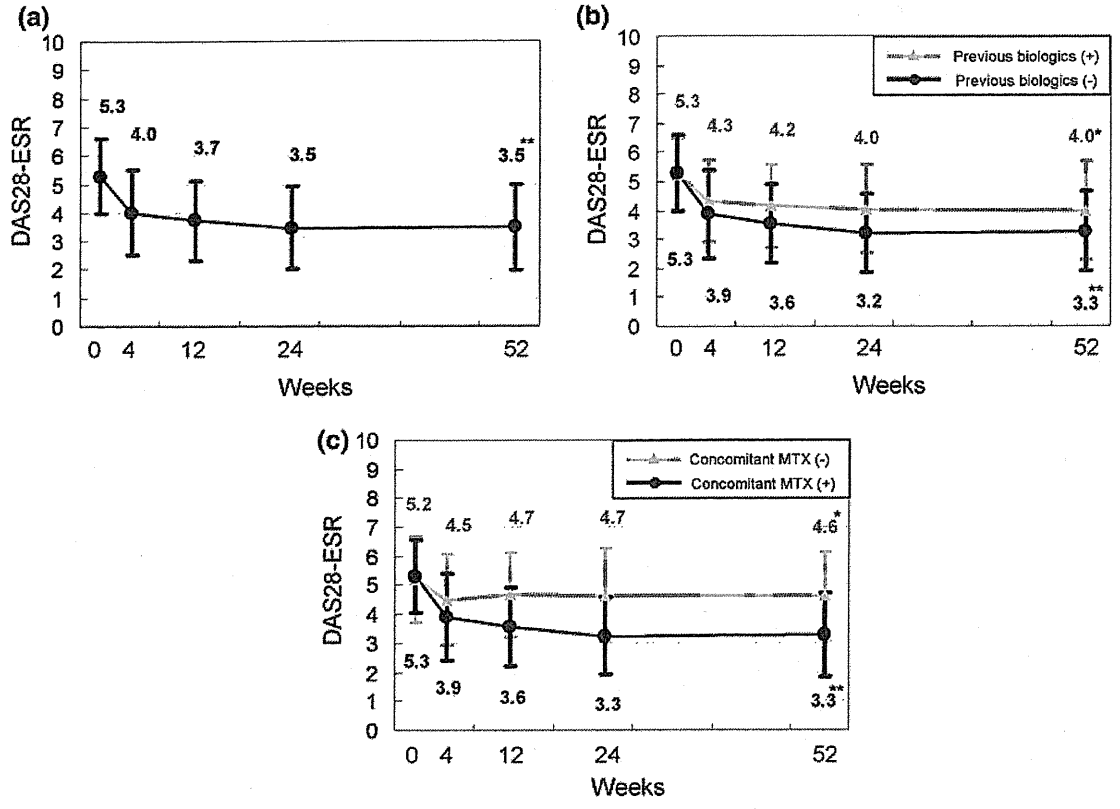

Fig. 1 Time course of the disease activity score over 52 weeks following the initiation of adalimumab treatment. Data were analyzed by the last observation carried forward (LOCF) method. *Points* and *bars* represent means and standard deviations, respectively. **a** All patients ($n = 167$), **b** previous 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

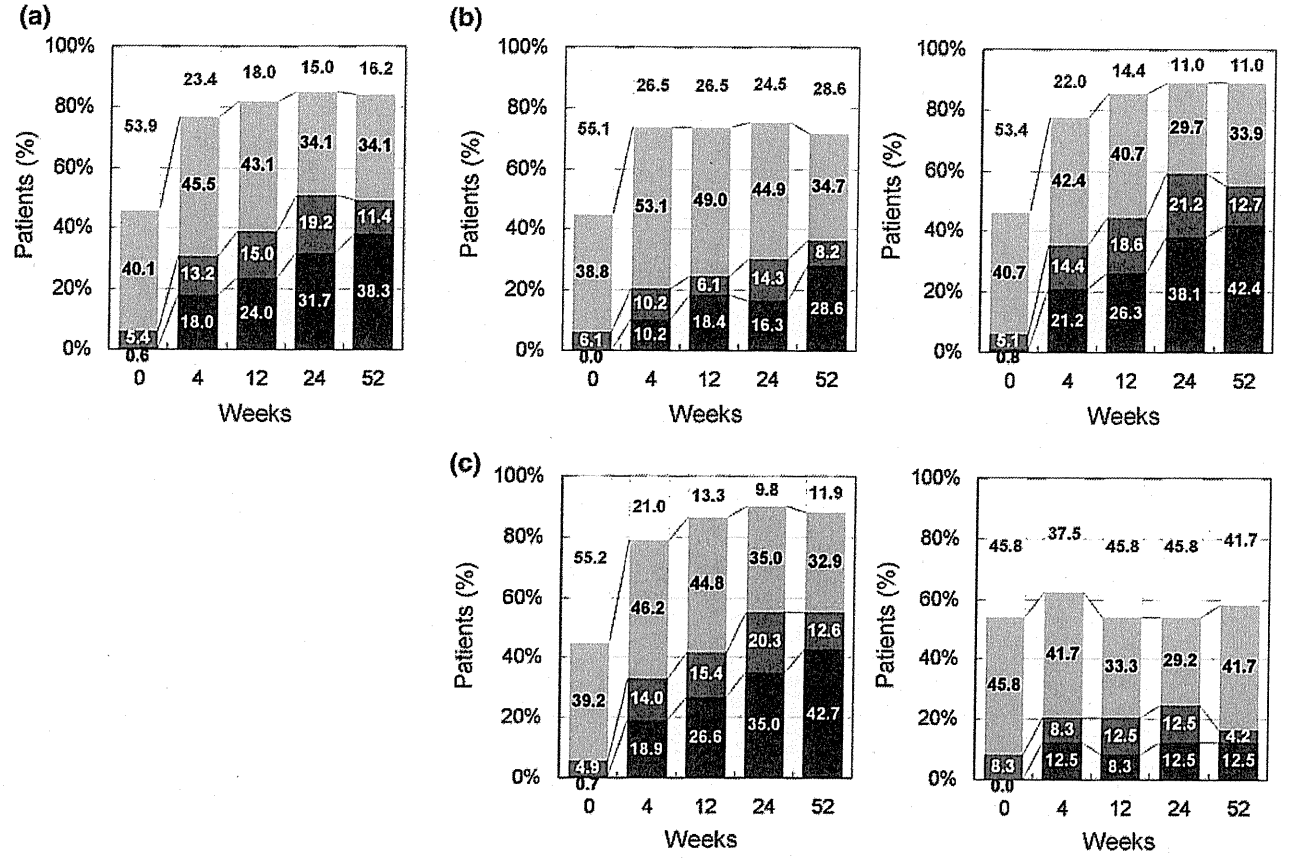

Fig. 2 Time course of disease activity over 52 weeks following initiation of adalimumab treatment. Data were analyzed by the last observation carried forward (LOCF) method. **a** All patients ($n = 167$), **b** previous biologics (+, *left*) ($n = 49$) and (−, *right*) ($n = 118$), and **c** concomitant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

- 5.1 < DAS28-ESR
- 3.2 ≦ DAS28-ESR ≦ 5.1
- 2.6 ≦ DAS28-ESR < 3.2
- DAS28-ESR < 2.6

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).

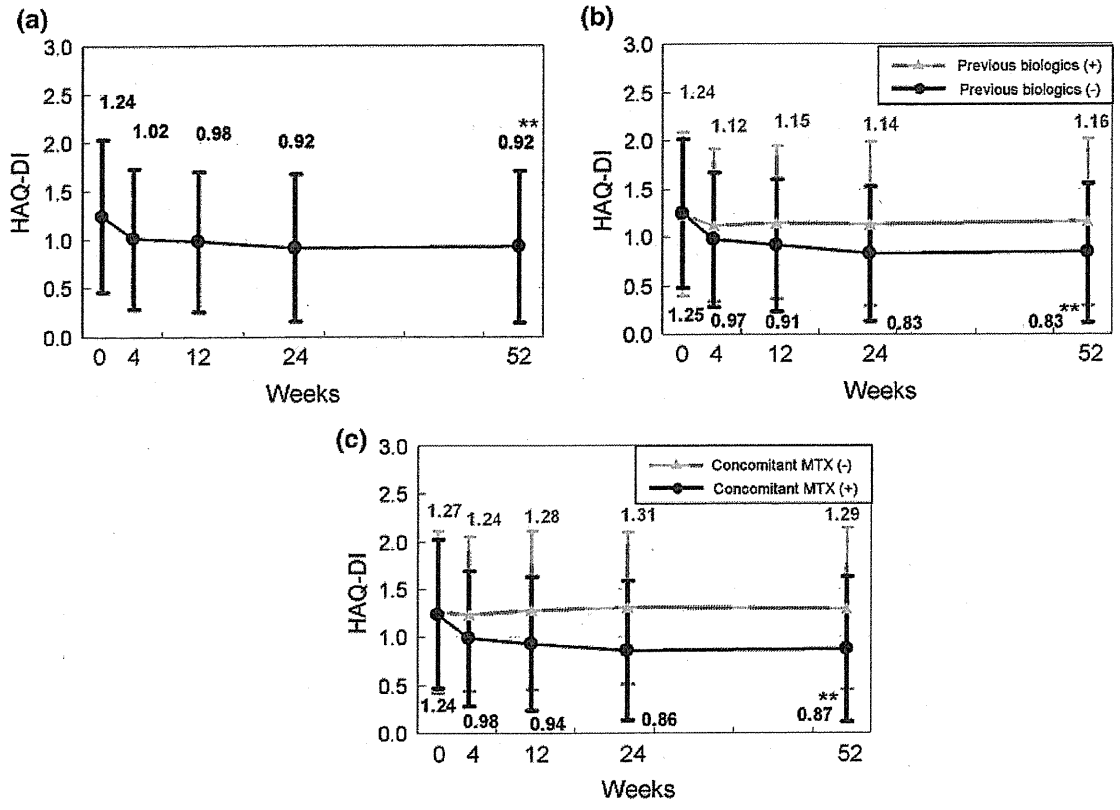

Fig. 3 Time course of Health Assessment Questionnaire—Disability Index (HAQ-DI) over 52 weeks following the initiation of adalimumab treatment. Data were analyzed by the last observation carried forward (LOCF) method. *Points* and *bars* represent the mean and standard deviation, respectively. **a** 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

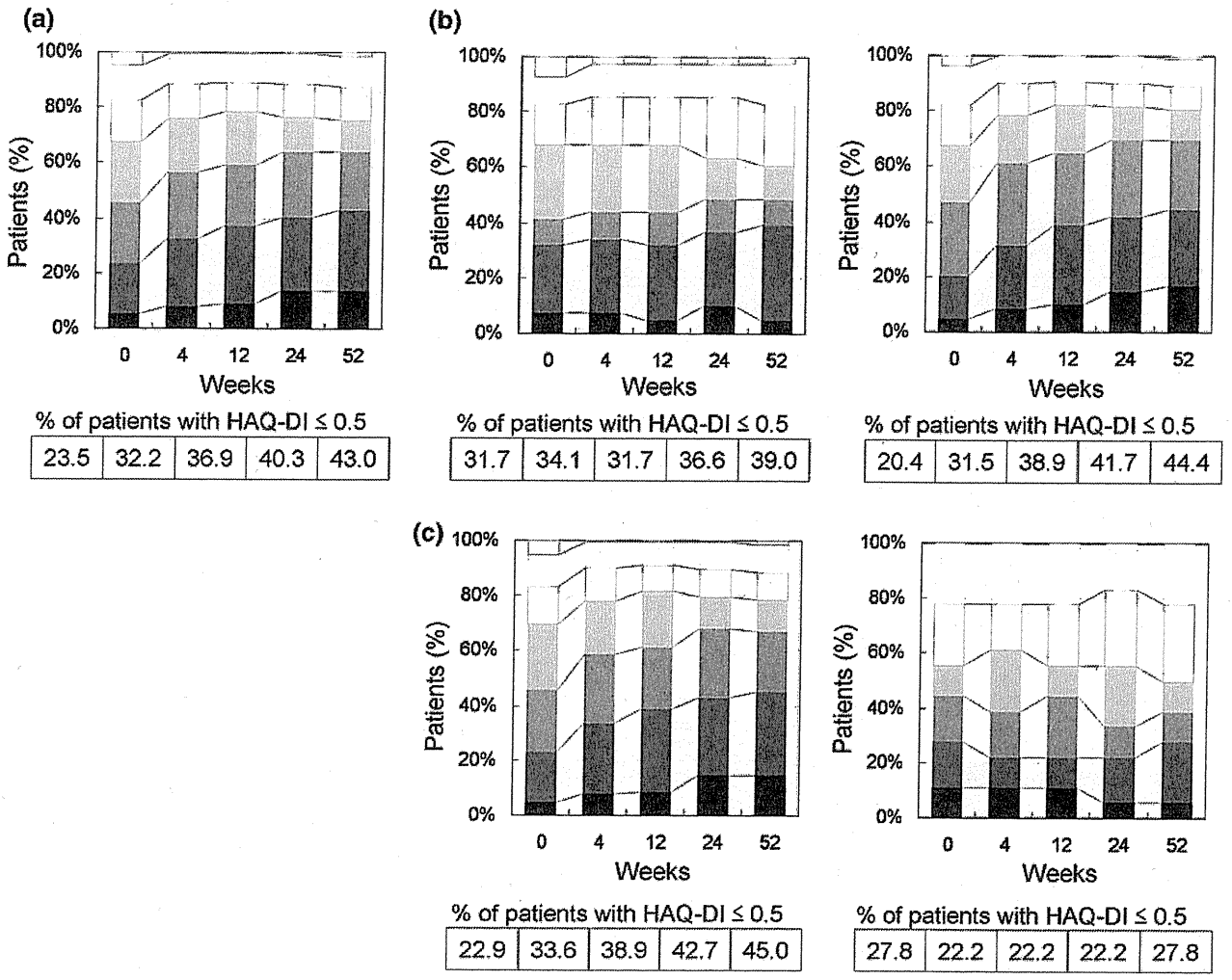

Fig. 4 Time course of the Health Assessment Questionnaire—Disability Index (HAQ-DI) over 52 weeks following the initiation of adalimumab treatment. Data were analyzed by the last observation carried forward (LOCF) method. **a** All patients ($n = 149$), **b** previous biologics (+, *left*) ($n = 41$) 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;

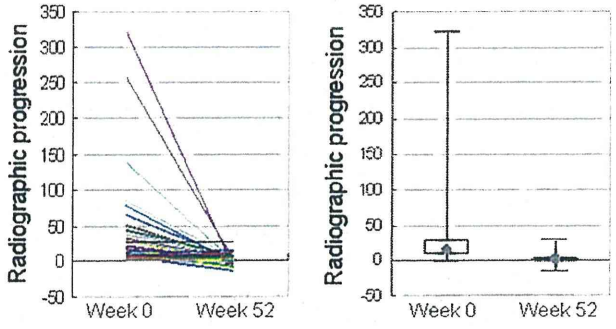

Fig. 5 Yearly progression of TSS in individual patients at weeks 0 and 52 of adalimumab treatment ($n = 87$). Radiographic images were available for 71 of 167 patients at weeks 0 and 52. Linear imputation was used for missing data at week 52 for 16 patients who received adalimumab treatment for at least 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 ($P < 0.0001$)

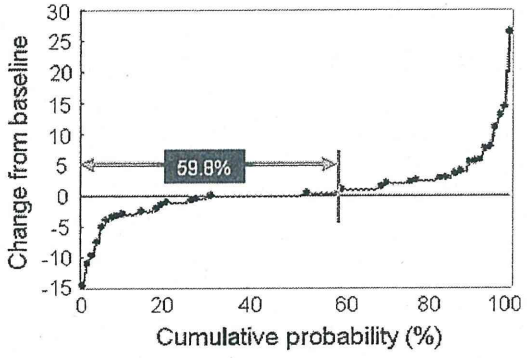

Fig. 6 Cumulative probability plot of change in the total modified Sharp score from baseline to week 52 ($n = 87$). Radiographic images were available for 71 of 167 patients at baseline and week 52. Linear imputation was used for missing data at week 52 for 16 patients who received adalimumab treatment 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%

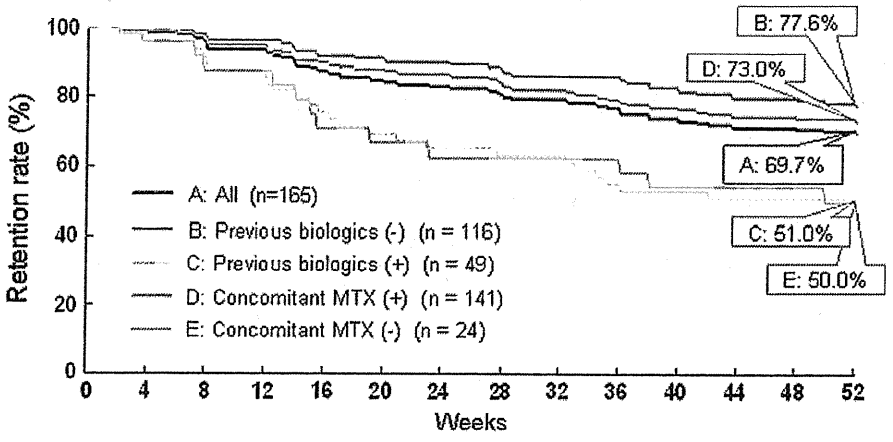

Fig. 7 Retention rates of adalimumab treatment over 52 weeks (Kaplan–Meier plots). Two patients were excluded from the plots because of an unknown date of discontinuation. $P < 0.0001$ between previous biologics (+) versus (−), and $P = 0.0109$ between concomitant MTX (+) versus (−) by the log-rank test

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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CASE REPORT

A case of catastrophic antiphospholipid antibody syndrome complicated with systemic lupus erythematosus, double positive for anti-cardiolipin/β_2 glycoprotein I and anti-phosphatidylserine/prothrombin autoantibodies

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Abstract A 16-year-old male with severe thrombocytopenia and progressive multiple organ infarctions was diagnosed as having catastrophic antiphospholipid syndrome (CAPS) complicated with systemic lupus erythematosus, and was successfully treated with combination of anticoagulants, corticosteroids, plasma exchange, and intravenous cyclophosphamide. Antibodies to phosphatidylserine/prothrombin (PS/PT) complex and cardiolipin (CL)/β_2-glycoprotein I (β_2GPI) were simultaneously detected, indicating that the different pathways of both PS/PT and CL/β_2GPI might be associated with the radical manifestation of CAPS.

Keywords Anti-cardiolipin/β_2-glycoprotein I (anti-CL/β_2GPI) antibody · Anti-phosphatidylserine/prothrombin (anti-PS/PT) antibody · Catastrophic antiphospholipid antibody syndrome (CAPS)

Introduction

Antiphospholipid syndrome (APS) is one of the autoimmune diseases characterized by both arterial and venous thrombotic events such as deep vein thrombosis (DVT), cerebrovascular accidents, etc. or by pregnancy morbidity, related to the presence of anti-phospholipid (PL) antibodies [1]. Anti-PL antibodies have been shown to be an independent risk factor for thrombosis [2]. Lupus anticoagulant (LAC), anti-cardiolipin (CL) and anti-β_2-glycoprotein I (β_2GPI) antibodies are conventionally measured to confirm a diagnosis of APS as established anti-PL antibodies (aPLs). aPLs are not directed against anionic phospholipids, but are part of a large family of autoantibodies against phospholipid-binding plasma proteins or phospholipid–protein complexes. The most common and characteristic antigen in APS is β_2GPI. Autoantibodies against β_2GPI have been considered as thrombogenic, and are detectable either by aCL enzyme-linked immunosorbent assay (ELISA) or by anti-β_2GPI ELISA. The second major antigen for aPLs is prothrombin, and APS-related anti-prothrombin antibodies are detectable by phosphatidylserine-dependent anti-prothrombin assay (aPS/PT).

Catastrophic APS (CAPS) is the most severe form of APS, with mortality rate of 50%. CAPS has been defined as acute infarctions in more than three different organs predominantly caused by small vessel thrombosis. Although clarification of the full picture of CAPS is urgently required because of its poor prognosis, the pathogenesis of the disease and the factors responsible for its severity still need to be elucidated.

We report herein a case of CAPS, complicated with systemic lupus erythematosus (SLE), in a patient who was positive for anti-PS/PT (IgG and IgM together) with anti-CL (IgM) in his serum, possibly indicating that multiple autoantibodies induced the severe multiple organ infarctions. This is the first report of a case with SLE-CAPS positive for both anti-CL/β_2GPI and anti-PS/PT antibodies, and we document that there may be association of multiple aPLs with the radical manifestations of CAPS.

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Case report

A 16-year-old male was admitted to our hospital for intolerable peri-umbilical pain, severe fatigue, and high fever that suddenly occurred 3 days previously. He had history of continuous abdominal pain and thrombocytopenia (platelet count 23,000/μl) 3 months earlier in local hospital. Radiographical examinations including contrast-enhanced computed tomography (CT) scan were normal. At that time, positive test for antinuclear antibodies (ANA, 1:640) and positive test for anti-double stranded DNA autoantibodies (ds-DNA, 62.4 IU/mL) were revealed; however, his symptom had completely improved within a few days.

On admission, he showed impaired consciousness due to severe abdominal pain, and multiple petechiae were evident on the skin of both his lower limbs. His body temperature was 38.0°C with blood pressure of 109/65 mmHg and regular heart rate of 78 per minute. Initial laboratory investigations revealed marked thrombocytopenia (platelet count 19,000/μl), renal dysfunction (serum creatinine concentration 1.20 mg/dL, urine protein 3+, various casts), acute inflammatory reaction (C-reactive protein 11 mg/dL), aPTT prolonged to 62.6 s (control 27 s), and biological false-positive syphilis test (Table 1). Including the previous data of positivity for ANA and anti-ds-DNA autoantibodies the patient fulfilled 5 out of the 11 American College of Rheumatology criteria and was diagnosed as having systemic lupus erythematosus.

Instantaneously enforced contrast-enhanced computed tomography (CT) scan showed lower-density areas in the spleen (Fig. 1a) and both kidneys (Fig. 1b), thus indicating multiple organ infarctions, considered to be the cause of his severe pain. Although heparin 10,000 U/day was started, platelet gradually decreased. Next day he complained of weakness of his left limb, and magnetic resonance imaging showed fresh cerebral infarction in the right temporal to parietal lobe (Fig. 1c). Moreover, echocardiography revealed cardiac vegetation (size 11 × 8 mm^2) attached to the mitral valve that had not destroyed the valve structure, considered to be Libman–Sacks endocarditis (Fig. 1d). Infectious endocarditis was unlikely since the patient's blood culture was negative. To investigate additional infarction, ^{99m}Tc perfusion scintigraphy examination was performed and revealed diffusely distributed defects in both lungs (Fig. 1e), suggesting pulmonary arterial thromboembolism (PTE), and we started anticoagulant therapy. Severe arterial and venous thrombosis progressively occurred in multiple organs in a few days despite continued antithrombotic prophylaxis, which led us to consider catastrophic antiphospholipid syndrome (CAPS). Disseminated intravascular coagulation (DIC) was ruled out since the fibrinogen level was high and the DIC score was less than the diagnostic threshold of 5 points, according to the diagnostic criteria proposed by the Japan Ministry of Health and Welfare (JMHW). Although ADAMTS13 activity was decreased, thrombotic thrombocytopenic purpura (TTP) was also unlikely since schistocytes were not evident in the peripheral blood smear. PA-IgG was elevated to 389 ng/10^7 cells (<46) and we considered that both SLE and CAPS affected thrombocytopenia.

Table 1 Laboratory data on admission

	Value	Unit	Normal range
WBC	10,800	/μL	3,100–9,100
Hb	10.2	g/dL	13.6–17.2
Hct	29.9	%	41.1–51.3
Plt	19 × 10^3	/μL	157–340
Alb	3.8	g/dL	4.0–5.0
AST/ALT	59/30	IU/L	13–33/8–42
LDH	827	IU/L	119–229
CK	115	IU/L	62–287
BUN	25	mg/dL	8–22
Cre	1.2	mg/dL	0.6–1.1
CRP	11.78	mg/dL	0.0–0.2
ESR	98	mm/h	0–10
APTT	62.6	%	27
PT-INR	1.27		0.9–1.26
PT	15.0	s	12.3
Fibrinogen	433	mg/dL	200–400
D-dimer	2.1	μg/mL	0.0–1.0
TAT	5.3	μg/mL	<3.0
Protein C	81	%	64–135
Protein S	76	%	74–132
Coagulation factor XIII	180	%	70–140
vWF activity	198	%	50–150
ADAMTS13	21.3	%	70–120
IgG	2,328	IU/L	778–1,604
CH50	11	U/mL	28–48
Haptoglobin	30	mg/dL	
PAIgG	389	ng/10^7 cells	<46
ANA	×640		
Anti-ds-DNA Ab	68.0	U/mL	0.4–5.7
Anti-SM Ab	30	U/mL	0–14
Urinalysis			
pH	5.5		5.0–7.5
Glucose	Negative		Negative
Protein	+3		Negative
Occult blood	+3		Negative
Hyaline cast	<1	/LPF	
Granular cast	1–4	/LPF	
Waxy cast	<1	/LPF	
Epithelial cast	1–4	/LPF	

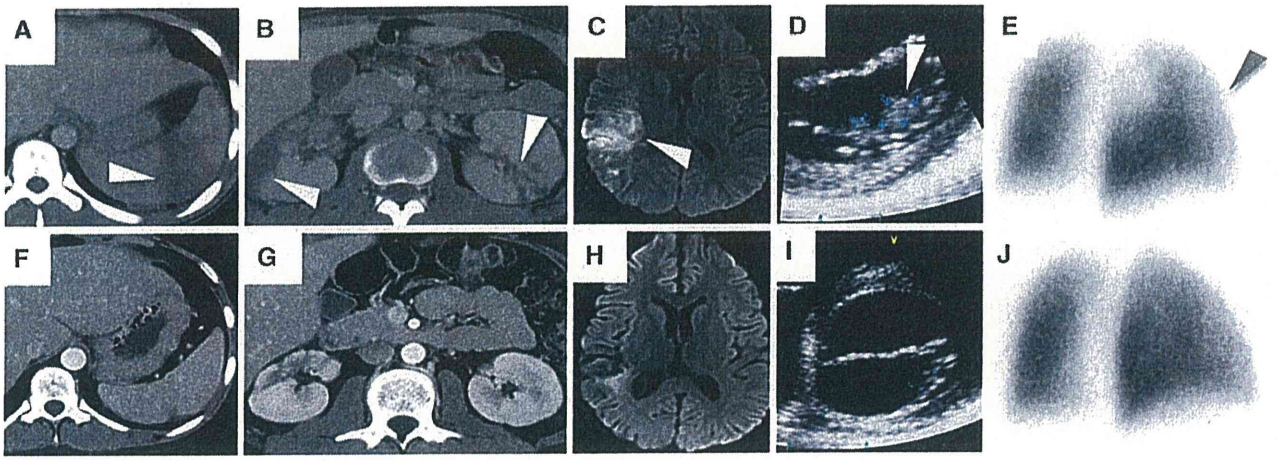

Fig. 1 Imaging of the patient. **a**, **b** Computed tomography (CT) showed spleen and kidney infarction. **c** Magnetic resonance imaging (MRI) showed a cerebral infarction. **d** Echocardiography showed Libman–Sacks endocarditis. **e** A ^{99m}Tc perfusion scintigraphy scan showed pulmonary infarction. **f–j** After treatment, the multi-organ infarctions were markedly improved

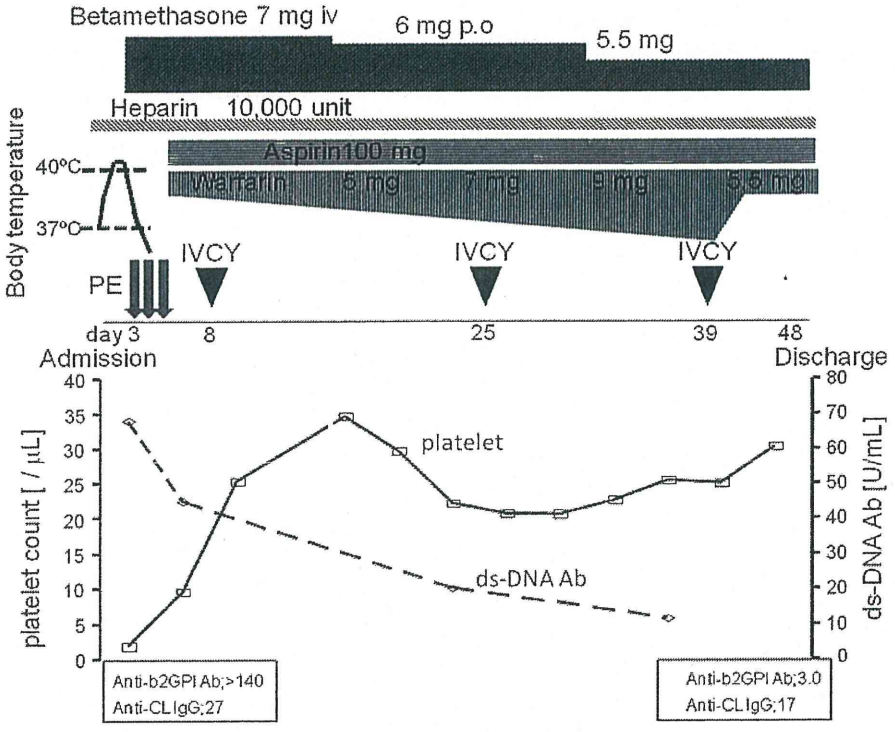

Fig. 2 Clinical course. *PE* plasma exchange, *IVCY* intravenously administered cyclophosphamide pulse therapy

Because his platelet count progressively decreased to 9,000/μl, plasma exchange (PE) and betamethasone (0.1 mg/kg body weight) were added, resulting in gradual recovery of platelet count to 170,000/μl. The fever and abdominal pain also disappeared. Later, extremely high titers of various aPLs measured using specific enzyme-linked immunosorbent assay (ELISA) were reported as follows: IgG aCL 27 GPL, IgM aCL >76 MPL, IgG anti-β_2GPI >140 U/mL (normal <2.0 U/mL), IgG aPS/PT 22 U (normal <2.0 U), IgM aPS/PT 34 U (normal <9.4 U) (Table 2).

These results supported our diagnosis of CAPS, secondary to SLE. Although no triggers of CAPS such as infection, trauma, or surgery were observed, the episode of abdominal pain and thrombocytopenia 3 months earlier could be a possible predictor for CAPS, being noticed in many CAPS patients [3].

Intravenous administration of high-dose cyclophosphamide (IVCY) (15 mg/kg; 850 mg/body) was initiated for highly active systemic lupus erythematosus [SLE disease activity index (SLEDAI) score 30, British Isles Lupus

Table 2 Specific estimation for antiphospholipid antibodies

	Value	Unit	Normal range
Anti-CL IgG	27	U/mL	<18.7
Anti-CL IgM	>76	U/mL	<7
Anti-β2GPI Ab	>140	U/mL	<6.0
Anti-PS/PT IgG	22	U/mL	<2.0
Anti-PS/PT IgM	34	U/mL	<9.4

All measured using specific enzyme-linked immunosorbent assay (ELISA)

Assessment Group (BILAG) index: 45 points] with possible lupus nephritis and a considerable amount of proteinuria and casts. Unfortunately, it was not possible to perform renal biopsy because continuous anticoagulant therapy was essential. After initiating the treatment, the patient's platelet count was normalized, his anti-double stranded DNA autoantibody titer was decreased, complement levels were increased, and proteinuria was normalized (Fig. 2). The international normalized ratio (INR) value was controlled in the range 2.5–3.5 with continuous anticoagulant and antiplatelet therapy. His left-sided hemiparalysis disappeared, and contrast-enhanced CT, MRI, and perfusion scintigraphy revealed marked improvement of the multiple infarctions (Fig. 1f–h, j). Echocardiography showed that the vegetation had also disappeared (Fig. 1i). SLE disease activity was also improved, with SLEDAI score of 0 and 2 points on the BILAG index. After discharge from our hospital, he has been maintained well with tapered glucocorticoids and IVCY six times every other week followed by azathioprine 100 mg daily, without any recurrence. The aPLs tests were repeated 7 weeks after the event; IgG aCL decreased to 17 U/mL, and IgG anti-β_2GPI normalized to 3.0 U/mL.

Discussion

We report herein a case of CAPS complicated with SLE that showed severe thrombocytopenia and multiple infarctions that developed in a short period, successfully treated with combination of plasma exchange, corticosteroids, cyclophosphamide, anticoagulant therapy, and antiplatelet therapy. Additionally, multiple anti-PL antibodies, including anti-PS/PT IgG, anti-PS/PT IgM, together with anti-CL/β_2GPI, were characterized in the present case. We believe that these various and highly concentrated anti-PL autoantibodies might be associated with the severe clinical manifestations of CAPS in this patient.

Antibodies against the CL/β_2GPI complex are involved in the pathogenic mechanisms in APS [4–6]. The roles of anti-CL/β_2GPI complex autoantibodies in APS are considered to include the following: (1) to enhance the binding ability of β_2GPI to anionic phospholipids, and inhibit protein C activation, (2) to form a cross-link between the anti-β_2GPI antibody–β_2GPI–oxidized low-density lipoprotein (LDL) complex and promote uptake by subendothelial macrophages, resulting in atherosclerosis, (3) to dimerize β_2GPI on the surface of platelets and activate platelets via ApoE receptor 2, leading to subsequent signal transduction, and (4) to stimulate monocytes via the p38 mitogen-activated protein (MAP) kinase pathway and induce tissue factor production [7].

Recently, antibodies against prothrombin, a precursor of coagulation factor II (thrombin), have also attracted considerable interest, and several groups have investigated anti-PT autoantibodies to elucidate their immunologic characteristics and role in thrombosis. Anti-PT autoantibodies represent a heterogeneous family of antibodies that includes antibodies against PT alone and against the anti-PS/PT complex. PT molecules bind with phosphatidylserine (PS), a phospholipid in the cell membrane, and form a PS/PT complex. Certain autoantibodies that recognize a domain on the PS/PT complex (anti-PS/PT autoantibodies) have a close association with hypercoagulation by activating prothrombin to thrombin in APS patients [8, 9]. These antibodies (or immune complexes) activate endothelial cells via a specific pathway through Fcγ receptors, resulting in release of procoagulant substances, activation of coagulant factors, platelet aggregation, and finally, formation of thrombosis [10]. Therefore, anti-PS/PT complex antibodies have a close correlation with thrombosis and are associated with APS and lupus anticoagulant (LAC) [10]. However, anti-PS/PT is not yet routinely measured in clinical practice, despite its establishment as a new marker of APS [11]. Differential pathological mechanisms are probably involved in the development of arterial and venous thrombosis, and they are likely to correlate with different aPL antibodies. There are some reports that the combination of various aPLs corresponds to higher risk of thrombosis than in APS patients [12, 13]. Szodoray et al. [12] also reported that thrombotic complications occur more often in the presence of rare aPL antibodies (namely aPS IgG and IgM, as well as aPT IgG). Nojima et al. [14] examined levels of anti-CL/β_2GPI and anti-PS/PT in 126 patients with SLE. In this report, prevalence of cerebral infarction was obviously higher in patients who had both anti-CL/β_2GPI and anti-PS/PT than in the other patients having anti-CL/β_2GPI or anti-PS/PT alone or neither of them. Furthermore, they studied the in vivo effects of anti-CL/β_2GPI and/or anti-PS/PT on the enhancement platelet activation induced by stimulation with low concentration of adenosine diphosphate (ADP). Platelet activation was generated by the mixture of anti-CL/β_2GPI-IgG and anti-PS/PT-IgG prepared from individual patients, but not by each fraction alone. Moreover, in patients with thrombosis,

the prevalence and concentration of aPLs such as LA, aCL, and anti-β_2GPI antibodies were increased [15]. Together with these previous investigations, the present severe CAPS case indicates that the different pathways targeted by the two types of anti-PL autoantibodies, anti-CL/β_2GPI and anti-PS/PT, might cause the severe clinical manifestations observed in CAPS patients.

The present patient recovered with combination of anticoagulant (aCs) therapy, corticosteroids (CS), plasma exchange (PE), and intravenously administered cyclophosphamide pulse therapy (IVCY). Earlier initiation of combination therapy is recommended for CAPS, and a combination composed of aCs plus CS plus PE is recommended as first-line therapy by the CAPS Registry Project Group [16]. The role of cyclophosphamide for treatment of CAPS is controversial. Cyclophosphamide was associated with increased mortality in primary CAPS patients (P-CAPS) but improved survival in patients with systemic lupus erythematosus-associated CAPS (SLE-CAPS) [17]. In the present case, early combination therapy including cyclophosphamide was effective and led to patient recovery. Taken together, we recommend that not only the aCL, but also the aPS/PT titer should be measured in cases of CAPS, allowing clarification of the full picture of the syndrome. It should be emphasized that the appearance of multiple anti-aPLs may be associated with the development of CAPS, and that measurement of the various antibodies may be of benefit to predict the severity of CAPS. Further multiple case studies or cohort studies may clarify the relationship between aCL/β_2GPI–aPS/PT combination and prognosis of CAPS.

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Conflict of interest None.

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Steroid psychosis in a polyarthritis nodosa patient successfully treated with risperidone: tracking serum brain-derived neurotrophic factor levels longitudinally

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