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ORIGINAL ARTICLE

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

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

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

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Introduction

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

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

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

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

Methods

Participating centers

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

Patient eligibility

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

Data recording

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

Safety surveillance

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

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

Clinical course

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

Data analysis

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

Statistical analysis

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

Results

Patient demographics and clinical characteristics

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

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

Table 1 Baseline demographic and clinical characteristics

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

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

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

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

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

[d] Includes MTX

Postmarketing safety surveillance

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

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

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

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

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

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

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

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

[a] $p < 0.01$

[b] $p < 0.05$

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

Table 3 Adverse drug reactions (ADRs) of interest

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

PCP Pneumocystis jirovecii pneumonia

[a] 2,991 RA and nine other diseases

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

[c] Number of serious ADRs

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

Effectiveness

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

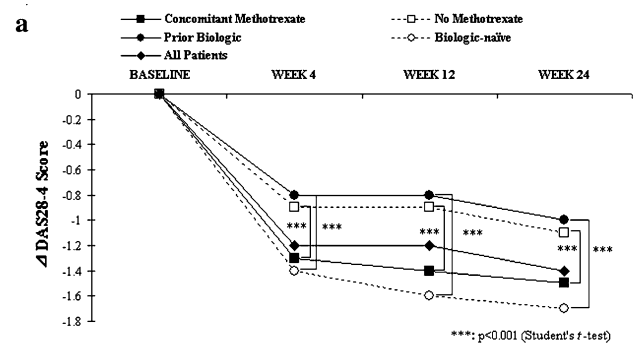
Fig. 1 Change in 28-joint Disease Activity Score (DAS28)-4 [erythrocyte sedimentation rate (ESR)] over time. **a** Overall and stratified by concomitant methotrexate (MTX) and prior biologic use. $P < 0.001$ for concomitant use of MTX versus no MTX use at weeks 4, 12, and 24 (Student's *t* test). $P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

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

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

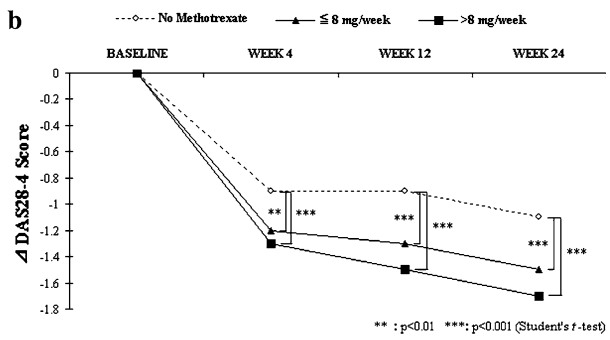
Discussion

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

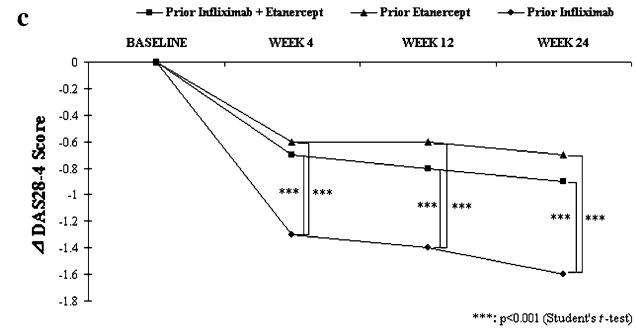


All Patients	5.3±1.3 (N=1939)	4.1±1.4 -1.2±1.1 (N=1401)	4.0±1.4 -1.2±1.3 (N=1662)	3.9±1.5 -1.4±1.4 (N=1915)
Concomitant Methotrexate	5.2±1.2 (N=1344)	4.0±1.3 -1.3±1.1 (N=993)	3.9±1.3 -1.4±1.2 (N=1170)	3.7±1.4 -1.5±1.3 (N=1342)
No Methotrexate	5.4±1.3 (N=595)	4.5±1.5 -0.9±1.2 (N=408)	4.4±1.5 -0.9±1.4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

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



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



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

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

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

Table 4 Steinbrocker's rheumatoid arthritis (RA) stage-specific mean ΔDAS28 stratified by prior biologic and concomitant MTX use

Steinbrocker's RA stage	Week 4	Week 12	Week 24
All patients			
Stages I and II			
No MTX			
Number	118	134	153
ΔDAS28 ± SD	−1.00 ± 1.14	−0.92 ± 1.36	−1.14 ± 1.52
With MTX			
Number	351	404	444
ΔDAS28 ± SD	−1.24 ± 1.12	−1.39 ± 1.27	−1.51 ± 1.35
Student's *t* test[a]	$p = 0.053$	$p < 0.001$	$p = 0.005$
Stages III and IV			
No methotrexate			
Number	268	324	378
ΔDAS28 ± SD	−0.90 ± 1.19	−0.95 ± 1.38	−1.04 ± 1.41
With MTX			
Number	605	706	808
ΔDAS28 ± SD	−1.26 ± 1.05	−1.34 ± 1.19	−1.46 ± 1.28
Student's *t* test[a]	$p < 0.001$	$p < 0.001$	$p < 0.001$
Biologic-naïve			
Stages I and II			
No MTX			
Number	66	74	83
ΔDAS28 ± SD	−1.32 ± 1.15	−1.29 ± 1.31	−1.48 ± 1.37
With MTX			
Number	226	265	288
ΔDAS28 ± SD	−1.45 ± 1.01	−1.58 ± 1.13	−1.68 ± 1.23
Student's *t* test[a]	$p = 0.377$	$p = 0.063$	$p = 0.202$
Stages III and IV			
No MTX			
Number	134	152	174
ΔDAS28 ± SD	−1.28 ± 1.05	−1.45 ± 1.23	−1.51 ± 1.28
With MTX			
Number	309	343	403
ΔDAS28 ± SD	−1.55 ± 1.01	−1.72 ± 1.09	−1.85 ± 1.16
Student's *t* test[a]	$p = 0.012$	$p = 0.015$	$p = 0.001$
Prior biologic			
Stages I and II			
No MTX			
Number	52	60	70
ΔDAS28 ± SD	−0.60 ± 1.01	−0.46 ± 1.28	−0.74 ± 1.60
With MTX			
Number	125	139	156
ΔDAS28 ± SD	−0.85 ± 1.19	−1.03 ± 1.43	−1.19 ± 1.49
Student's *t* test[a]	$p = 0.193$	$p = 0.008$	$p = 0.042$
Stages III and IV			
No MTX			
Number	134	172	204
ΔDAS28 ± SD	−0.52 ± 1.19	−0.50 ± 1.35	−0.63 ± 1.39
With MTX			

Table 4 continued

Steinbrocker's RA stage	Week 4	Week 12	Week 24
Number	296	363	405
ΔDAS28 ± SD	−0.96 ± 1.00	−0.97 ± 1.17	−1.07 ± 1.28
Student's *t* test[a]	$p < 0.001$	$p < 0.001$	$p < 0.001$

ΔDAS28 change in 28-joint Disease Activity Score from baseline, *MTX* methotrexate, *SD* standard deviation

[a] *P* values comparing concomitant MTX use to no MTX use (Student's *t* test)

with RA emphasizes that certain genetic and environmental factors may predispose Japanese patients to serious risks associated with biologic therapies: namely, bacterial pneumonia, tuberculosis, PCP, and interstitial pneumonia [16]. The 0.1% incidence of tuberculosis in our population is consistent with the incidence observed in a PMS for etanercept and the latter 2,000 patients in the infliximab PMS study cohort after the percentage of patients given chemoprophylaxis for tuberculosis increased [1, 2]. Comparison of the incidence of tuberculosis with other countries is difficult because of differences in epidemiologic factors influencing the incidence of tuberculosis and different regional guidelines. These factors lead to differing screening and chemoprophylaxis practices worldwide. Even though the incidence of tuberculosis in Japan is higher than in Western countries, intensive screening and chemoprophylaxis in Japanese patients receiving biologic therapy appear to be effective. Evidence indicates a >70% reduction in the risk of tuberculosis with screening and chemoprophylaxis [14].

Several studies have characterized the small but clinically important increased risk for serious infection in RA patients receiving anti-TNF therapy [17–23]. In our study, the incidence of infectious ADRs, including serious infections, was not changed by concomitant DMARD or MTX use. Our results are consistent with the study by the Consortium of Rheumatology Researchers of North America (CORRONA) in which the rate of infections did not increase in patients treated with combination anti-TNF plus MTX therapy compared with monotherapy with these agents [24]. Infection rates between biologic-naïve and biologic-experienced patients were also similar. Consistent with prior studies [24–28], we found that concomitant glucocorticoid therapy is associated with greater risk of developing infections. In particular, serious infections were significantly more common in patients receiving glucocorticoid dosages >5 mg/day. The incidences of bacterial/bronchial pneumonia, PCP, and interstitial pneumonia among adalimumab-treated patients in this study were generally similar to those of infliximab and etanercept PMS studies [1, 2]. These finding are supported by an analysis of serious infections in the British Society for Rheumatology Biologics Register (BSRBR) study, which found similar overall risk among adalimumab, etanercept, and infliximab treatment [22].

Risk factors for developing serious infections included age ≥65 years, diabetes mellitus history or comorbidity, interstitial pneumonitis history or comorbidity, and advanced Steinbrocker's RA class. Similar risk factors for pneumonia or serious infection were reported from PMS programs for infliximab [1] or etanercept [29], respectively. In addition, older age, functional disability, and concomitant use of glucocorticoid were reported as risk factors for infection in RA patients in general [25]. When adalimumab is administrated to patients who have multiple risk factors described above, risk–benefit balance should be carefully considered after proper evaluation of these risk factors.

Because nonresponse and loss of response are factors in biologic therapy for RA, our database provided an opportunity to assess response in patients treated with another anti-TNF therapy before receiving adalimumab. Biologic-naïve patients responded better to adalimumab therapy than did biologic-experienced patients, especially patients who had received etanercept. The concomitant use of anti-TNF therapies and MTX is recommended by the updated Japanese guidelines for use of infliximab and etanercept in RA patients [9]. We found that patients receiving concomitant adalimumab and MTX have more improvement in ΔDAS28 than patients receiving adalimumab alone. Importantly, there were no clinically important differences in the incidence of AEs with increasing MTX dosage, indicating a positive risk–benefit profile for adalimumab plus MTX, even at dosages >8 mg/week.

A limitation of this PMS registry study is the relatively short duration of follow-up; however, our data were rigorously collected, and the 24-week follow-up period should be sufficient to capture most serious infections. Support for this view comes from Galloway et al. [22], who found the risk of serious infection in patients with RA is greatest during the first 6 months of anti-TNF therapy [22]. One advantage of PMS registry studies is that they can be applied more generally than clinical trials because they typically enroll larger numbers of patients under less-restrictive inclusion/exclusion criteria, and patients are evaluated in an actual clinical practice setting [30]. In addition, the patient population in our study is similar to

those in large US and European RA registries. The mean age among the biologic cohorts in the Western registries ranged from 50 to 64 years; 72–86% were women, with the exception of the one registry that targeted US veterans, which had only 11% women; duration of RA ranged from 9 to 19 years, with the exception of one registry targeting early RA in which patients had an average disease duration of 1.5 years; baseline DAS28 scores ranged from 3.5 to 6.6; and 38–93% of patients used concomitant glucocorticoids [21].

In conclusion, this interim analysis of postmarketing data for the first 3,000 patients treated with adalimumab following its approval in Japan supports the safety and effectiveness demonstrated in clinical trials. No new safety concerns were identified, and the incidence of clinically important AEs with this anti-TNF therapy was similar to those of other biologic agents approved for RA treatment. The use of adalimumab was most favorable for RA patients naïve to biologic therapy and who were treated concomitantly with MTX.

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Conflict of interest Doctors T. Koike, M. Harigai, N. Ishiguro, S. Inokuma, S. Takei, T. Takeuchi, H. Yamanaka and Y. Tanaka are members of the Postmarketing Surveillance (PMS) Committee of the Japan College of Rheumatology. It is the belief of the authors that this does not constitute a conflict of interest. The doctors participated in review and analysis of the PMS data in their capacity as committee members and are so listed. The financial relationships of the authors with manufacturers of biological products used in the management of RA are listed as: #1, a research grant to the institute to which they are affiliated; #2 a consulting fee; and #3 membership of a speakers' bureau. T. Koike, Abbott Japan, 1; Bristol-Myers Squibb, 1; Chugai Pharmaceutical Co. Ltd., 1; Eisai Co. Ltd., 1; Mitsubishi Tanabe Pharma, 1; Takeda Pharmaceutical Co. Ltd., 1; Wyeth KK, 1; Otsuka Pharmaceutical Co. Ltd., 2; Abbott Japan, 3; Bristol-Myers Squibb, 3; Chugai Pharmaceutical Co. Ltd., 3; Eisai Co. Ltd., 3; Mitsubishi Tanabe Pharma, 3; Takeda Pharmaceutical Co. Ltd., 3; Wyeth KK, 3; M. Harigai, Abbott Japan, 1; Astellas, 1; Bristol-Myers Squibb, 1; Chugai Pharmaceutical Co. Ltd., 1; Eisai Co. Ltd., 1; Mitsubishi Tanabe Pharma, 1; Pfizer Japan Inc., 1; Takeda Pharmaceutical Co. Ltd., 1; Abbott Japan, 2; Bristol-Myers Squibb, 2; Chugai Pharmaceutical Co. Ltd., 2; Jansen Pharma, 2; Mitsubishi Tanabe Pharma, 2; Abbott Japan, 3; Bristol-Myers Squibb, 3; Chugai Pharmaceutical Co. Ltd., 3; Eisai Co. Ltd., 3; Mitsubishi Tanabe Pharma, 3; Pfizer Japan Inc., 3; Takeda Pharmaceutical Co. Ltd., 3; N. Ishiguro, Abbott Japan, 1; Chugai Pharmaceutical Co. Ltd., 1; Daiichi-Sankyo Pharmaceutical Co. Ltd., 1; Eisai Co. Ltd., 1; Mitsubishi Tanabe Pharma, 1; Takeda Pharmaceutical Co. Ltd., 1; Wyeth KK, 1; Abbott, 3; Bristol-Myers Squibb, 3; Chugai Pharmaceutical Co. Ltd., 3; Daiichi-Sankyo Pharmaceutical Co. Ltd., 3; Eisai Co. Ltd., 3; Mitsubishi Tanabe Pharma, 3; Takeda Pharmaceutical Co. Ltd., 3; Wyeth KK, 3; S. Inokuma, None; S. Takei, None; T. Takeuchi, Abbott Japan, 3; Bristol-Myers Squibb, 3; Mitsubishi Tanabe Pharma, 3; Novartis, 3; Chugai Pharmaceutical Co. Ltd., 3; Eisai Pharma, 3; Janssen Pharmaceutica, 3; Takeda Pharmaceutical Co. Ltd., 3 Pfizer Japan Inc., 3; H. Yamanaka, Abbott Japan, 1; Chugai Pharmaceutical Co. Ltd., 1; Eisai Co. Ltd., 1; Mitsubishi Tanabe Pharma, 1; Takeda Pharmaceutical Co. Ltd., 1; Bristol-Myers Squibb, 3; Y. Tanaka, Abbott, 1; Astellas Pharma Inc., 1; Chugai Pharmaceutical Co. Ltd., 1; Eisai Co. Ltd., 1; Mitsubishi Tanabe Pharma, 1; MSD KK, 1; Pfizer Inc., 1; Takeda Pharmaceutical Co. Ltd., 1; Mitsubishi Tanabe Pharma, 2; Abbott, 3; Astellas Pharma Inc., 3; Chugai Pharmaceutical Co. Ltd., 3; Eisai Co. Ltd., 3; Mitsubishi Tanabe Pharma, 3; Takeda Pharmaceutical Co. Ltd., 3.

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