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ORIGINAL RESEARCH

Real-World Postmarketing Study of the Impact of Adalimumab Treatment on Work Productivity and Activity Impairment in Patients with Psoriatic Arthritis

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ABSTRACT

Introduction: This study investigated the effectiveness of adalimumab treatment in improving Work Productivity and Activity Impairment (WPAI) in patients with psoriatic arthritis (PsA) in real-world settings in Japan.
Methods: This 24-week, single-arm, postmarketing surveillance study (2014–2017), conducted at 75 centers in Japan, enrolled adalimumab-naïve patients (paid workers, including part-time) meeting ClASsification criteria for Psoriatic ARthritis (CASPAR). The primary endpoint was improvement in overall work impairment (OWI) scores from baseline to week 24. Secondary endpoints included changes in WPAI-PsA (OWI, absenteeism, presenteeism, and activity impairment), Psoriasis Area and Severity Index (PASI), psoriatic arthritis screening and evaluation (PASE) scores, Disease Activity Scores in 28 joints using C-reactive protein (DAS28[CRP]), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores, Health Assessment Questionnaire-Disability Index (HAQ-DI) scores, and PASI75/90 and American College of Rheumatology (ACR) 20/50/70 rates.
Results: In the effectiveness population (n = 106; 72.6% men; mean ± standard deviation [SD] age,

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49.3 ± 10.7 years), OWI scores significantly improved (mean ± SD change, − 25.2 ± 35.3; $p < 0.0001$) from baseline to week 24. Other WPAI domain scores also improved significantly. Changes in OWI were significantly correlated ($p < 0.0001$) with PASE ($r = 0.6284$), DAS28(CRP) ($r = 0.6059$), BASDAI ($r = 0.7281$), and HAQ-DI ($r = 0.6161$) scores and were significantly influenced by previous nonsteroidal anti-inflammatory drug use ($p = 0.0142$), and baseline PASE ($p = 0.0098$), DAS28(CRP) ($p = 0.0026$), HAQ-DI ($p = 0.0004$), and BASDAI ($p < 0.0001$) scores. At the last evaluation, rate (95% confidence interval) of PASI 75 and 90 ($n = 100$) was 58.0% (47.7–67.8) and 39.0% (29.4–49.3), respectively, and that of ACR 20, 50, and 70 ($n = 58$) was 86.2% (74.6–93.9), 70.7% (57.3–81.9), and 53.4% (39.9–66.7), respectively. No new safety signals were observed in the safety population ($n = 148$).
Conclusion: Adalimumab treatment improved WPAI in patients with PsA. Improvements in OWI and joint symptoms were significantly associated.
Trial Registration Number: ClinicalTrials.gov identifier: NCT02414633.
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Keywords: Adalimumab; Japan; Postmarketing surveillance study; Psoriasis; Psoriatic arthritis; Rheumatology; TNF inhibitor; Work disability; Work productivity; Activity impairment

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic, debilitating, inflammatory disease that substantially affects work disability (absenteeism and presenteeism), activity impairment (AI) and productivity, and the employment status of patients [1–3]. The exact global prevalence of PsA in the general population is unknown, but is estimated to be 0.3%–1.0% [4]. In Japan, the mean prevalence of PsA among patients with psoriasis was estimated to be 3.3% between 2002 and 2008 [5, 6]. Based on annual surveys by the Japanese Society for Psoriasis Research, the prevalence of PsA has risen over the years, and was 15.3% in 2016 [7]. PsA is almost twice as common in men as women, with a mean age of onset in the late 40s [8], indicating a working cohort. Similar to the rest of the world [3], PsA in Japanese patients is significantly associated with overall work impairment (OWI) and AI [9].

In the European League Against Rheumatism (EULAR) updated 2015 guidelines, conventional synthetic disease-modifying antirheumatic drugs (cs-DMARDs) are recommended for the initial management of patients with PsA after failure of nonsteroidal anti-inflammatory drugs (NSAIDs) and local therapy for active disease. In cases of inadequate response to cs-DMARDs, treatment with biologics, usually a tumor necrosis factor (TNF)-α inhibitor, is recommended [10]. According to the 2013 version of the Japanese guidance for the use of biologics for psoriasis, biologics are recommended in the early stages of PsA to prevent irreversible joint destruction [11].

The TNF inhibitor adalimumab (HUMIRA®; AbbVie Inc., North Chicago, IL, USA) was one of the first biologic agents approved in Japan for the treatment of patients with psoriasis, including PsA [12]. For the treatment of PsA, adalimumab is administered subcutaneously at an initial loading dose of 80 mg, followed by 40-mg doses every other week (q2w) starting from the second week. The dosage may be increased to 80 mg q2w when the response to the 40-mg dose is inadequate [13]. In a phase 2/3 trial involving Japanese patients with moderate to severe chronic plaque psoriasis, adalimumab treatment resulted in significantly greater improvements in Psoriasis Area and Severity Index (PASI) 75 scores at three different dosing regimens (40 mg q2w, 40 mg q2w with an 80-mg loading dose, and 80 mg q2w) than placebo (57.9%, 62.8%, and 81.0%, respectively, vs 4.3%) [14]. In a subgroup analysis of 16-week data from the Randomized controlled EValuation of adalimumab Every other week dosing in moderate to severe psoriasis triAL (REVEAL), which included employed patients with moderate to severe psoriasis, including 25% with PsA, adalimumab treatment resulted in improvements of 11.1% and 15.5% in total work productivity impairment and total AI, respectively, compared with placebo [15].

Although the safety and effectiveness of adalimumab in Japanese patients with psoriasis

has been demonstrated in a postmarketing surveillance (PMS) study [16], the impact of treatment with biologics on Work Productivity and Activity Impairment (WPAI) in Japanese patients with PsA has not been reported. Therefore, we conducted this PMS study to investigate the effectiveness of adalimumab treatment in reducing WPAI in patients with PsA in real-world clinical practice in Japan.

METHODS

Study Design

This single-arm, multicenter, prospective cohort, PMS study was conducted from December 2014 to March 2017 at 75 centers in Japan. Patients were registered from December 2014 to September 2016 and were followed up for 24 weeks. Patient assessment data were collected from case report forms at the study centers. This study was conducted in compliance with Good Postmarketing Study Practice (GPSP) in Japan and was registered at ClinicalTrials.gov (NCT02414633). The study protocol was reviewed and approved in advance by the Pharmaceuticals and Medical Devices Agency of Japan. As per GPSP regulations, institutional review board approval and written informed consent from patients were not required.

Patients

This study included adalimumab-naïve patients meeting the ClASsification criteria for Psoriatic ARthritis (CASPAR) [17] who were paid workers (including part-time). Bedridden and hospitalized patients with decreased activities of daily living and patients in whom adalimumab was contraindicated were excluded from the study.

Study Endpoints

The primary endpoint was improvement in OWI score from baseline to week 24 of treatment. Secondary endpoints included changes in WPAI-PsA score (OWI, absenteeism, presenteeism, AI), PsA screening and evaluation (PASE) scores, Disease Activity Scores in 28 joints (DAS28) using C-reactive protein (DAS28[CRP]) and erythrocyte sedimentation rate (DAS28[ESR]), tender joint count (TJC; 68 joints), swollen joint count (SJC; 66 joints), PASI score and response rates (PASI75 and PASI90), patient global assessment (PGA), physician global assessment (PhGA), and pain visual analog scale (VAS) at baseline, weeks 4, 12, 16, and 24; change in American College of Rheumatology (ACR) 20/50/70 rates, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score, and Health Assessment Questionnaire-Disability Index (HAQ-DI) score at baseline, week 12, and 24; and presence or absence of spondylitis, dactylitis, enthesitis, and nail psoriasis at baseline and last evaluation. Safety was evaluated using the incidence of adverse events (AEs) and serious AEs. In addition, baseline factors impacting OWI were analyzed, and correlation between changes from baseline to last evaluation in OWI scores and effectiveness scores were assessed.

Study Measures

Scores of the WPAI-PsA were assessed using a questionnaire adapted from the WPAI:PsA V2.0 [18] that comprises the following questions: Q1—Currently employed or not; Q2—Number of hours of work missed due to PsA; Q3—Number of hours of work missed due to other reasons; Q4—Number of actual hours worked; Q5—Effect of PsA in reducing productivity during work on a scale of 0 (no effect) to 10 (substantial effect); and Q6—Effect of PsA on regular daily activities on a scale of 0 (no effect) to 10 (substantial effect). OWI, absenteeism, presenteeism, and AI scores were calculated as a percentage of $[Q2/(Q2 + Q4)] + [(1 - Q2/(Q2 + Q4)) \times (Q5/10)]$, $Q2/(Q2 + Q4)$, $Q5/10$ and $Q6/10$, respectively, where Q2 to Q6 were responses to the respective questions, with the past 7 days as the recall period. Higher scores indicated greater work impairment and lower work productivity.

For assessment details of the other effectiveness measures, including PASE, HAQ-DI, BASDAI, PASI, ACR responses, DAS28(CRP), and

DAS28(ESR), see the appendix in the electronic supplementary material.

Statistical Analysis

The target sample size was 130 patients, taking into consideration the number of cases required to detect the same amount of changes in OWI, with a two-sided significance level of 5% and a detection power of 80%, as observed in the OWI study by Kimball et al. [15], the dropout rate up to 24 weeks in a previous PMS study of psoriasis vulgaris and PsA [16], and the proportion of OWI-evaluable patients (85%) in a previous PMS study of patients with rheumatoid arthritis (RA) [19].

The safety population included all patients in whom case report forms were completed. Patients who did not receive adalimumab, received adalimumab before signing the contract, were not registered during the registration period, did not meet the enrollment criteria, were duplicate cases, or in whom safety was unevaluable were excluded from the safety population. The effectiveness population comprised all patients from the safety population in whom effectiveness could be evaluated, that is, those patients in whom OWI data at baseline and after administration of adalimumab were available. Categorical data were summarized as number and percentage of cases and quantitative data were summarized as number, percentage, mean, standard deviation (SD), median, and range (minimum, maximum). The descriptive statistics of baseline effectiveness scores and changes from baseline were summarized, and a paired *t* test was performed to calculate *p* values. Missing data were not imputed for analysis. The observed effectiveness scores at the last evaluation time point were analyzed for all patients, including those who discontinued early, to adjust for the missing data of patients who discontinued early because of insufficient response to adalimumab treatment. The numbers and percentages of PASI75, PASI90, ACR20, ACR50, and ACR70 responders were summarized, and the 95% confidence intervals (CIs) were calculated using the Clopper–Pearson method for the response rates.

Correlations between changes from baseline to last evaluation in OWI scores and each effectiveness score were evaluated using a Pearson correlation coefficient, and *p* values were calculated using the correlation coefficient test. For subgroup analysis of baseline factors affecting OWI, *t* tests (for factors with two categories) and one-way analysis of variance (for factors with three or more categories) were used. Inferential statistical analyses were performed at a nominal two-sided significance level of 0.05. Statistical analysis was performed using SAS version 9.3 or higher (SAS Institute, Cary, NC, USA).

Safety events were summarized using the *Medical Dictionary for Regulatory Activities* version 20.0. Multiple events by preferred term within the same system organ class (SOC) in one patient were counted only once.

RESULTS

Patient Disposition, Demographics, and Characteristics

Overall, 148 patients were registered in the study and were included in the safety population. Effectiveness could not be evaluated in 42 patients; therefore, the effectiveness population comprised 106 patients. Among the safety population, 25 patients (16.9%) discontinued treatment for at least one reason, including onset of AEs ($n = 11$), ineffectiveness ($n = 7$), patient request ($n = 2$), financial reasons (inability to afford copayment; $n = 2$), hospital transfer/lost to follow-up ($n = 3$), improvement in symptoms ($n = 1$), and other reasons ($n = 1$).

The effectiveness population comprised mostly men (72.6%); the mean (SD) age was 49.3 (± 10.7) years (Table 1). Mean (SD) weight, body mass index (BMI), and duration of skin and joint symptoms were 71.2 (± 14.5) kg ($n = 85$), 25.3 (± 4.4) kg/m^2 ($n = 79$), 14.8 (± 12.2) years ($n = 91$), and 4.4 (± 5.1) years ($n = 94$), respectively. In 72 patients, 15.0% (± 18.2%) of body surface area was affected by psoriasis, mostly plaque-type (85.8%). Overall, 40.6% of patients had received methotrexate, 10.4% had received biologics, and 9.4% had

Table 1 Baseline demographics and patient characteristics (effectiveness population)

Characteristic	Number[a]	Value
Age (years)	106	49.3 ± 10.7
Sex, male	106	77 (72.6)
Weight (kg)	85	71.2 ± 14.5
BMI (kg/m^2)	79	25.3 ± 4.4
Type of rash	106	
Plaque		91 (85.8)
Erythrodermic		7 (6.6)
Pustular		4 (3.8)
Guttate		1 (0.9)
No rash		3 (2.8)
BSA of rash (%)	72	15.0 ± 18.2
Duration of skin symptoms (years)	91	14.8 ± 12.2
Duration of joint symptoms (years)	94	4.4 ± 5.1
Comorbidities, present	106	46 (43.4)
Past medical history, present	106[b]	20 (18.9)
Smoking history	106	
Nonsmoker		42 (39.6)
Current smoker		26 (24.5)
Past smoker		15 (14.2)
Unknown		23 (21.7)
Previous treatment, present	106	102 (96.2)
Biologics[c]		11 (10.4)
Infliximab		7 (6.6)
Ustekinumab		3 (2.8)
Other		1 (0.9)
Topical[c]		75 (70.8)
Corticosteroid		67 (63.2)
Vitamin D_3 derivatives		53 (50.0)
Other		12 (11.3)
Oral[c]		84 (79.2)
NSAID		47 (44.3)
Methotrexate		43 (40.6)
Corticosteroid		18 (17.0)

Table 1 continued

Characteristic	Number[a]	Value
Cyclosporin		13 (12.3)
DMARD (except methotrexate)		10 (9.4)
Retinoid		7 (6.6)
Other		11 (10.4)
Concomitant treatment, present	106	90 (84.9)
Topical[c]		
Corticosteroid		30 (28.3)
Vitamin D_3 derivatives		27 (25.5)
Other		14 (13.2)
Oral[c]		
Methotrexate		38 (35.8)
NSAID		28 (26.4)
Corticosteroid		13 (12.3)
Cyclosporin		0 (0.0)
DMARD (except methotrexate)		5 (4.7)
Retinoid		2 (1.9)
Other		55 (51.9)

Results are presented as the mean ± standard deviation or *n* (%)
BMI body mass index, *BSA* body surface area, *DMARD* disease-modifying antirheumatic drug, *NSAID* nonsteroidal anti-inflammatory drug
[a] Number of cases excluding unknown or cases with missing values
[b] Past medical history was unknown in one patient
[c] Data are not mutually exclusive because at least one treatment was possible in a single patient

received a disease-modifying antirheumatic drug (DMARD) other than methotrexate. The baseline demographics and characteristics of the 42 patients who were excluded from the effectiveness population were similar to that of those who were included.

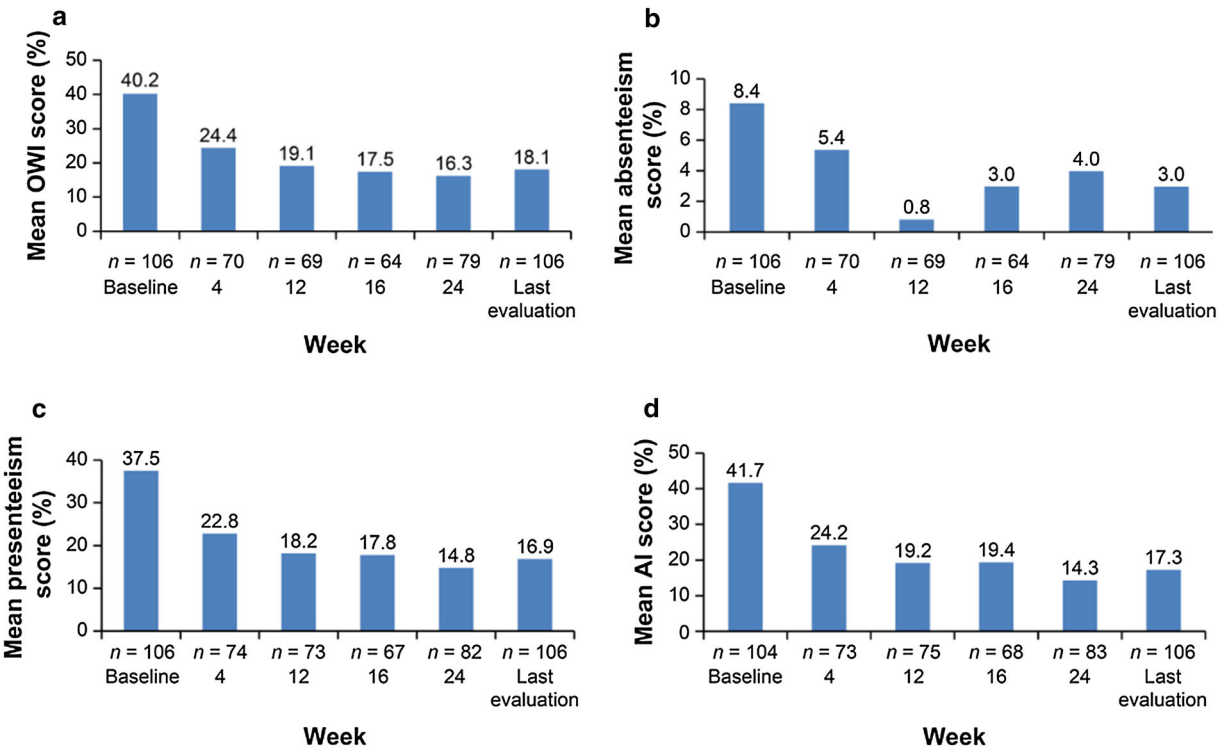
Treatment Duration and Dosage

The safety population received 11.6 (± 2.9) adalimumab injections throughout 24 weeks. Among those who received an initial dose of 80 mg, 15 and 54 patients continued with 80- and 40-mg q2w regimens, respectively, and 10 patients had dose escalation to 80 mg after receiving 40 mg as the second dose. The initial and maintenance dosage in 22 patients was 40 mg q2w; most of these patients (77.3%) were receiving concomitant methotrexate. Other dosing regimens were used in the five remaining patients. Patients who escalated to the 80-mg dose due to inadequate response had higher baseline body weight (86.4 [± 17.1] kg),

BMI (30.3 [± 5.7]) kg/m^2, and VAS scores (PGA, 76.3 [± 34.4]; PhGA, 49.3 [± 41.1], pain, 68.5 [± 41.3]) than those receiving the other dosing regimens.

Effectiveness

Adalimumab treatment significantly improved OWI scores from baseline (40.2 ± 32.8; n = 106) to week 24 (16.3 ± 23.9; n = 79; difference, − 25.2 ± 35.3; $p < 0.0001$; Fig. 1). Significant improvement ($p < 0.05$) in all WPAI-PsA domain scores was observed as early as 4 weeks after starting treatment with adalimumab (Fig. 1). Presenteeism scores (37.5 [± 32.0] to 14.8 [± 21.0]; difference, − 24.3 [± 33.4]; $p < 0.0001$) and AI (41.7 [± 30.1] to 14.3 [± 19.0]; difference, − 27.1 [± 32.7]; $p < 0.0001$) scores improved significantly and consistently from baseline to week 24. Although the absenteeism score did not improve consistently over time, a significant improvement



e	Change in score, mean ± SD[a]		
	16 weeks	24 weeks	At last evaluation time point
OWI, %	− 25.9 ± 32.3*	− 25.2 ± 35.3*	− 22.2 ± 35.5*
Absenteeism, %	− 5.4 ± 17.5**	− 4.9 ± 20.1**	− 5.5 ± 20.7**
Presenteeism, %	− 24.9 ± 31.5*	− 24.3 ± 33.4*	− 20.6 ± 34.0*
AI, %	− 25.0 ± 32.0*	− 27.1 ± 32.7*	− 24.1 ± 32.7*

Fig. 1 Change in WPAI domain scores: **a** overall work impairment; **b** absenteeism; **c** presenteeism; **d** AI; **e** change at 16 weeks, 24 weeks, and last evaluation time point. [a]Median (range) scores at baseline and 24 weeks are presented in Table S2. *$p < 0.0001$; **$p < 0.05$. *AI* activity impairment, *SD* standard deviation, *OWI* overall work impairment, *WPAI* Work Productivity and Activity Impairment

(− 4.9 [± 20.1]; $p = 0.0334$) was obtained at week 24.

After 24 weeks of adalimumab treatment, PASI75 and PASI90 rates (95% CI) were 63% (51.5–73.4) and 42% (31.1–53.5), respectively, and were 58% (47.7–67.8) and 39% (29.4–49.3) at the last evaluation (Fig. 2a). ACR20, ACR50, and ACR70 response rates (95% CI) were 91.3% (79.2–97.6), 76.1% (61.2–87.4), and 58.7% (43.2–73.0), respectively, after 24 weeks of adalimumab treatment, and 86.2% (74.6–93.9), 70.7% (57.3–81.9), and 53.4% (39.9–66.7) at the last evaluation (Fig. 2b). Joint symptoms, skin symptoms, disease activity associated with PsA/spondyloarthritis, and functional parameters significantly improved ($p < 0.0001$) over the study period, as indicated by consistent improvements in corresponding effectiveness endpoints from baseline to week 24 or the last evaluation (Table 2).

Among patients with enthesitis (36.8%), dactylitis (55.7%), spondylitis (29.2%), and nail psoriasis (50.9%) at baseline, symptoms resolved in 53.8%, 61.0%, 67.7%, and 20.4%, respectively, by the last evaluation (Table 3). Among patients without these symptoms at baseline, one each developed enthesitis (1.6%), dactylitis (2.4%), and nail psoriasis (2.3%), and none developed spondylitis by the last evaluation.

Factors Affecting OWI Improvement

Past medical history; previous oral NSAID use; and PASE, DAS28(CRP), HAQ-DI, and BASDAI scores at baseline significantly affected improvement in OWI scores from baseline to the last evaluation. Patients with previous oral NSAID use and higher PASE, DAS28(CRP), HAQ-DI, and BASDAI scores had higher OWI scores at baseline and showed greater improvement in OWI at the last evaluation (Table 3). The improvements in OWI scores from baseline to the last evaluation for all baseline factors are shown in Table S1. A significant correlation was observed between improvement from baseline to the last evaluation in PASE ($r = 0.6284$; $p < 0.0001$; Fig. S1a), DAS28(CRP) ($r = 0.6059$; $p < 0.0001$; Fig. S1b), BASDAI ($r = 0.7281$; $p < 0.0001$; Fig. S1c), and HAQ-DI ($r = 0.6161$; $p < 0.0001$; Fig. S1d) scores, and OWI scores. A weak correlation was seen between improvement from baseline to the last evaluation in TJC ($r = 0.3371$; $p = 0.0007$) and SJC ($r = 0.2847$; $p = 0.0049$) and OWI scores, and no correlation was noted between improvement in PASI ($r = 0.0622$; $p = 0.5493$) and OWI scores.

Safety

Overall, 39 AEs were reported in 32 patients (21.6%), with four serious AEs in four patients (2.7%). The SOCs with the highest incidences

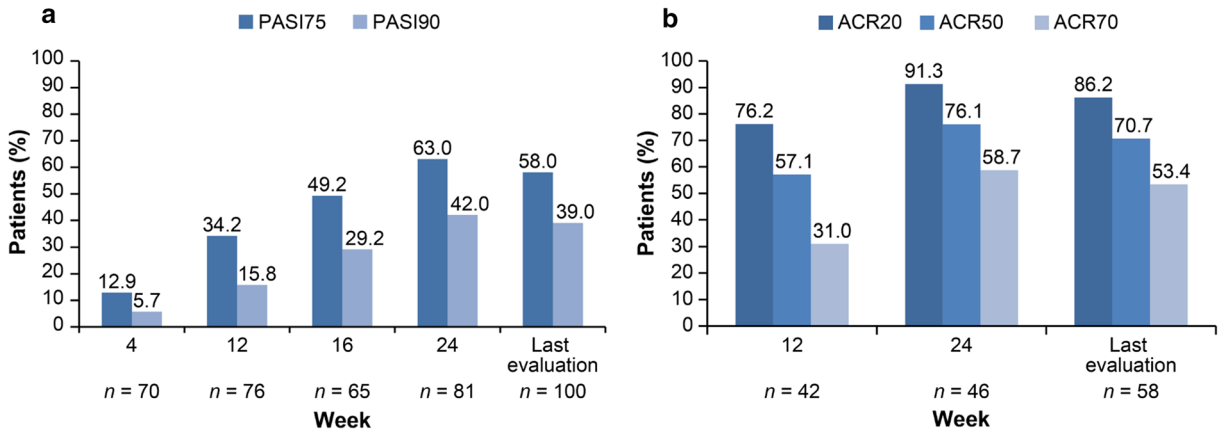


Fig. 2 Change in rate of skin symptoms and joint symptoms over the study: **a** skin symptoms (PASI); **b** joint symptoms (ACR). *ACR* American College of Rheumatology, *PASI* Psoriasis Area and Severity Index

Table 2 Effectiveness results (effectiveness population)

Effectiveness measure[a]	*n*[b]	Baseline	*n*[b]	Week 4[c]	*N*[b]	Week 12[c]	*n*[b]	Week 16[c]	*N*[b]	Week 24[c]	*n*[b]	Last evaluation[c]
Skin symptoms, PASI	98	8.97 ± 8.55	70	4.77 ± 4.46	76	3.11 ± 3.39	65	2.23 ± 3.31	81	1.73 ± 2.81	100	2.03 ± 2.99
Joint symptoms												
TJC	99	7.2 ± 8.7	66	3.6 ± 5.7	75	2.2 ± 4.8	61	1.9 ± 4.4	78	1.2 ± 2.6	100	1.5 ± 3.2
SJC	99	5.3 ± 7.0	66	3.3 ± 4.5	75	1.6 ± 3.0	61	1.3 ± 2.7	78	0.5 ± 1.2	100	0.9 ± 2.2
DAS28(ESR)	48	4.25 ± 1.40	19	2.94 ± 1.34	24	2.10 ± 1.00	22	1.90 ± 1.05	24	1.87 ± 0.99	39	2.00 ± 1.16
DAS28(CRP)	61	3.77 ± 1.33	28	2.45 ± 1.15	31	1.98 ± 0.89	27	1.93 ± 0.73	29	1.94 ± 0.65	48	2.00 ± 0.86
BASDAI	99	4.203 ± 2.334			56	1.971 ± 1.583			68	1.615 ± 1.720	98	1.775 ± 1.747
PASE	106	47.4 ± 11.7	74	36.0 ± 13.6	75	31.9 ± 12.9	67	31.5 ± 13.0	83	29.7 ± 12.8	106	31.0 ± 13.8
Patient-reported outcomes												
HAQ-DI	105	0.5429 ± 0.5017			58	0.2522 ± 0.3555			67	0.1642 ± 0.2780	98	0.1939 ± 0.3115
PGA	105	58.2 ± 28.6	74	28.5 ± 24.4	74	21.8 ± 21.4	67	22.0 ± 23.2	81	17.3 ± 20.3	105	19.8 ± 22.9
VAS	105	53.7 ± 28.9	74	23.1 ± 25.2	74	19.5 ± 22.1	67	21.0 ± 24.4	81	14.5 ± 19.2	105	16.9 ± 21.9
PhGA VAS	99	44.1 ± 24.3	66	20.4 ± 15.3	74	13.4 ± 14.0	59	11.6 ± 11.3	76	11.3 ± 16.4	99	11.6 ± 15.3
Extra-articular manifestations, *n* (%)[d]												
Enthesitis	106	39 (36.8)	–	–	–	–	–	–	–	–	39	11 (28.2)
Dactylitis	106	59 (55.7)	–	–	–	–	–	–	–	–	59	7 (11.9)
Spondylitis	106	31 (29.2)	–	–	–	–	–	–	–	–	31	5 (16.1)
Nail psoriasis	106	54 (50.9)									54	29 (53.7)

BASDAI Bath Ankylosing Spondylitis Disease Activity Index, *CRP* C-reactive protein, *DAS28* Disease Activity Score in 28 joints, *ESR* erythrocyte sedimentation rate, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *PASE* Psoriatic Arthritis Screening and Evaluation, *PASI* Psoriasis Area and Severity Index, *PGA* patient global assessment, *PhGA* physician global assessment, *SD* standard deviation, *SJC* swollen joint count, *TJC* tender joint count, *VAS* visual analog scale

[a] Data are presented as mean ± SD unless indicated otherwise. Median (range) effectiveness scores at baseline and 24 weeks are presented in Table S2

[b] Patients with unknown or missing values were excluded

[c] $p < 0.0001$ for change from baseline at all assessment time points

[d] Data at last evaluation were missing for 7 (17.9%), 16 (27.1%), 5 (16.1%), and 14 (25.9%) patients for enthesitis, dactylitis, spondylitis, and nail psoriasis, respectively

Table 3 Factors affecting OWI score (effectiveness population)

Baseline factor[a,b]	*n*[c]	Baseline	Last evaluation	Change in score	*p* value[d]
PASE					0.0098[e]
≥ 47	63	54.60 ± 29.66	25.13 ± 28.12	− 29.47 ± 36.78	
< 47	43	19.16 ± 25.18	7.67 ± 17.02	− 11.49 ± 30.95	
DAS28(CRP)					0.0026[f]
> 5.1	10	75.92 ± 22.67	24.00 ± 30.98	− 51.92 ± 32.89	
> 3.2 to ≤ 5.1	32	50.49 ± 29.42	17.99 ± 20.41	− 32.50 ± 35.39	
> 2.6 to ≤ 3.2	8	15.00 ± 14.14	16.25 ± 27.74	1.25 ± 26.42	
≤ 2.6	11	15.45 ± 29.79	8.18 ± 12.50	− 7.27 ± 31.33	
Unknown/missing	45	35.53 ± 31.11	19.51 ± 29.75	− 16.02 ± 33.14	
HAQ-DI					0.0004[f]
> 1.5	4	86.43 ± 9.44	27.50 ± 17.08	− 58.93 ± 25.35	
> 1.0 to ≤ 1.5	12	75.42 ± 21.47	28.33 ± 32.15	− 47.08 ± 35.06	
> 0.5 to ≤ 1.0	29	53.21 ± 31.09	23.45 ± 28.19	− 29.76 ± 36.93	
≤ 0.5	60	24.33 ± 24.87	13.06 ± 22.62	− 11.28 ± 31.07	
Unknown/missing	1	10.00	0.00	− 10.00	
BASDAI					< 0.0001[e]
≥ 4	48	61.86 ± 28.05	25.70 ± 30.19	− 36.16 ± 37.70	
< 4	51	19.42 ± 21.76	10.78 ± 16.83	− 8.63 ± 22.73	
Unknown/missing	7	43.47 ± 36.50	18.57 ± 32.88	− 24.90 ± 59.13	
Previous oral NSAID					0.0142[e]
Absent	59	31.08 ± 30.15	16.40 ± 25.01	− 14.67 ± 33.47	
Present	47	51.70 ± 32.77	20.12 ± 26.52	− 31.58 ± 36.10	
Past medical history					0.0455[e]
Absent	85	43.13 ± 33.51	17.13 ± 24.92	− 26.00 ± 34.07	
Present	20	29.39 ± 28.05	20.89 ± 29.13	− 8.50 ± 37.82	
Unknown	1	10.00	40.00	30.00	

BASDAI Bath Ankylosing Spondylitis Disease Activity Index, *CRP* C-reactive protein, *DAS28* Disease Activity Score in 28 joints, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *NSAID* nonsteroidal anti-inflammatory drug, *OWI* overall work impairment, *PASE* Psoriatic Arthritis Screening and Evaluation, *SD* standard deviation

[a] All values are mean ± SD

[b] Patients with values missing before treatment initiation (between 28 days prior to and the first administration day of adalimumab) were classified as "unknown/missing"

[c] Patients with missing values were excluded from this analysis

[d] The significance test was performed on the score before administration and the amount of change at final evaluation

[e] *p* values were assessed using the *t* test

[f] *p* values were assessed using a one-way analysis of variance

were infections and infestations (8.1%), followed by respiratory, thoracic, and mediastinal disorders (3.4%), and general disorders and administration site conditions, and blood investigations (2.7% each; Table 4).

DISCUSSION

The effect of adalimumab on RA-related WPAI and the association between changes in disease activity and WPAI outcomes in routine rheumatology practice in Japan were first evaluated in the ANOUVEAU study [19]. The current PMS study is the first to evaluate the effectiveness of a biologic (adalimumab) in improving WPAI using a validated Japanese version of the WPAI instrument in Japanese patients with PsA. Results from this PMS study indicated that adalimumab treatment is effective in improving PsA-related WPAI and overall disease activity in Japanese patients with PsA

Table 4 Safety profile (safety population)

***n* =148**	**Total AEs**	**Serious AEs**
Overall, *n* (%)	32 (21.6)	4 (2.7)
Number of events	39	4
AEs by SOC and PT[a], *n* (%)		
Infections and infestations	12 (8.1)	1 (0.7)
Viral URTI	3 (2.0)	0
Staphylococcal cellulitis	1 (0.7)	1 (0.7)
Bronchiolitis	1 (0.7)	0
Bronchitis	1 (0.7)	0
Cellulitis	1 (0.7)	0
Paronychia	1 (0.7)	0
Pharyngitis	1 (0.7)	0
Sinusitis	1 (0.7)	0
Viral infection	1 (0.7)	0
Herpes zoster infection neurological	1 (0.7)	0
Respiratory, thoracic, and mediastinal disorders	5 (3.4)	1 (0.7)
Interstitial lung disease	1 (0.7)	1 (0.7)
Asthma	1 (0.7)	0
Cough	1 (0.7)	0
Upper respiratory tract inflammation	1 (0.7)	0
Pulmonary mass	1 (0.7)	0
Blood investigations	4 (2.7)	0
Alanine aminotransferase increased	1 (0.7)	0
Aspartate aminotransferase increased	1 (0.7)	0
Transaminases increased	1 (0.7)	0
Antinuclear antibody positive	1 (0.7)	0
Hepatic enzyme increased	1 (0.7)	0
Cell marker increased	1 (0.7)	0
General disorders and administration site conditions	4 (2.7)	1 (0.7)
Paradoxical drug reaction	2 (1.4)	1 (0.7)
Injection site erythema	1 (0.7)	0
Injection site pruritus	1 (0.7)	0
Edema	1 (0.7)	0

Table 4 continued

n =148	Total AEs	Serious AEs
Hepatobiliary disorders	3 (2.0)	0
Hepatic function abnormal	2 (1.4)	0
Liver disorder	1 (0.7)	0
Skin and subcutaneous tissue disorders	3 (2.0)	0
Eczema	1 (0.7)	0
Rash	1 (0.7)	0
Skin symptoms	1 (0.7)	0
Musculoskeletal and connective tissue disorders	2 (1.4)	0
Arthralgia	1 (0.7)	0
Psoriatic arthropathy	1 (0.7)	0
Renal and urinary disorders	1 (0.7)	1 (0.7)
Lupus nephritis	1 (0.7)	1 (0.7)
Nervous system disorders	1 (0.7)	0
Hypoesthesia	1 (0.7)	0
Gastrointestinal disorders	1 (0.7)	0
Oral disorders	1 (0.7)	0

AE adverse event, *PT* preferred term, *SOC* system organ class, *URTI* upper respiratory tract infection
[a] Multiple events by PT in one patient were counted once in the corresponding SOC

over a 24-week observation period. There were consistent improvements in OWI, presenteeism, and AI over time with adalimumab treatment. Although absenteeism also improved significantly by study end, the improvement was not consistent over time, perhaps because only a few patients had a score greater than 0 before treatment initiation, leading to large variations at each time point during the study. Adalimumab treatment also led to significant improvement in joint, skin, and spinal symptoms and functional impairment associated with PsA. However, improvement in joint symptoms largely contributed to the improvement of OWI, and patients presenting with higher disease activity related to joint symptoms at baseline showed greater improvement in OWI at the final evaluation. In contrast, no significant association was observed between skin symptoms and OWI. Additionally, significant improvement in OWI with adalimumab treatment was observed regardless of sex, disease duration, or the presence of enthesitis, dactylitis, or spondylitis, suggesting that treatment directed at alleviating disease activity related to joints may lead to improvement of work productivity in patients with PsA.

Improvement in OWI was significantly impacted by past medical history; previous oral NSAID use; and PASE, DAS28(CRP), BASDAI, and HAQ-DI scores. Patients with moderate or high disease activity (DAS28[CRP] > 3.2) and higher PASE, HAQ-DI, and BASDAI scores at baseline, suggestive of more severe disease, had higher baseline OWI scores and showed greater improvement in work productivity. Similarly, patients with previous use of NSAIDs compared

with those without, likely due to more severe pain, had higher baseline OWI scores and showed greater improvement in work productivity.

Most of the demographic and clinical characteristics of the study population (e.g., a higher percentage of men, mean age in the late 40s, mean duration of skin symptoms approximately 10 years longer than that of joint symptoms, predominance of plaque-type psoriasis, and almost 25% of patients who were smokers) were consistent with those observed in a recent survey by the Japanese Society for Psoriasis Research [8]. As in a previous Japanese PMS study (SALSA) [16], where the safety and effectiveness of adalimumab in treating psoriasis was evaluated over 24 weeks, more than 90% of patients with PsA in our study had received previous treatment, mainly methotrexate, despite its status as an off-label treatment in Japan [11], and had received corticosteroid treatment, mainly in a topical form. However, the percentage of previous oral corticosteroid and methotrexate users was higher in the current PMS study than in the prior SALSA study. Compared with the SALSA study, fewer dermatology departments participated as study centers because arthritis symptoms were evaluated mainly by rheumatologists or orthopedic surgeons in this study. The differences between the treatment perspectives of dermatologists and rheumatologists/orthopedic surgeons could have been attributed to the variation in the percentage of corticosteroid and methotrexate users between the two studies.

The dosage of adalimumab varied in the present PMS study, with approximately 50% of patients receiving the recommended dosage. Most patients who initiated treatment and continued with a lower dose (40 mg) were using methotrexate, which is not surprising, given the potentially enhanced effectiveness of concomitant treatment. However, methotrexate is not approved for the treatment of patients with PsA in Japan [11]. Patients with escalation to the 80-mg adalimumab dose because of inadequate response to the 40-mg dose weighed more and had higher BMI or poorer VAS scores at baseline than those on other dosing regimens. The strong association between obesity and the severity of psoriasis has been described previously [20]. Moreover, in a subgroup analysis of the phase 3 REVEAL study of patients with moderate to severe psoriasis receiving adalimumab, treatment response was moderately lower with 40 mg q2w dosing in obese than in non-obese patients [21]. Similarly, patients with a dose escalation had a higher BMI than those without dose escalation and exhibited an improved treatment response following dose escalation in a long-term phase 2/3 trial of adalimumab in Japanese patients with moderate to severe plaque psoriasis [22]. Taken together, these results suggest that higher adalimumab doses should be considered in obese patients and those with severe disease. Furthermore, as observed in an earlier study, weight-control interventions in obese patients receiving treatment with a TNF inhibitor could potentially improve treatment response [23].

WPAI is a validated tool and has been used in other studies as well to determine the impact of biologic therapy in improving work disability. Similar to effectiveness results from this study (median [range] scores shown in Table S2), a UK study [24] reported improvement in median productivity loss (OWI; 50% to 10%), presenteeism (40% to 10%), and AI (60% to 20%) scores in patients with active PsA following 6-month treatment with TNF inhibitors in a real-world setting; improvement in patient-reported outcomes was also reported. However, only about 57% of patients were employed in the UK study, unlike in the present study, which included only patients who were employed. A central-eastern Europe study also reported improvements in mean WPAI scores (OWI, 59.9% to 22.1%; presenteeism, 56.7% to 20.1%) after 1 year of treatment with adalimumab in patients with ankylosing spondylitis (AS) and PsA (approx. 27% of the study population) [25]. Besides differences in the studied populations, the baseline scores were higher in the above studies [24, 25] compared with this study. Moreover, 65.8% of patients with AS compared with 25.8% of those with PsA were using NSAIDs in the European study [25], indicating more severe pain and potentially greater work impairment in patients with AS than in those with PsA. As a result of these differences,

it is challenging to compare the WPAI outcomes from the current study with those of other real-world studies. Treatment with other biologics (ustekinumab, apremilast, certolizumab pegol, golimumab, and infliximab) has also been reported to improve self-reported work productivity in patients with PsA in a systematic meta-analysis of five randomized controlled trials. However, randomized controlled settings and variations in WPAI measures used in the five trials that were analyzed preclude any comparison with the current study results [26].

Overall, approximately one-half and two-thirds of patients achieved PASI75 at weeks 16 and 24, respectively, and approximately one-third and two-fifths of patients achieved PASI90 at weeks 16 and 24, respectively, in this study. PASI achievement rates are similar to those reported in the aforementioned prior Japanese PMS study [16]. The changes from baseline to week 24 in DAS28(ESR), DAS28(CRP), and VAS pain scores were also comparable between these studies. The PASI90 rate at 24 weeks (42%) in this study was the same as that reported in the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT), comprising a primarily white cohort [27]. However, ACR20, ACR50, and ACR70 response rates obtained at weeks 12 (76.2%, 57.1%, and 31.0%, respectively) and 24 (91.3%, 76.1%, and 58.7%, respectively) in this study were numerically higher than those in ADEPT (58%, 36%, and 20%; and 57%, 39%, and 23%, respectively) [27], suggesting comparable effectiveness of adalimumab treatment in improving skin symptoms in white and Japanese patients, with potentially a better response for joint symptoms in Japanese patients. However, the difference could also be attributed to differences in study design and setting.

Multivariate regression analysis in a US study showed that patients with more severe PsA had increased odds of high WPAI domain scores, with the exception of absenteeism [28]. In the REVEAL study, all WPAI domain scores were significantly correlated with disease severity assessed using PASI, PhGA, and the Dermatology Life Quality Index [15]. In contrast, PASI scores were not significantly correlated with OWI in the current PMS study. However, other disease severity measures, particularly those related to joint symptoms such as PASE, DAS28(CRP), BASDAI, and HAQ-DI, were significantly correlated with OWI. These findings are supported by results from a large, multicenter UK study in which work disability was significantly associated with global, physical function, and joint-specific disease, assessed using global and joint activity measures (VAS and HAQ-DI), but not with skin-specific disease [29].

The incidence of AEs and serious AEs was comparable with that in the previous real-world study of patients with psoriasis in Japan [16], and no new or unexpected safety signals were observed.

This study had several strengths. First, the demographics and characteristics of the study population are representative of the real-world psoriasis population in Japan. Second, WPAI-PsA was measured from baseline to week 24, providing a glimpse of the long-term impact of adalimumab treatment on WPAI in patients with PsA. This study, however, also had some limitations. Although a central registration system was employed to reduce selection bias, results could still be biased because of the open-label and observational nature of the study. As a result of the observational design of the study, approximately one-third of enrolled patients had to be excluded from the efficacy analysis set because of unavailability of OWI scores. In addition, routine clinical settings resulted in several limitations, including the inability to control the use of concomitant treatment and the inability to obtain effectiveness scores at all time points.

CONCLUSIONS

Results from this PMS study suggest that adalimumab treatment improves work productivity and impairment, and reduces disease activity in patients with PsA. Improvement in work impairment was associated with greater joint-specific PsA severity and disability before treatment initiation and improvement in joint symptoms following adalimumab treatment. Finally, no new safety signals were identified

with adalimumab treatment in this real-world setting.

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Compliance with Ethics Guidelines. This study was conducted in compliance with Good Postmarketing Study Practice (GPSP) in Japan and was registered at ClinicalTrials.gov (NCT02414633). The study protocol was reviewed and approved in advance by the Pharmaceuticals and Medical Devices Agency of Japan. As per GPSP regulations, institutional review board approval and written informed consent from patients were not required.

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Data Availability. The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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