

Twenty-four-week clinical results of adalimumab therapy in Japanese patients with rheumatoid arthritis: retrospective analysis for the best use of adalimumab in daily practice

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Abstract

Objective We evaluated patient drug adherence to and efficacy and safety of adalimumab (ADA) based on data collected from approximately 200 patients to retrospectively examine the best use of ADA in Japanese patients with longstanding rheumatoid arthritis (RA) managed in daily practice.

Methods For explorative comparisons, patients were stratified by prior use or no use of biologics (Bio-naïve vs. Bio-switch) and concomitant use (+) or no use (−) of methotrexate (MTX) into four subgroups. The primary efficacy endpoint was extent of improvement in the Disease Activity Score in 28 joints using erythrocyte sedimentation rate (DAS28-ESR) from baseline to 24 weeks assessed as European League Against Rheumatism (EULAR) good response. Secondary endpoints included ADA treatment continuation as represented by Kaplan–Meier survival curves and percentages of patients achieving remission as defined by DAS28-ESR <2.6.

Results Overall, mean DAS28-ESR significantly decreased from 5.6 ± 1.2 at baseline to 4.1 ± 1.7 at week 24 ($p < 0.0001$), and >30 % of patients achieved EULAR good response. Subgroup analyses indicated that patients in the Bio-naïve and MTX (+) subgroup showed the highest EULAR good response rate of 37.3 % at week 24. The three most commonly reported adverse events (AEs) were skin allergies such as injection-site reactions, infections, and respiratory disorders such as interstitial lung lesions and organizing pneumonia.

Conclusion In conclusion, ADA therapy resulted in significant clinical response in established Japanese patients with RA treated in daily practice. It also demonstrated generally good safety and tolerability. It was suggested that the best use of ADA may be in biologically naïve patients with concomitant administration of MTX.

Keywords Adalimumab · Tsurumai Biologics Communication · Rheumatoid arthritis · Daily clinical practice · Methotrexate

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Introduction

Adalimumab (ADA), the first fully human antitumor necrosis factor alpha (anti-TNF- α) monoclonal antibody, was approved in April 2008 for treating rheumatoid arthritis (RA) in Japan. However, it does not produce antibodies against mouse-derived proteins [human anti-chimeric antibodies (HACA)], which does occur with infliximab (IFX), and thus theoretically it could be associated with a decreased risk of serious immune responses [1, 2]. ADA consists of 100 % human peptide sequences, and could be considered a leading product of TNF inhibitors (e.g., golimumab and certolizumab

pegol), which were launched or are currently under development in Japan.

It has been almost a decade since ADA was launched in Europe and the United States, and results from clinical trials on a great number of RA patients have been presented [3–5]. The therapeutic benefits of ADA with and without concomitant methotrexate (MTX) have been demonstrated: (1) ADA exerts fast onset of effects, even after one week of treatment, and maintains the effects for extended durations [3, 6]; (2) ADA is highly effective in improving clinical signs and symptoms in patients refractory to treatment with other disease-modifying antirheumatic drugs (DMARDs) [3–5]; (3) ADA significantly improves health-related quality of life and productivity [4, 7, 8]; and (4) ADA halts radiographic progression [4, 5]. Meanwhile, efficacy and safety of ADA in Japanese RA patients are yet to be firmly established, and thus all-case-registered postmarketing surveillance (PMS) was required as a condition for approval in Japan, as were cases with the two preceding TNF inhibitors, IFX and etanercept (ETN).

This multicenter study aimed at evaluating drug survival rate, efficacy, and safety of adalimumab based on clinical results in approximately 200 patients treated at institutes related to the Department of Orthopedic Surgery of Nagoya University [the Tsurumi Biologics Communication (TBC)] in order to retrospectively examine the best use of ADA in Japanese patients with RA managed in daily practice.

Patients and methods

The TBC group is composed of 31 RA specialists in 21 medical institutions that comprehensively manages the disease through pharmacological therapy, surgical interventions, and rehabilitation [9]. This study was approved by the Ethics Review Committee at the Nagoya University and carried out in accordance with the ethics principles of the Declaration of Helsinki. Patient inclusion and exclusion criteria were in reference to the ADA prescribed information in Japan [10]: In principle, patients had a diagnosis of active RA despite available DMARD therapy for at least 3 months at approved doses. Patients were treated with ADA if they fulfilled the American College of Rheumatology (ACR) 1987 revised criteria for RA classification [11] and in principle had a Disease Activity Score in 28 joints based on erythrocyte sedimentation rate (ESR) (DAS28-ESR) of ≥ 3.2 [12] despite earlier treatment with DMARDs, including biological agents.

In this study, data collected from registered TBC centers were pooled and analyzed; 201 patients were defined as having RA and in whom ADA treatment was initiated

between 24 June 2008 and 18 December 2009 at one of the TBC centers. The study examined ADA drug survival rate, reasons for drug discontinuation, and safety. Subsequently, among all pooled participants, 175 RA patients receiving at least 6 months of treatment from initiation to the cutoff date of 27 March 2010 were available for assessment of drug response and calculation of remission rates according to the DAS28-ESR < 2.6 at 24 weeks [13].

Effects of ADA therapy on matrix metalloproteinase-3 (MMP-3) and tapering of orally administered corticosteroids were also examined. Moreover, European League Against Rheumatism (EULAR) good response from baseline to 24 weeks was assessed [14]. Patients were further stratified by prior use or nonuse of biologics (Bio-naïve vs. Bio-switch) and concomitant use (+) or no use (−) of MTX into four subgroups: Bio-naïve and MTX (+), Bio-naïve and MTX (−), Bio-switch and MTX (+), and Bio-switch and MTX (−) for exploratory comparisons. Reasons for drug discontinuation were grouped into safety, treatment failure, and others. Treatment failure was further divided into primary (lack of efficacy) and secondary (loss of efficacy) failure at the discretion of the attending physician. For safety, we listed all adverse events (AEs) reported during the study. Patients who received at least one ADA injection were included in safety analyses.

Primary efficacy endpoint was extent of improvement in DAS28-ESR from baseline to 24 weeks assessed as EULAR good response in 175 patients. Secondary endpoints were ADA treatment continuation as represented by Kaplan–Meier survival curves for all patients, and percentages of patients achieving remission as defined by DAS28-ESR < 2.6 for 175 patients. Moreover, effects of ADA treatment on levels of various clinical markers including MMP-3, as well as tapering of orally administered corticosteroids, were assessed in 175 patients.

Statistical analysis

Patient baseline characteristics are summarized using mean [standard deviation (SD)] or number (percent), as appropriate, for all patients as well as for patient subgroups. In the efficacy analyses, the last observation carried forward (LOCF) approach was employed for missing data. Efficacy outcomes were evaluated using Wilcoxon signed rank test, Fisher's exact probability test, Pearson's chi-square test, and parametric paired *t* test. Kaplan–Meier analysis was used to estimate drug survival rates during the first 52 weeks, and the difference in retention curves was examined using the log-rank test. All reported *p* values are two-sided and not adjusted for multiple testing. *P* values < 0.05 are defined as significant. Statistical analysis was conducted by using JMP version 7.1.

Results

Baseline characteristics

Baseline characteristics of all 201 patients and the 175 patients for whom efficacy data for 24 weeks was analyzed are presented in Table 1. The 201 patients comprised approximately 81 % women and 19 % men. Mean age was 57.5 years, and the majority of patients in both data sets had relatively long disease duration (mean 12.7–12.9 years), with advanced RA at the time of ADA treatment initiation. Of the all and efficacy-analyzed groups, 62.2 % and 61.1 % of patients were biologically naïve and 79.1 % and 78.3 % of patients received concomitant MTX, respectively. Approximately 66 % of patients were receiving glucocorticoids at ADA therapy initiation in both groups. Although there was some inter-subgroup variability in characteristics among the four subgroups, it was considered difficult to directly compare, as the numbers of patients was unbalanced; more than half of patients were Bio-naïve and MTX (+) ($n = 103$ and 88 in both groups, respectively), followed by Bio-switch and MTX (+) ($n = 56$ and 49), Bio-naïve and MTX (–) ($n = 22$ and 19), and Bio-switch and MTX (–) ($n = 20$ and 19).

Clinical efficacy

Clinical parameters were compared between baseline and week 24 in 175 patients (Table 2). All patients demonstrated significant improvement in disease activity. Mean DAS28-ESR significantly decreased from 5.6 ± 1.2 at baseline to 4.1 ± 1.7 at week 24 ($p < 0.0001$). Similarly, mean DAS28-C-reactive protein (CRP) significantly decreased from 4.9 ± 1.2 at baseline to 3.4 ± 1.5 at week 24 ($p < 0.0001$). At week 24, swollen joint count (SJC), tender joint count (TJC), ESR, CRP, patient's global assessment (Pt GA), and MMP-3 were significantly reduced when compared to baseline values ($p < 0.0001$). At week 4, 12.2 % and 22.6 % of all patients demonstrated remission (DAS28-ESR < 2.6) and at least low disease activity (< 3.2), respectively. Thereafter, the proportion of patients achieving clinical remission increased steadily and reached 23.0 % at week 24 (data not shown). Percentages of patients who attained EULAR good response based on DAS28-ESR increased gradually with increase in duration of ADA treatment: 18.0 %, 22.3 %, and 30.9 % at weeks 4, 12, and 24, respectively (Table 3).

Comparison among subgroups

Subgroup analyses indicated that patients in the Bio-naïve and MTX (+) subgroup showed the highest remission rate

(30.7 %) at week 24 (Fig. 1). The clinical remission rates were 21.2 % in the Bio-switch and MTX (+) and 13.3 % in the Bio-naïve and MTX (–) subgroups at week 24. No patient achieved clinical remission in the Bio-switch and MTX (–) subgroup at week 24. Similarly, the highest EULAR good response rate of 37.3 % was observed in the Bio-naïve and MTX (+) subgroup at week 24, followed by 33.3 % in the Bio-naïve and MTX (–) subgroup and 27.3 % in the Bio-switch and MTX (+) subgroup. One of 16 evaluable patients (6.3 %) in the Bio-switch and MTX (–) groups reached EULAR good response at week 24 [Fisher's exact probability test: $p < 0.05$ vs. Bio-naïve and MTX (+)] (Table 3).

Effects on oral glucocorticosteroids

In 33 of 94 patients who were on glucocorticoid treatment at the entry and then received ADA therapy for at least 8 weeks (35.1 %), the glucocorticoid treatment was either withdrawn or reduced, significantly decreasing the mean dose from 5.0 mg/day at baseline to 4.1 mg/day at week 24 (paired t test: $p \leq 0.001$) (Table 4). Among four subgroups, only Bio-naïve and MTX (+) exhibited significant reduction in concomitant glucocorticoid dose from 4.5 mg/day to 3.5 mg/day at week 24 (paired t test: $p \leq 0.001$).

Drug survival rate

ADA drug survival rate in 201 patients was calculated using the Kaplan–Meier survival curve, as shown in Fig. 2. At week 52, 67.3 % of the 201 patients continued ADA treatment. For comparison of the four subgroups, 75.7 % of the Bio-naïve and MTX (+), 74.4 % of the Bio-naïve and MTX (–), 58.2 % of the Bio-switch and MTX (+), and 43.8 % of the Bio-switch and MTX (–) patients remained on ADA treatment at week 52. Overall, drug survival rate was higher in the biologically naïve patients than those who received biological therapy prior to ADA treatment. At week 52, a significant difference (log-rank test: $p = 0.0015$) was noted in survival rates between the Bio-naïve and MTX (+) and the Bio-switch and MTX (–) subgroups. Whereas comparisons were somewhat weak, statistically significant differences were also detected between the Bio-naïve and MTX (+) and the Bio-switch and MTX (+) subgroups (log rank test: $p = 0.0344$) and between the Bio-naïve and MTX (–) and the Bio-switch and MTX (–) subgroups (log rank test: $p = 0.0418$).

Reasons for discontinuation

Specific reasons for discontinuation were investigated for those who withdrew from the study up to and even after 52 weeks of ADA treatment among the 201 patients. The

Table 1 Baseline characteristics of 201 patients and 175 patients

Variables and characteristics at baseline						
All patients	Total (<i>n</i> = 201)	Bio-naïve and MTX (+) (<i>n</i> = 103)	Bio-naïve and MTX (−) (<i>n</i> = 22)	Bio-switch and MTX (+) (<i>n</i> = 56)	Bio-switch and MTX (−) (<i>n</i> = 20)	
Age (years)	57.5 (13.7)	55.8 (14.1)	60.9 (12.7)	56.2 (13.4)	66.0 (9.4)	
Gender, <i>n</i> (%) female	163 (81.1)	89 (86.4)	18 (81.8)	43 (76.8)	13 (65.0)	
Disease duration (years)	12.7 (10.6)	13.2 (11.1)	15.7 (10.48)	9.6 (7.6)	14.4 (13.1)	
Stage (I/II/III/IV, %)	(12.7/17.3/31.0/39.1)	(12.9/19.8/34.7/32.7)	(13.6/4.5/22.7/59.1)	(13.0/18.5/27.8/40.7)	(10.0/15.0/30.0/45.0)	
Class (I/II/III/IV, %)	(12.7/52.3/32.5/2.5)	(10.9/58.4/30.7/0)	(18.2/40.9/36.4/4.5)	(18.5/44.4/29.6/7.4)	(0/55.0/45.0/0)	
Prior use of biologics, <i>n</i> (%)	76 (37.8)	—	—	56 (100)	20 (100)	
MTX use, <i>n</i> (%)	159 (76.1)	103 (100)	—	56 (100)	—	
MTX dose (mg/week)	7.0 (1.9)	7.0 (2.1)	—	7.0 (1.6)	—	
Folic acid use, <i>n</i> (%)	90 (51.1)	58 (66.7)	1 (5.3)	31 (62.0)	—	
Oral steroid use, <i>n</i> (%)	119 (65.7)	52 (57.8)	18 (85.7)	36 (70.6)	13 (68.4)	
Oral steroid dose (mg/ml)	4.9 (2.5)	4.5 (2.0)	5.2 (1.7)	5.1 (3.4)	5.8 (2.6)	
DMARD use, <i>n</i> (%)	20 (10.9)	7 (7.6)	9 (42.9)	1 (2.0)	3 (15.8)	
TAC use, <i>n</i> (%)	15 (8.1)	3 (3.2)	4 (21.1)	1 (1.9)	7 (35.0)	
Efficacy for 24 weeks	Total (<i>n</i> = 175)	Bio-naïve and MTX (+) (<i>n</i> = 88)	Bio-naïve and MTX (−) (<i>n</i> = 19)	Bio-switch and MTX (+) (<i>n</i> = 49)	Bio-switch and MTX (−) (<i>n</i> = 19)	
Age (years)	57.5 (13.5)	55.5 (14.0)	62.7 (11.4)	56.2 (13.6)	65.2 (9.0)	
Gender, <i>n</i> (%) female	141 (80.6)	75 (85.2)	16 (84.2)	37 (75.5)	13 (68.4)	
Disease duration (years)	12.9 (10.7)	13.6 (11.3)	15.4 (9.6)	9.8 (7.9)	15.1 (13.0)	
Stage (I/II/III/IV, %)	(12.0/17.7/31.4/38.9)	(11.4/21.6/34.1/33.0)	(10.5/5.3/26.3/57.9)	(14.3/18.4/28.6/38.8)	(10.5/10.5/31.6/47.4)	
Class (I/II/III/IV, %)	(12.0/50.9/34.3/2.9)	(10.2/56.8/33.0/0)	(15.8/36.8/42.1/5.3)	(18.4/44.9/28.6/8.2)	(0/52.6/47.4/0)	
Prior use of biologics, <i>n</i> (%)	68 (38.9)	—	—	49 (100)	19 (100)	
MTX use, <i>n</i> (%)	137 (78.3)	88 (100)	—	49 (100)	—	
MTX dose (mg/week)	7.0 (1.9)	7.0 (2.1)	—	6.8 (1.6)	—	
Folic acid use, <i>n</i> (%)	85 (50.6)	55 (66.3)	1 (5.3)	29 (61.7)	—	
Oral steroid use, <i>n</i> (%)	110 (65.9)	49 (59.8)	16 (84.2)	33 (68.8)	12 (66.7)	
Oral steroid dose (mg/ml)	4.9 (2.5)	4.5 (2.0)	5.2 (1.7)	5.1 (3.5)	5.5 (2.4)	
DMARS use, <i>n</i> (%)	18 (11.3)	7 (9.0)	7 (38.9)	1 (2.2)	3 (16.7)	
TAC use, <i>n</i> (%)	15 (8.1)	3 (3.5)	4 (21.1)	1 (2.1)	7 (36.8)	

Mean (standard deviation) or *n* (%): prednisolone equivalents

ADA adalimumab, MTX methotrexate, DMARD disease-modifying drug, TAC tacrolimus

Table 2 Changes in clinical parameters from baseline to week 24 in 175 patients

Variables	Week	All	Bio-naïve						Bio-switch												
			MTX (+)			MTX (−)			MTX (+)			MTX (−)									
			<i>n</i>	Mean	SD	<i>p</i>	<i>n</i>	Mean	SD	<i>p</i>	<i>n</i>	Mean	SD	<i>p</i>	<i>n</i>	Mean	SD	<i>p</i>			
SJC28 (<i>n</i>)	0	157	4.3	4.8	<0.0001*	85	4.4	5.0	<0.0001*	16	4.0	6.5	0.0036	40	3.1	3.0	<0.0001*	16	6.6	4.7	0.7554
	24	157	2.9	4.1		85	2.9	4.7		16	2.4	2.7		40	2.1	2.6		16	5.0	4.5	
TJC28 (<i>n</i>)	0	157	7.4	6.3	<0.0001*	85	8.2	6.7	<0.0001*	16	6.5	4.4	0.0006	40	5.8	5.5	<0.0001*	16	7.7	6.9	0.1134
	24	157	3.5	4.8		85	3.7	5.4		16	2.0	2.6		40	2.8	2.7		16	6.0	6.1	
ESR (mm/h)	0	144	55.6	31.4	<0.0001*	78	53.0	30.6	<0.0001*	16	62.2	33.2	0.0032	34	50.7	26.1	0.0168	16	71.7	39.7	0.6292
	24	144	41.0	32.6		78	33.6	26.1		16	45.0	29.1		34	41.9	33.7		16	71.1	44.6	
CRP (mg/dl)	0	160	3.0	3.1	<0.0001*	85	2.8	2.6	<0.0001*	16	3.9	3.5	0.0016	43	2.5	2.4	0.0017	16	4.1	5.6	0.1578
	24	160	1.5	2.5		85	1.3	2.7		16	1.6	2.1		43	1.5	2.1		16	2.7	3.1	
PrGA (0–100)	0	153	57.5	23.1	<0.0001*	82	58.3	24.5	<0.0001*	16	56.2	22.6	0.0038	39	56.2	20.9	<0.0001*	16	58.0	23.6	0.1182
	24	153	36.8	25.3		82	34.1	26.3		16	33.1	26.2		39	38.6	21.6		16	50.3	25.1	
MMP-3 (ng/ml)	0	139	333.1	339.5	<0.0001*	73	377.0	411.4	<0.0001*	15	272.2	162.4	0.0038	36	289.5	263.5	0.0173	15	285.0	210.0	0.3343
	24	139	231.5	360.6		73	231.4	443.9		15	166.0	112.9		36	233.5	243.2		15	292.9	314.1	
DAS28-ESR	0	139	5.6	1.2	<0.0001*	75	5.7	1.2	<0.0001*	15	5.5	0.8	0.0008	33	5.3	1.2	<0.0001*	16	5.7	1.4	0.0787
	24	139	4.1	1.7		75	3.9	1.7		15	3.8	1.5		33	4.0	1.5		16	5.3	1.5	
DAS28-CRP	0	151	4.9	1.2	<0.0001*	81	5.1	1.1	<0.0001*	15	4.8	0.9	0.0008	39	4.5	1.2	<0.0001*	16	4.9	1.4	0.0151
	24	151	3.4	1.5		81	3.3	1.6		15	3.1	1.2		39	3.2	1.3		16	4.4	1.5	

MTX methotrexate, SJC swollen joint count, TJC tender joint count, ESR erythrocyte sedimentation rate, PrGA patient's global assessment, MMP-3 matrix metalloproteinase, DAS28 Disease Activity Score in 28 joints, SD standard deviation

* *p* values are versus baseline by Wilcoxon signed rank test

Table 3 Time course of European League Against Rheumatism (EULAR) good response in 175 patients

Week	All (<i>n</i> = 139)	Bio-naïve and MTX (+) (<i>n</i> = 75)	Bio-naïve and MTX (−) (<i>n</i> = 15)			Bio-switch and MTX (+) (<i>n</i> = 33)			Bio-switch and MTX (−) (<i>n</i> = 16)		
			<i>n</i>	<i>p</i>	OR (95 % CI)	<i>n</i>	<i>p</i>	OR (95 % CI)	<i>n</i>	<i>p</i>	OR (95 % CI)
4.0	18.0	24.0	20.0	1.000	0.7917 (0.2008–3.1206)	12.1	0.1999	0.4368 (0.1353–1.4102)	0.0	0.0347	0.0922 (0.0053–1.6110)
12.0	22.3	24.0	26.7	1.000	1.1515 (0.3263–4.0641)	21.2	0.8097	0.8526 (0.3172–2.2912)	12.5	0.3551	0.4524 (0.0938–2.1821)
24.0	30.9	37.3	33.3	1.000	0.8393 (0.2602–2.7070)	27.3	0.3815	0.6295 (0.2565–1.5446)	6.3	0.0171	0.1119 (0.0140–0.8936)

MTX methotrexate, OR odds ratio, 95% CI 95 % confidence interval

Fig. 1 Proportions of patients achieving different disease activity states as defined by Disease Activity Score in 28 joints using erythrocyte sedimentation rate (DAS28-ESR) over 24 weeks. Data were analyzed by the last observation carried forward (LOCF) method. **a** Bio-naïve and MTX (+) (*n* = 75), **b** Bio-naïve and MTX (−) (*n* = 15), **c** Bio-switch and MTX (+) (*n* = 33), and **d** Bio-switch and MTX (−) (*n* = 16). MTX methotrexate

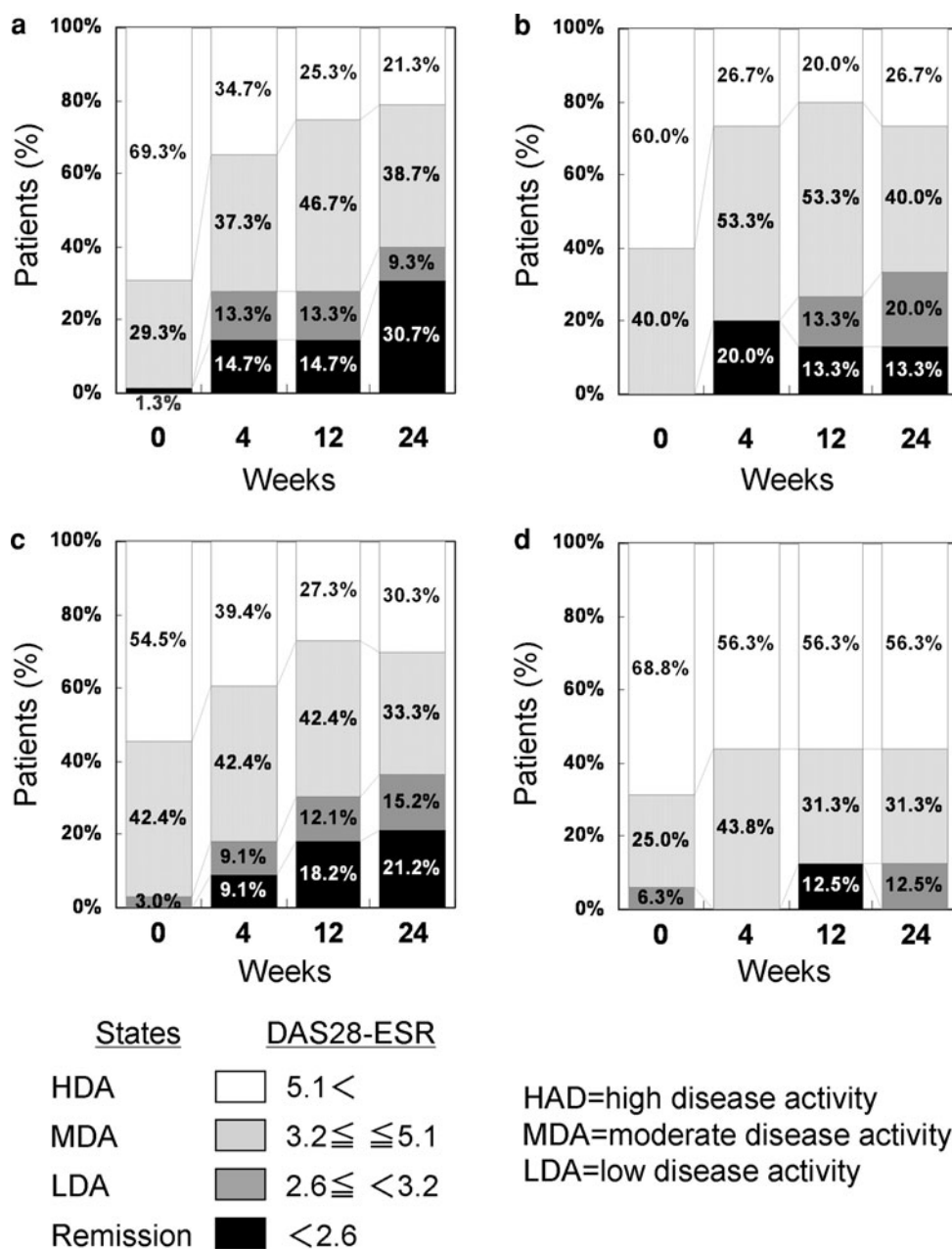


Table 4 Glucocorticoid-sparing effect over 24 weeks in 175 patients

Variables	All patients (<i>n</i> = 94)			Bio-naïve						Bio-switch					
				MTX (+) (<i>n</i> = 45)			MTX (−) (<i>n</i> = 14)			MTX (+) (<i>n</i> = 25)			MTX (−) (<i>n</i> = 10)		
	<i>n</i>	%		<i>n</i>	%		<i>n</i>	%		<i>n</i>	%		<i>n</i>	%	
Discontinued	4	4.3		3	6.7		0	0.0		1	4.0		0	0.0	
Dose reduced	29	30.9		18	40.0		3	8.6		5	7.1		3	12.5	
No change	59	62.8		22	48.9		11	31.4		19	27.1		7	29.2	
Dose increased	2	2.1		2	4.4		0	0.0		0	0.0		0	0.0	
Dose (mg/day)	0 W	12 W	24 W	0 W	12 W	24 W	0 W	12 W	24 W	0 W	12 W	24 W	0 W	12 W	24 W
Mean	5.0	4.5	4.1	4.5	3.9	3.5	5.4	5.3	5.1	5.2	4.6	4.1	5.9	5.7	5.4
SD	2.6	2.4	2.4	2	2.5	2.7	1.6	1.6	1.8	3.8	2.4	2.3	2.3	2.4	1.9
Median	5	5	4.5	5	4	3	5	5	5	5	5	4	5	5	5
<i>p</i> by paired <i>t</i> test	–	0.0056	0.0001	–	0.0101	0.001	–	0.3356	0.1039	–	0.2297	0.0671	–	0.1679	0.1382

MTX methotrexate, W week, SD standard deviation

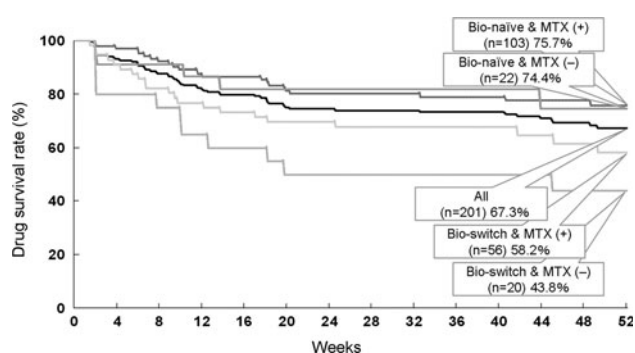


Fig. 2 Drug survival rates of 201 adalimumab-treated patients over 52 weeks (Kaplan–Meier plots). $P = 0.9067$ between Bio-naïve and MTX (+) versus Bio-naïve and MTX (−); $p = 0.2131$ between Bio-switch and MTX (+) versus Bio-switch and MTX (−); $p < 0.05$ between Bio-naïve and MTX (+) versus Bio-switch and MTX (+), Bio-naïve and MTX (+) versus Bio-switch and MTX (−), and Bio-naïve and MTX (−) versus Bio-switch and MTX (−); $p = 0.2271$ between Bio-naïve and MTX (−) versus Bio-switch and MTX (+). MTX methotrexate

reasons for discontinuation were examined every 4 weeks from baseline to 52 weeks and thereafter (Fig. 3). As a result, safety ($n = 8$) and others ($n = 6$) were the only reasons for discontinuation within 4 weeks of ADA initiation. The majority of the withdrawals due to safety were allergic reactions with widespread drug eruption expanded to the trunk and entire body from the injection site. Patients were stratified into four subgroups in the same manner as above, and the Bio-switch subgroups were further divided into two subgroups according to the prior medication, either IFX ($n = 23$) or ETN ($n = 40$). In the stratified analysis, discontinuation due to safety within 4 weeks after ADA treatment initiation was high in patients without concomitant MTX administration, particularly among those who received ETN prior to ADA treatment [five of

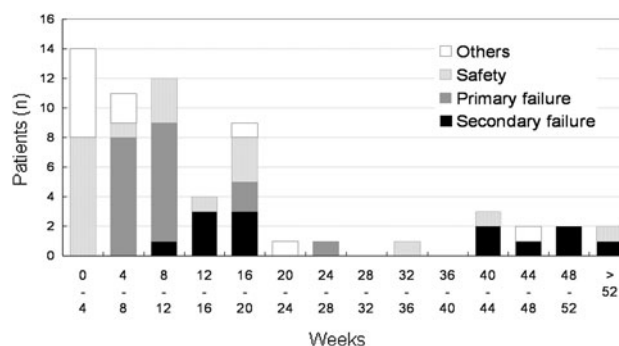


Fig. 3 Reasons for adalimumab discontinuation in 201 patients

13 Bio-switch from ETN and MTX (−) patients]. Primary failure was the most common reason for discontinuation between 4 and 12 weeks after the treatment start ($n = 16$). This was true with Bio-naïve and MTX (+), Bio-switch and MTX (+) and Bio-switch from ETN and MTX (−) subgroups. Although secondary failure was observed occasionally as the reason for discontinuation after week 12, it was not remarkably common in general. Overall, the main reasons for ADA discontinuation were skin allergies (such as early-stage injection-site reaction), infections, and primary failure within 12 weeks following ADA treatment initiation. Of the 201 patients, three desired the drug withdrawal because of financial reasons, which were categorized as others.

Adverse events

Nine serious AEs were reported in nine patients, who required hospitalization; respiratory complications (four events), infections (one event), aggravation of joint symptoms (two events), and orthopedic complications (two

Table 5 Safety in 201 patients

Adverse events	Total (n = 201)	Bio-naïve		Bio-switch	
		MTX (+) (n = 103)	MTX (-) (n = 22)	MTX (+) (n = 56)	MTX (-) (n = 20)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any adverse events (AEs)	65 (32.3)	24 (23.3)	12 (54.5)	21 (35.7)	8 (40.0)
Serious AEs which led to hospitalization	9 (4.5)	4 (3.9)	1 (4.5)	3 (5.4)	1 (0.5)
AEs which led to discontinuation	20 (10.0)	5 (4.9)	4 (18.2)	6 (10.7)	5 (25.0)
Blood and lymphatic system disorders	1 (0.5)	0	1 (4.5)	0	0
Thrombocytopenia	1	0	1	0	0
Cardiac disorders	1 (0.5)	0	1 (4.5)	0	0
Pericarditis	1	0	1	0	0
Ear and labyrinth disorders	1 (0.5)	1 (1.0)	0	0	0
Vertigo	1	1	0	0	0
Eye disorders	1 (0.5)	1 (1.0)	0	0	0
Dry eye	1	1	0	0	0
Gastrointestinal disorders	2 (1.0)	2 (1.9)	0	0	0
Dry mouth	1	1	0	0	0
Vomiting	1	1	0	0	0
General disorders and administration site conditions	3 (1.5)	2 (1.9)	1 (4.5)	0	0
Injection site reaction ^a	3	2	1	0	0
Hepatobiliary disorders	2 (1.0)	0	0	2 (3.6)	0
Abnormal hepatic function	2	0	0	2	0
Immune system disorders	4 (2.0)	1 (1.0)	1 (4.5)	0	2 (10.0)
Drug eruption	2	1	0	0	1
Generalized eruption	1	0	1	0	0
Truncal eruption	1	0	0	0	1
Infections and infestations	19 (9.5)	6 (5.8)	1 (4.5)	9 (16.1)	3 (15.0)
<i>Pneumocystis jiroveci</i> pneumonia	1	1	0	0	0
Acute sinusitis	1	1	0	0	0
Aspergillosis(suspicious)	1	1	0	0	0
Common cold	1	0	0	1	0
Herpes labialis	1	0	0	1	0
Herpes zoster	1	0	0	0	1
Infections and infestations	19 (9.5)	6 (5.8)	1 (4.5)	9 (16.1)	3 (15.0)
Influenza	3	0	0	3	0
Pharyngitis	1	0	0	1	0
Pneumonia	3	0	1	1	1
Pyogenic arthritis of the elbow	1	0	0	1	0
Tuberculosis	1	0	0	1	0
Tuberculosis (suspicious)	1	1	0	0	0
Urinary tract infection	1	1	0	0	0
Upper respiratory infection	2	1	0	0	1
Injury, poisoning and procedural complications	2 (1.0)	1 (1.0)	0	1 (1.8)	0
Fracture	2	1	0	1	0
Investigations	3 (1.5)	2 (1.9)	0	1 (1.8)	0
Decreased WBC count	3	2	0	1	0
Musculoskeletal and connective tissue disorders	3 (1.5)	1 (1.0)	0	1 (1.8)	1 (5.0)
4th Lumbar spondylolisthesis	1	1	0	1	0

Table 5 continued

Adverse events	Total (<i>n</i> = 201)	Bio-naïve		Bio-switch	
		MTX (+) (<i>n</i> = 103)	MTX (–) (<i>n</i> = 22)	MTX (+) (<i>n</i> = 56)	MTX (–) (<i>n</i> = 20)
Aggravation of affected joints	1	0	0	0	0
Worsening RA	1	0	0	0	1
Neoplasms benign, malignant and unspecified	1 (0.5)	0	0	0	1 (5.0)
Non-Hodgkin's lymphoma	1	0	0	0	1
Respiratory, thoracic and mediastinal disorders	8 (4.0)	2 (1.9)	3 (13.6)	3 (5.4)	0
Expectoration	1	0	1	0	0
Bronchitis	1	0	0	1	0
Cough	1	0	1	0	0
Interstitial pneumonia	3	2	0	1	0
Organizing pneumonia	2	0	1	1	0
Skin and subcutaneous tissue disorders	14 (7.0)	5 (4.9)	4 (18.2)	4 (7.1)	1 (5.0)
Acne	1	1	0	0	0
Eruption	1	0	0	1	0
Hair loss	1	1	0	0	0
Prurigo	1	1	0	0	0
Pruritus	1	0	0	0	1
Purpura	1	0	1	0	0
Rash	6	1	2	3	0
Scar	1	1	0	0	0
Skin erythema	1	0	1	0	0

MTX methotrexate

^a Erythema, and/or itching, hemorrhage, pain or swelling

events) (Table 5). The three most commonly reported AEs were skin allergies, such as injection-site reactions; infections; and respiratory disorders, such as interstitial lung lesions and organizing pneumonia. Of those, six of 103 patients in the Bio-naïve and MTX (+) subgroup developed AEs that led to discontinuation of treatment: dry mouth/dry eye (*n* = 1), decreased white blood cell (WBC) count (*n* = 1), drug eruption (*n* = 1), interstitial pneumonia (*n* = 2), and fracture (*n* = 1). Four of 22 patients in the Bio-naïve and MTX (–) subgroup stopped ADA therapy due to AEs: organizing pneumonia (*n* = 1), pericarditis (*n* = 1), thrombocytopenia (*n* = 1), and generalized eruption (*n* = 1). Six of 56 patients in the Bio-switch and MTX (+) subgroup discontinued treatment due to rash (*n* = 2), tuberculosis (*n* = 1), herpes labialis (*n* = 1), organizing pneumonia (*n* = 1), and decreased WBC count (*n* = 1). Five of 20 patients in the Bio-switch and MTX (–) subgroup discontinued treatment due to pruritus (*n* = 1), non-Hodgkin's lymphoma (*n* = 1), worsening RA (*n* = 1), truncal eruption (*n* = 1), and drug eruption (*n* = 1). The patient reported as having non-Hodgkin's lymphoma was diagnosed right after the first dose of ADA and therefore withdrawn from the study at 2 weeks. Drug causality of the event was excluded, rendering the discontinuation

categorized into others. During the study observation, no death was observed.

Discussion

The mainstay of RA treatment is the use of MTX in the early stage of disease onset, increase in dosage if disease activity is not adequately controlled, and then combination with a biological agent. In Japan, recent widespread use of MTX is noteworthy, replacing conventional DMARDs, such as injectable gold, bucillamine, and salazosulapyridine, which had been frequently used in the 1990s [15]. In February 2011, partial variations in MTX label were approved so that it could be used as a first-line DMARD up to the maximum dose of 16 mg/week when tolerated. Consequently, it is highly likely that its use will be further accelerated. When complications are present, other treatment option may be adopted while taking safety into consideration. However, concomitant use of MTX and a biological agent is possible in many patients, and it has become a realistic goal to achieve comprehensive disease remission (clinical, structural, and functional) with the combination of MTX and a biological agent [16, 17].

Van der Heijde et al. [16] reported that 35 % of 5-year completers of the initial ADA + MTX arm in the PREMIER trial achieved comprehensive disease remission (triple criteria) defined as the combination of DAS28 remission (DAS28-CRP <2.6), normal function (Health Assessment Questionnaire ≤ 0.5), and radiographic non-progression (change in modified total Sharp score from baseline to year 5 ≤ 0.5). It is noteworthy that patients who received initial combination therapy for 2 years experienced better comprehensive disease control over 5 years than patients who received initial therapy with MTX or ADA alone, although all three treatment groups received the same open-label ADA therapy (with variable MTX use) during years 3–5. In the DE019 trial, 26.1 % of patients who received ADA 40 mg every other week with concomitant MTX for 5 years achieved the triple comprehensive disease remission [17]. Based on the results from the current 6-month observational study, ADA with concomitant use of MTX could be positioned as a first-line biologic therapy to be recommended for RA patients who inadequately responded to MTX.

In our study, efficacy and safety of ADA 40 mg every other week were retrospectively examined in RA patients mainly with long disease duration at multiple sites. Results from explorative stratified analyses indicated that Bio-naïve and MTX (+) patients responded most to ADA treatment among the four subgroups examined. A phase II–III, multicenter, double-blind, randomized, placebo-controlled study of ADA was conducted in Japan without concomitant administration of MTX (CHANGE) [18]. In pharmacokinetic analyses, serum anti-ADA antibody (AAA) concentrations, at least in part with neutralizing effects, were found at a relatively high rate in the Japanese population. It has been reported that the ACR 20 response rate is lower but injection-site reactions occurred at a higher rate in the AAA-positive group than in the AAA-negative group. Although we did not perform AAA measurement in this study, it would not be unexpected that AAA formation has reduced clinical response to ADA, particularly in patients without concomitant MTX, as reported elsewhere [19, 20]. Administration of ADA at a dose of 80 mg every other week is an alternative option for patients who have not responded adequately to ADA. However, as clinical responses to ADA seem not always to be high in patients who do not receive concomitant MTX, ADA at a dose of 80 mg should be employed only after giving thorough consideration [21].

ADA is the third TNF inhibitor approved in Japan 5 and 3 years after the launch of IFX and ETN, respectively. Accordingly, in this study, the majority of the patients previously treated with TNF inhibitors were switched to ADA treatment due to inadequate response to the prior treatment with IFX and/or ETN. The drug survival rates

(74.5–75.7 %) over the first 52 weeks in biologically naïve patients with or without concomitant MTX in our study are comparable with those reported in registries in Europe [22, 23]. As reported elsewhere, the drug survival rate for the second anti-TNF agent is not as high as that of the first anti-TNF agent [24]. In Japan, ADA is being used as a second-line biologic agent in a relatively large number proportion of patients. The first-line use of ADA in earlier RA patients, who can receive concomitant MTX, carries a notable amount of potential for much greater efficacy. In our study, drug survival rates were much lower in patients with a history of biologic treatment than those in biologically naïve patients with and without concomitant MTX treatment.

Overall, more than 30 % of all patients achieved EULAR good response to ADA over the 24-week treatment period, reassuring effectiveness of ADA in patients with long-standing, active RA. In the stratified analyses, patients in the Bio-naïve and MTX (+) subgroup showed the greatest clinical remission rate and highest improvement according to EULAR good criteria. On the other hand, clinical responses to ADA tend to be slightly lower in the Bio-naïve and MTX (–) group. The Bio-switch and MTX (–) group showed the least response to ADA, as no patient in this group achieved clinical remission, suggesting that the use of ADA without concomitant MTX administration in patients previously treated with other TNF inhibitors may be the least recommended usage. When data on Bio-switch patients were analyzed per prior treatment, patients who received prior treatment with ETN appeared to have not only lower clinical responses to ADA but also higher rates of adverse events. This may be due to the fact that 13 of the 40 patients who had been previously treated with ETN did not receive concomitant MTX. Although other factors, such as reason for drug termination and perhaps the molecule itself, may be also at play [25], further investigation in more detail with a larger number of patients is warranted.

As stated in the 2010 EULAR recommendations, due to their toxicity, particularly in the intermediate to long term, glucocorticoids should be tapered as rapidly as possible in accordance with the clinical situation [26]. In the Anti-TNF Research Study Program of the Monoclonal Antibody D2E7 in Rheumatoid Arthritis (ARMADA) long-term extension study [6], dosages of glucocorticoids were decreased in long-standing RA patients while efficacy was maintained with ADA. In this study, treatment was either withdrawn or reduced by 24 weeks after initiation of ADA treatment in 35 % of all glucocorticoid users. Of note were adverse dermatological events following injection-site reactions. According to US prescribing information, allergic reactions including allergic rash and urticaria have been observed in approximately 1 % of patients in clinical trials

[27]. Pathogenesis of such immune-mediated skin reactions has been discussed. Immediate type I hypersensitivity response was implicated in two patients who experienced worsening injection-site reactions to ADA [28]. On the other hand, in another report, two patients showed positive results to intradermal test with ADA after 24 h [29]. Further research is needed to ascertain the immune mechanisms of these reactions. Overall, there were no unexpected AEs reported in this study. The safety profile reported here with ADA may be similar to or even further improved than those with other precedent anti-TNF agents.

There are some potential limitations in this observational study. First, missing data are inherent to observational studies. In order to impute missing values, the LOCF method was employed, which is more conservative than with observed values. Nonetheless, the study confirmed good efficacy of ADA treatment with a favorable risk–benefit ratio even in long-standing RA patients. Second, no control was set in this retrospective observational study. Consequently, comparisons made among subgroups should be interpreted with caution, as, for example, history of biological therapy and/or contraindication of MTX at the entry may be predisposed to a different prevalence of comorbidities. In addition, as there was imbalance in the number of patients in each group, comparisons made among subgroups should therefore be considered exploratory. Third, as the maximum dose approved for MTX was 8 mg/week during the study, caution must be exercised when comparing it with future investigations with higher MTX doses. Finally, radiographic and functional outcomes were not assessed in this study. However, patient global assessment obtained as a simple form of patient-reported outcome resulted in significant improvement. Moreover, the suppressive effect of ADA treatment on MMP-3, which is known as a marker of cartilage degradation [30], was observed. Therefore, it will be interesting to confirm the improvement in functional status and inhibitory effects on radiographic progression in Japanese RA patients by comparing with overseas studies.

In conclusion, ADA therapy resulted in significant clinical response in established Japanese patients with RA treated in daily practice. It also demonstrated generally good safety and tolerability. The study suggests that the best use of ADA may be in biologically naïve patients with concomitant administration of MTX.

Conflict of interest N. Ishiguro, T. Kojima, Y. Hirano, and A. Kaneko have received speaking fees (<US\$5,000) from Abbott Japan Co. Ltd.; Eisai Co. Ltd.; Mitsubishi Tanabe Pharma Corporation; Pfizer Co. Ltd.; Chugai Pharmaceutical Co. Ltd.; and Bristol-Myers Squibb Co. Ltd. The other authors declare no conflicts of interest.

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