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ORIGINAL RESEARCH

Impact of Adalimumab on Work Productivity and Activity Impairment in Japanese Patients with Rheumatoid Arthritis: Large-Scale, Prospective, Single-Cohort ANOUVEAU Study

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ABSTRACT

Introduction: The Adalimumab Non-interventional Trial for Up-verified Effects and Utility (ANOUVEAU) was a large-scale, multicenter, prospective, observational, single-cohort study that evaluated the effects of adalimumab (ADA) on rheumatoid arthritis (RA)-related work productivity and activity impairment (RA-related WPAI) and disease activity in routine rheumatology care in Japan.

Methods: Patients with RA were categorized as paid workers (PWs, ≥35 h/week), part-time workers (PTWs, <35 h/week), or homemakers (HMs, unemployed) and were administered the WPAI for RA (WPAI/RA) questionnaire. All patients who received ADA were followed for 48 weeks to evaluate safety and effectiveness.

Results: Of the 1808 patients analyzed, 825, 243, and 740 patients were PWs, PTWs, and HMs, respectively. WPAI/RA domain scores significantly improved at weeks 12, 24, and 48 in all groups, with maximum improvement observed for PWs ($p < 0.05$). Additionally, remission rates (according to Disease Activity Score 28, erythrocyte sedimentation rate, Simplified Disease Activity Index, or Health Assessment Questionnaire-Disability Index scores) and EuroQol 5-Dimension 3-Level scores significantly increased from baseline to 48 weeks in all groups ($p < 0.0001$). Analysis of patient subgroups revealed better WPAI/RA outcomes for patients who were biologic-naïve, treated with concomitant methotrexate, or with RA duration of ≤2 years ($p < 0.05$). The rate of serious adverse events over 48 weeks of ADA treatment was 5.23%.

Conclusions: Treatment with ADA provided sustained improvement in WPAI and had an acceptable safety profile in patients with RA.

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Keywords: Patient safety; Post-marketing surveillance study; Rheumatoid arthritis; TNF inhibitor; Work productivity and activity impairment

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by inflammation and joint destruction [1]. The global prevalence of RA is approximately 0.24% [2]. Based on analysis of a Japanese health insurance database (Institute of Rheumatology, Rheumatoid Arthritis [IORRA], 2005 to 2011), the estimated prevalence of RA in Japan is between 0.6% and 1.0% [3].

Within 6 months of the onset of RA, patients often experience inflammatory synovitis, articular cartilage destruction, joint erosion, and consequent disability that leads to functional loss and impairment in many aspects of daily living, including work and home activities, recreation, and social relations [4–8]. Furthermore, pain associated with RA is an important predictor of sick leave and reduced productivity among employed patients with RA [9]. Physical symptoms of RA and associated functional limitations negatively impact quality of life (QoL), as demonstrated in numerous clinical trials, including one evaluating EuroQol 5-Dimension 3-Level (EQ-5D-3L) scores and their relationship with other clinical outcomes among 5284 Japanese patients with RA [10].

In addition to the personal burden RA imposes on patients and their families, RA exacts a substantial economic burden on society, particularly on employers and the healthcare system. According to an analysis of the direct medical costs and the indirect costs of care of more than 10,000 patients with RA in the IORRA database (2007, 2008), costs were considerable and grew with increasing disease activity and disability level or worsening QoL [11]. Much of the indirect cost associated with RA is work-related, including absenteeism (percentage of work time missed due to RA) and presenteeism (percentage of impaired work time due to RA), which are common in the first years following an RA diagnosis, even among those with mild disease [4, 12].

The goals of RA treatment are clinical remission or low disease activity, depending on patient-related factors [13, 14]. Proactive control of disease activity using early interventions that prevent irreversible damage may help mitigate the personal and socioeconomic burdens of this chronic disease. In addition to early treatment, combination treatment with conventional disease-modifying antirheumatic drugs (DMARDs), such as methotrexate (MTX), and biologic DMARDs, such as those targeting tumor necrosis factor-α (TNF-α; infliximab, etanercept, and adalimumab [ADA; AbbVie Inc., North Chicago, IL, USA]), interleukin-6 (IL-6; tocilizumab), IL-1 (anakinra), or T cells (abatacept) provide favorable short- and long-term outcomes [13, 14]. Results of multiple studies (including several conducted in Japan) also indicate that TNF-α inhibitors such as etanercept and infliximab improve patients' employability and ability to perform work and housekeeping tasks [4, 15–20].

ADA is a human anti-TNF-α monoclonal antibody approved in Japan for the treatment of RA; it reduces the signs and symptoms of disease and induces a major clinical response, thus inhibiting the progression of structural damage and improving physical function in adult patients with moderate to severely active RA [21, 22]. The efficacy and safety of ADA has been demonstrated in short- and long-term international and Japanese clinical trials involving varied treatment regimens and patient populations. Results from several trials, including "Optimal Protocol for Treatment Initiation with Methotrexate and Adalimumab" (OPTIMA) and "Adalimumab, a Human Anti-TNF Monoclonal Antibody, Outcome Study for the Persistent Efficacy Under allocation to treatment strategies in early RA" (HOPEFUL 1) in Japan, demonstrated the benefits of early initiation of treatment with ADA, particularly among patients with high disease activity [23–27].

Although the efficacy and safety of ADA have been clearly established in patients with RA, including its effect on work ability, workplace and household productivity, and QoL in studies

conducted around the world [19, 28–32], large-scale evidence of its long-term impact on work productivity and activity impairment (WPAI) in Japan is lacking [15, 33]. This real-world Adalimumab Non-interventional Trial for Up-verified Effects and Utility (ANOUVEAU) study was conducted to evaluate the effects of ADA on RA-related work productivity and activity impairment (RA-related WPAI), as well as the association of disease activity changes on work outcomes in routine rheumatology care in Japan.

METHODS

Study Design

ANOUVEAU was a large-scale, multicenter, prospective, observational, single-cohort study conducted between May 2011 and January 2015 at 432 centers in Japan. The objectives of the study were (1) to evaluate the effect of ADA on RA-related WPAI, as well as associations between disease activity, patient characteristics, and disease duration and work outcomes; and (2) to determine changes in clinical and functional disease activity, as well as associations between these activities and disease duration. The study (ClinicalTrials.gov: NCT01346488) was approved by the Pharmaceuticals and Medical Devices Agency and was conducted in accordance with Good Post-marketing Study Practice (GPSP). Documentation was in accordance with Good Vigilance Practice/GPSP. For this reason, no ethical review by the individual facilities participating in the study was conducted. Because informed consent is not required for post-marketing observational studies that are conducted under the GPSP in Japan, the present study did not solicit informed consent from patients.

Patients

Patients were eligible for the study if they had an inadequate response to conventional therapy (e.g., conventional DMARDs or biologics other than ADA) as stated in the current Japanese labeling for ADA [34, 35] and met the Japanese guidelines issued by the Japan College of Rheumatology (JCR) for the use of TNF-α inhibitors [36]. Patients were categorized on the basis of employment status: paid worker (PW; employed for ≥35 h/week), part-time worker (PTW; employed for <35 h/week), or homemaker (HM; unemployed or employed in a capacity other than PW or PTW and able to perform basic activities of daily life [household duties, shopping, child care, exercise, and study]. Patients who were hospitalized or bedridden, had been previously treated with ADA, or were considered otherwise ineligible by investigators were excluded from the study.

Treatment

Before the initiation of ADA therapy, patients were examined for eligibility in accordance with current Japanese labeling for ADA [34, 35] and were determined to meet JCR guidelines for the use of TNF-α inhibitors [36]. Patients were allowed to continue prior RA treatments, such as DMARDs, glucocorticoids, and nonsteroidal anti-inflammatory drugs during the observation period. All eligible patients received ADA and were followed for 48 weeks. Patients who did not respond to therapy and were not receiving DMARDs (including MTX) were allowed a dose adjustment to 80 mg every other week. If a patient withdrew from the study, the date and reason for discontinuation were recorded. Reasons for discontinuation of ADA treatment included insufficient efficacy and occurrence of adverse events.

Assessments and Outcomes

Patient demographics and characteristics were recorded in a case report form at baseline, and patients were administered validated questionnaires at baseline and at weeks 12, 24, 36, and 48. Work-related outcomes were measured using the Work Productivity and Activity Impairment questionnaire for RA (WPAI/RA [Japanese-Japan v 2.1]), which comprises four domains: absenteeism,

presenteeism, percentage of overall work impairment (OWI) due to RA, and percentage of activity impairment (AI) due to RA. For HMs, only AI data were obtained. Absenteeism was calculated as

$$\text{Absenteeism} = \frac{[\text{hours absent from work due to RA}]}{[\text{hours absent from work due to RA} + \text{hours actually worked}]} \times 100\%.$$

Missed work days per year were calculated from WPAI/absenteeism. Presenteeism was calculated using a visual analog scale (VAS) as the percentage of reduction in productivity while working due to RA. OWI was calculated as

$$\text{OWI} = \text{Absenteeism} + [(1 - \text{absenteeism}) \times \text{presenteeism}] \times 100\%.$$

AI was assessed using a VAS as a percentage of impairment due to RA in regular daily activities other than working at a job.

Disease activity, including functional and clinical response, was assessed using the Health Assessment Questionnaire-Disability Index (HAQ-DI) for RA; Disease Activity Score based on 28 joints and erythrocyte sedimentation rate (DAS28ESR); Disease Activity Score based on 28 joints and C-reactive protein (DAS28CRP); Clinical Disease Activity Index (CDAI); Simplified Disease Activity Index (SDAI) [14]; and EQ-5D-3L (descriptive sections: mobility, self-care, usual activities, pain-discomfort, and anxiety-depression).

Safety was assessed throughout the study by recording adverse events, including abnormal laboratory findings, in the case report form.

Statistical Analysis

Sample size calculations were based on results of a previous study conducted in Germany [37] in which 469 RA patients were deemed necessary to detect an average difference of 5 days (absence from work for an average of 21 days) at the 0.05 significance level (two-sided) with a power of 0.90. To ensure 500 eligible PWs and 500 eligible HMs, enrollment targets were 1000 patients for each group, assuming a 50% withdrawal rate. Data were analyzed using the last observation carried forward (LOCF) method when there were missing values before week 48 and are presented as mean ± SD unless indicated otherwise. To compare differences between groups at baseline, the Chi square test was used for categorical variables, and the Wilcoxon rank sum test or Kruskal–Wallis test was used for continuous variables. For WPAI/RA scores, the Wilcoxon signed-rank test was used to compare baseline scores with scores at 12, 24, and 48 weeks; the Wilcoxon rank sum test or Kruskal–Wallis test was used to compare the differences in the changes from baseline between groups. Absenteeism was also assessed in a subgroup of patients with baseline absenteeism >0 days. The Fisher exact test was used to compare remission rates at baseline and at 12, 24, and 48 weeks. The Wilcoxon signed-rank test was used to compare EQ-5D-3L at baseline and at 12, 24, and 48 weeks. For regression coefficients, Pearson product-moment was used to examine the correlations between WPAI/RA domains (absenteeism, presenteeism, OWI, and AI) and clinical responses (DAS28CRP, SDAI, HAQ-DI, and EQ-5D-3L). PWs were stratified on the basis of their baseline characteristics (biologic use, MTX use, MTX dose, RA duration, and age) to evaluate the effect of baseline characteristics on WPAI/RA domains at week 48. The Wilcoxon signed-rank test was used to compare differences between baseline and 48 weeks, and the Wilcoxon rank sum test was used to compare the differences between subgroups. SAS® 9.2 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis.

RESULTS

Patient Disposition and Clinical Characteristics

Of the 1973 patients enrolled in this study, 1968 and 1808 were eligible for safety and effectiveness analyses, respectively. Most cases of ineligibility were due to a lack of clinical data. Of the 1808 patients that were evaluable for efficacy analyses, 825, 243, and 740 were PWs, PTWs, and HMs, respectively. The groups were significantly different with respect to age ($p < 0.0001$); HMs were older (mean [SD], 62.2 [12.6] years) than PWs (49.9 [11.7] years) and PTWs (53.9 [11.8] years). PTWs and HMs were predominantly women. The overall disease duration of RA was longer in HMs (8.6 [9.2] years) than PWs (5.0 [6.2] years) and PTWs (6.1 [7.1] years), with significant group differences ($p < 0.0001$). Additionally, baseline characteristics varied among the three groups in terms of stage of RA, class of RA, MTX dose, ESR, CRP, Patient Global Assessment (PtGA)/VAS, Physician Global Assessment (PhGA)/VAS, DAS28ESR, DAS28CRP, HAQ-DI, EQ-5D-3L, and AI scores (Table 1). In all groups, the majority of patients belonged to RA stages I and II and RA classes I and II.

Changes in WPAI/RA Domain Scores

Based on the estimation from WPAI/absenteeism results, missed work days per year in PWs ($n = 677$) decreased significantly from 7.48 ± 19.64 (mean $\pm$ SD) at baseline to 3.97 ± 14.81 at the final assessment ($p < 0.0001$). A total of 525/677 PWs (77.5%) and 134/180 PTWs (74.4%) had a baseline absenteeism of 0 days. Among patients with baseline absenteeism of >0 days, there was a similar decrease ($p < 0.0001$) in absenteeism in the PW ($n = 152$) and PTW ($n = 46$) groups over 48 weeks (Fig. 1a). Relative to baseline, the remaining WPAI/RA domain scores also significantly decreased at all time points in all study groups ($p < 0.001$ for all comparisons; Fig. 1b–d). Reduction in absenteeism and AI did not differ between groups, whereas improvements in presenteeism and OWI were greater in the PW than the PTW group at all time points ($p < 0.05$). This was true except at week 48, when the group differences indicated marginal improvements ($p = 0.0579$ for presenteeism, $p = 0.0808$ for OWI).

Achievement of Remission at Week 48

The proportion of patients achieving remission according to DAS28CRP, SDAI, or HAQ-DI scores significantly increased at 12, 24, and 48 weeks compared with baseline in all groups ($p < 0.0001$ for all comparisons; Fig. 2). Although the proportion of patients in HAQ-DI remission was higher at baseline in the PW (44.8%) and PTW (40.6%) groups in comparison to the HM group (27.7%), there was a similar increase in the proportion of patients achieving remission over 48 weeks in all groups ($p < 0.0001$; Fig. 2).

Change in QoL

The improvement in disease activity as assessed by DAS28CRP, SDAI, or HAQ-DI scores was also reflected in the significant improvement in QoL assessed by EQ-5D-3L scores in all groups through week 48, with differences from baseline occurring at all time points ($p < 0.0001$ for all comparisons; Fig. 2).

Correlation with WPAI/RA Domain Scores and Clinical Responses at Week 48

There was a trend toward a positive linear correlation between improvement in WPAI/RA domain scores and decrease in disease activity, as assessed by DAS28CRP, SDAI, and HAQ-DI scores at week 48, except absenteeism (DAS28CRP and SDAI) in PTWs. There was a trend toward a negative linear correlation between improvements in WPAI/RA domain scores and increases in EQ-5D-3L for all groups except absenteeism in PTWs ($p < 0.0001$; Table 2).

Table 1 Baseline demographics and clinical characteristics

Characteristic	PW (employed ≥35 h/week)	PTW (employed <35 h/week)	HM (unemployed)
[a]Age (years): mean ± SD, *n*	49.9 ± 11.7, 825	53.9 ± 11.8, 243	62.2 ± 12.6, 740
[a]Women: *n* (%)	523 (63.4)	219 (90.1)	629 (85)
[a]RA duration (years): mean ± SD, *n*	5.0 ± 6.2, 785	6.1 ± 7.1, 229	8.6 ± 9.2, 688
[a,f] RA stage: *n* (%)			
I	289 (35.2)	71 (29.3)	137 (18.6)
II	304 (37.0)	82 (33.9)	231 (31.3)
III	146 (17.8)	48 (19.8)	194 (26.3)
IV	83 (10.1)	41 (16.9)	175 (23.7)
[a,g]RA class: *n* (%)			
I	269 (32.7)	61 (25.1)	136 (18.4)
II	485 (58.9)	162 (66.7)	444 (60.0)
III	66 (8.0)	19 (7.8)	149 (20.1)
IV	3 (0.4)	1 (0.4)	11 (1.5)
[a]MTX dose (mg/week): mean ± SD, *n*	10.0 ± 3.9, 761	9.4 ± 2.9, 224	9.0 ± 3.1, 631
[a]ESR (mm/h): mean ± SD, *n*	32.8 ± 26.7, 663	38.5 ± 28.8, 202	44.2 ± 30.0, 606
[a]CRP (mg/dL): mean ± SD, *n*	1.67 ± 3.10, 796	1.50 ± 2.15, 240	1.84 ± 2.37, 714
TJC (0–28): mean ± SD, *n*	5.7 ± 5.6, 797	5.8 ± 5.5, 240	5.9 ± 5.7, 722
SJC (0–28): mean ± SD, *n*	5.7 ± 5.3, 797	6.1 ± 5.0, 239	5.6 ± 5.0, 722
[a]PtGA/VAS (0–100 mm): mean ± SD, *n*	48.1 ± 26.1, 795	49.5 ± 25.3, 241	53.3 ± 26.0, 722
[a]PhGA/VAS (0–100 mm): mean ± SD, *n*	46.2 ± 22.8, 778	49.3 ± 22.7, 231	50.2 ± 23.0, 708
[a]DAS28ESR: mean ± SD, *n*	4.6 ± 1.4, 653	4.8 ± 1.3, 197	5.0 ± 1.3, 600
[a]DAS28CRP: mean ± SD, *n*	4.1 ± 1.3, 779	4.2 ± 1.2, 234	4.3 ± 1.2, 704
SDAI: mean ± SD, *n*	22.5 ± 13.5, 766	23.1 ± 13.0, 225	23.7 ± 12.7, 690
CDAI: mean ± SD, *n*	20.8 ± 12.4, 775	21.7 ± 12.1, 230	22.0 ± 12.0, 705
[a]HAQ-DI: mean ± SD, *n*	0.750 ± 0.652, 761	0.828 ± 0.650, 224	1.165 ± 0.806, 676
[a]EQ-5D-3L: mean ± SD, *n*	0.654 ± 0.155, 756	0.638 ± 0.138, 218	0.597 ± 0.154, 663
[b]Absenteeism (%): mean ± SD, *n*	7.5 ± 19.6, 677	11.1 ± 23.5, 180	NA
[c]Presenteeism (%): mean ± SD, *n*	41.1 ± 29.1, 726	38.6 ± 28.6, 197	NA
[d]OWI (%): mean ± SD, *n*	42.3 ± 29.8, 665	42.0 ± 31.3, 178	NA

Table 1 continued

Characteristic	PW (employed ≥35 h/week)	PTW (employed <35 h/week)	HM (unemployed)
[a,e]AI (%): mean ± SD, *n*	44.2 ± 28.4, 759	47.9 ± 28.2, 219	54.3 ± 26.7, 653

Some data for almost all characteristics (except for age and sex) were missing; therefore, the evaluation is based on available data only

AI activity impairment, *CDAI* Clinical Disease Activity Index (to assess clinical response), *CRP* C-reactive protein, *DAS28CRP* Disease Activity Score based on 28 joints and CRP, *DAS28ESR* Disease Activity Score based on 28 joints and ESR, *EQ-5D-3L* EuroQol 5-Dimension 3-Level, *ESR* erythrocyte sedimentation rate, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *HM* homemaker, *MTX* methotrexate, *NA* data not available, *OWI* overall work impairment, *PhGA/VAS* physician global assessment using VAS, *PtGA/VAS* patient global assessment using VAS, *PTW* part-time worker, *PW* paid worker, *RA* rheumatoid arthritis, *SD* standard deviation, *SDAI* Simplified Disease Activity Index (to assess functional response), *SJC* swollen joint count, *TJC* tender joint count, *VAS* visual analog scale

[a] Significant differences ($p < 0.05$) existed between the comparison groups in terms of these baseline characteristics. Statistical significance was calculated using a Chi square test for categorical variables and a Wilcoxon rank sum test or Kruskal–Wallis test for continuous variables

[b] Absenteeism: percentage of work time missed due to RA

[c] Presenteeism: percentage of impairment while working due to RA (calculated using a numerical rating scale)

[d] OWI (%): percentage of overall work impairment due to RA = [absenteeism + {(1 − absenteeism) × presenteeism}] × 100%

[e] AI (%): percentage of impairment in daily activities (other than work) due to RA (assessed using a VAS)

[f] Stage of RA: I, early; II, moderate; III, severe; and IV; end stage [38]

[g] Class of RA: I, complete functional capacity with ability to carry on all usual duties without handicaps; II, functional capacity adequate to conduct normal activities despite handicap of discomfort or limited mobility of one or more joints; III, functional capacity adequate to perform only few or none of the duties of usual occupation or of self-care; IV, largely or wholly incapacitated with patient bedridden or confined to wheelchair, permitting little or no self-care [38]

Association Between Change in WPAI/RA Domain Scores and Baseline Characteristics in PW Group

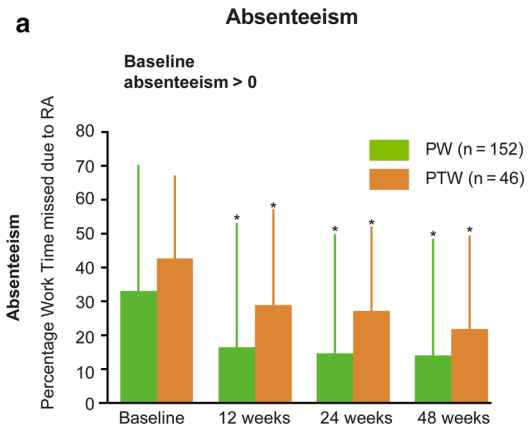
There was a significant improvement in WPAI/RA domain scores at week 48 in biologic-naïve patients compared with biologic-experienced patients ($p < 0.05$; Table 3). Concomitant use of MTX has been shown to increase the efficacy of ADA treatment, decreasing RA disease activities more efficiently than ADA alone [39]. Along these lines, patients treated with concomitant MTX versus those treated without MTX showed greater improvement in presenteeism (19.1 vs. 9.8), OWI (19.4 vs. 7.5), and AI (22.4 vs. 12.9) ($p < 0.05$). Additionally, when initiated at an early stage of RA, biologics treatment shows higher efficiency to reduce disease activity [40]. Consistent with this notion, patients with ≤2 years of RA duration exhibited significantly improved AI compared to those with an RA duration of >2 years ($p < 0.05$).

Safety

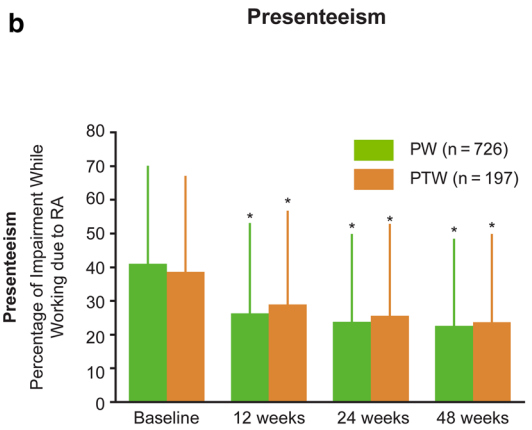
The safety profile of ADA in the present study was consistent with previous reports [39, 41]. The rate of serious adverse events over 48 weeks of ADA treatment was 5.23% (103/1968 cases), with infections and infestations being the most commonly reported adverse events (Table 4). Other common serious adverse events were neoplasms (benign, malignant, and unspecified [including cysts and polyps]), which were reported in 14 patients (17 events [0.9%]), followed by respiratory, thoracic, and mediastinal disorders, which were reported in 11 patients (14 events [0.7%]).

DISCUSSION

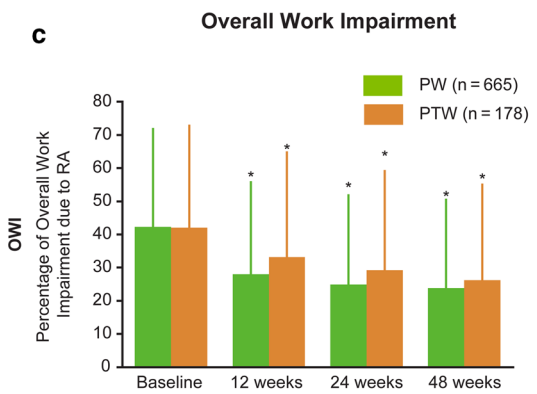
The efficacy and safety of ADA in patients with RA is well established; however, its impact on work productivity and activity impairment in



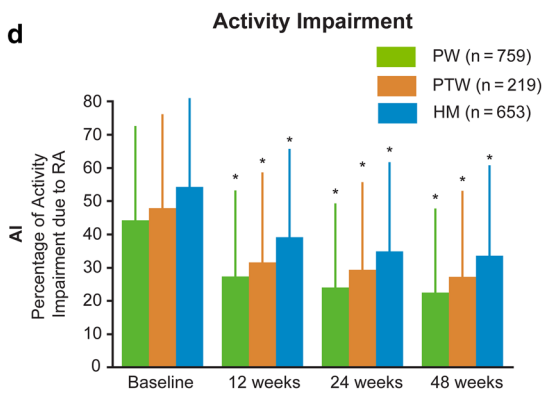
	Mean (SD)		Change from baseline	
	PW	PTW	PW	PTW
Baseline	33.3 (29.3)	43.2 (27.9)	—	—
			—	—
12 weeks	16.5 (26.2)	29.1 (33.1)	-16.8	-14.1
			$p = 0.5222$	
24 weeks	14.7 (26.4)	27.4 (32.6)	-18.7	-15.9
			$p = 0.3711$	
48 weeks	14.2 (26.2)	22.1 (30.7)	-19.2	-21.2
			$p = 0.7158$	



	Mean (SD)		Change from baseline	
	PW	PTW	PW	PTW
Baseline	41.1 (29.1)	38.6 (28.6)	—	—
			—	—
12 weeks	26.3 (26.8)	28.9 (28.4)	-14.8	-9.7
			$p = 0.0102$	
24 weeks	23.8 (26.1)	25.6 (26.5)	-17.2	-13.0
			$p = 0.0226$	
48 weeks	22.6 (25.8)	23.7 (25.8)	-18.4	-14.9
			$p = 0.0579$	



	Mean (SD)		Change from baseline	
	PW	PTW	PW	PTW
Baseline	42.3 (29.8)	42.0 (31.1)	—	—
			—	—
12 weeks	28.0 (28.0)	33.2 (31.8)	-14.3	-8.8
			$p = 0.0107$	
24 weeks	24.9 (27.1)	29.2 (30.1)	-17.4	-12.8
			$p = 0.0145$	
48 weeks	23.8 (26.9)	26.2 (29.2)	-18.5	-15.8
			$p = 0.0808$	



	Mean (SD)			Change from baseline		
	PW	PTW	HM	PW	PTW	HM
Baseline	44.2 (28.4)	47.9 (28.2)	54.3 (26.7)	—	—	—
				—	—	—
12 weeks	27.4 (25.9)	31.6 (27.0)	39.1 (26.6)	-16.8	-16.3	-15.2
				$p = 0.6940$		
24 weeks	24.1 (25.3)	29.3 (26.4)	35.0 (26.8)	-20.1	-18.6	-19.4
				$p = 0.7659$		
48 weeks	22.5 (25.3)	27.2 (25.9)	33.6 (27.2)	-21.7	-20.8	-20.7
				$p = 0.8631$		

Fig. 1 Change from baseline in WPAI/RA domain scores. **a** Patients with baseline absenteeism >0 days, **b** presenteeism, **c** OWI, and **d** AI. Only patients with absenteeism >0 are shown in **a**, whereas all eligible RA patients are included in **b**–**d**. *AI* activity impairment, *HM* homemaker, unemployed, *OWI* overall work impairment, *PTW* part-time worker employed for <35 h/week, *PW* paid worker employed for ≥35 h/week, *RA* rheumatoid arthritis, *SD* standard deviation, *WPAI* work productivity and activity impairment. $^{*}p < 0.0001$ compared to the corresponding baseline values. The Wilcoxon signed-rank test was used to compare baseline and 12, 24, and 48 weeks, and the Wilcoxon rank sum test or the Kruskal–Wallis test was used to compare the difference in the changes from baseline between the two groups. Data were analyzed using the last observation carried forward method

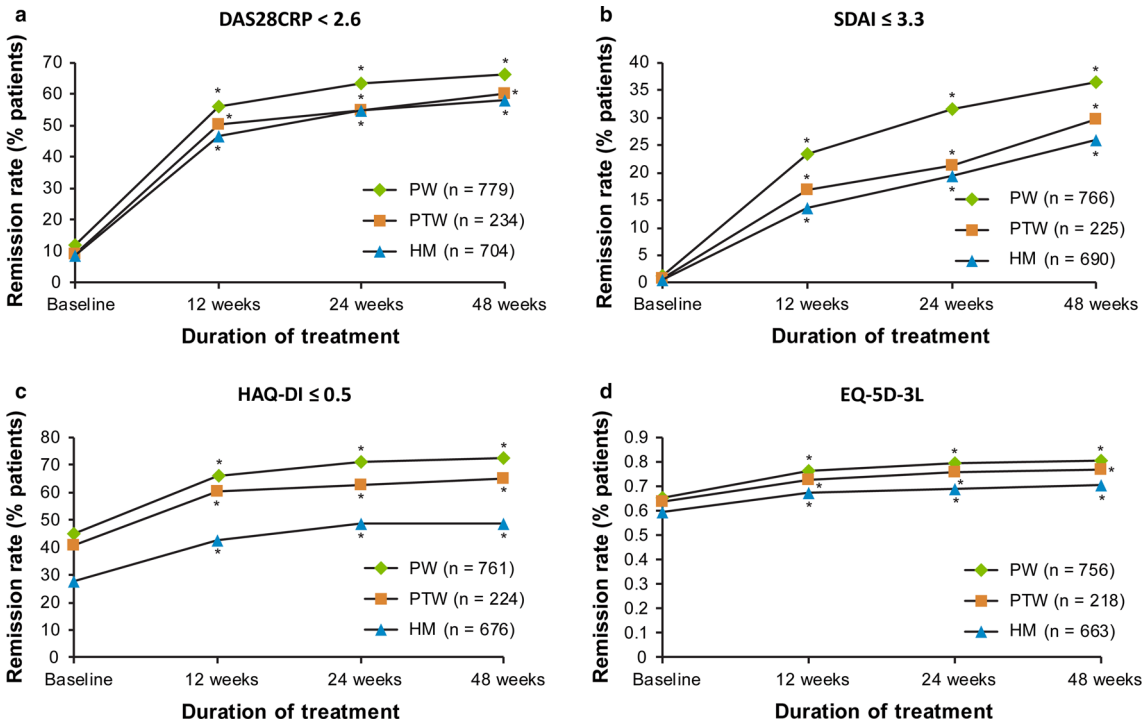


Fig. 2 Remission rates based on DAS28CRP, SDAI, and HAQ-DI along with EQ-5D-3L scores. *CRP* C-reactive protein, *DAS28CRP* Disease Activity Score based on 28 joints and CRP, *EQ-5D-3L* EuroQol 5-Dimension 3-Level, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *HM* homemaker, *PTW* part-time worker, *PW* paid worker, *SDAI* Simplified Disease Activity Index (to assess functional response). $^{*}p < 0.0001$; the Fisher exact test was used to compare remission rate at baseline and at 12, 24, and 48 weeks. Data were analyzed using the last observation carried forward method. The Wilcoxon signed-rank test was used to compare EQ-5D-3L at baseline and at 12, 24, and 48 weeks

Japan has not been studied until now. ANOUVEAU was the first study to evaluate the effect of ADA on RA-related WPAI as well as the association between changes in disease activity and outcomes in routine rheumatology care in Japan. Results demonstrated that treatment with ADA significantly improved remission rates as defined by several disease activity measures (DAS28CRP, SDAI, and HAQ-DI scores), and thereby may have improved work productivity (including absenteeism, presenteeism, and OWI) and AI over 48 weeks. Correlation analysis showed a trend toward a positive linear correlation between improvement in WPAI/RA domain scores and decrease in disease activity at week 48, except for absenteeism in PTWs. The more prominent improvement in work productivity was noted in PWs compared with PTWs. In general, despite differences in work culture and baseline work productivity scores, these results are consistent with findings from studies evaluating the effect of ADA on work and household productivity in other countries [19, 28]. Treatment with ADA also resulted in substantial improvements in health-related QoL (as assessed by EQ-5D-3L scores) in PWs and HMs. Additionally, correlation analysis suggested that improvement in WPAI domain scores is associated with better QoL.

The safety profile in this large, real-world study was consistent with previous reports, and no new safety signals were identified [39, 41]. Serious adverse events occurred in 5.23% of patients in this 48-week study, which is similar to the results of a previously reported ADA post-marketing surveillance study in Japan (4.5% at week 28, $n = 7740$ patients) [39].

In patients with longstanding RA, evidence indicates that work disability is associated with

Table 2 Correlations between WPAI/RA domain scores and clinical responses at 48 weeks

WPAI/RA domains	Clinical responses			
	DAS28CRP *r*	SDAI *r*	HAQ-DI *r*	EQ-5D-3L *r*
PW				
Absenteeism	0.2138[a]	0.2213[a]	0.3023[a]	−0.1997[a]
Presenteeism	0.4520[a]	0.4235[a]	0.5675[a]	−0.4834[a]
OWI	0.4669[a]	0.4333[a]	0.5741[a]	−0.4888[a]
AI	0.5159[a]	0.4904[a]	0.6344[a]	−0.5235[a]
PTW				
Absenteeism	0.1150 ($p = 0.1318$)	0.0983 ($p = 0.2022$)	0.2350[b]	−0.0610 ($p = 0.4170$)
Presenteeism	0.4574[a]	0.4871[a]	0.5565[a]	−0.3624[a]
OWI	0.4043[c]	0.4154[a]	0.4950[a]	−0.3290[a]
AI	0.5045[a]	0.5328[a]	0.6516[a]	−0.4877[a]
HM				
AI	0.4473[a]	0.4327[a]	0.5500[a]	−0.5054[a]

For regression coefficient (*r*), Pearson product-moment was used to examine the correlations between WPAI/RA domains (absenteeism, presenteeism, OWI, and AI) and clinical responses (DAS28CRP, SDAI, HAQ-DI, and EQ-5D-3L)

AI activity impairment, *CRP* C-reactive protein, *DAS28CRP* Disease Activity Score based on 28 joints and CRP, *EQ-5D-3L*, EuroQol 5-Dimension 3-level, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *HM* homemaker, *OWI* overall work impairment, *PTW* part-time worker, *PW* paid worker, *r* regression coefficient, *RA* rheumatoid arthritis, *SDAI* Simplified Disease Activity Index (to assess functional response), *WPAI/RA* RA-related work productivity and activity impairment

[a] $p < 0.0001$ indicates significance

[b] $p = 0.0015$

[c] $p = 0.0033$

disease activity and duration of RA, as well as decreased physical function [42–44]. Therefore, the importance of achieving and maintaining early remission cannot be understated. In the present study, PWs at high risk of work disability showed significantly improved WPAI outcomes after treatment with ADA, as assessed by widely used WPAI/RA domain scores (absenteeism, presenteeism, OWI, and AI) [45, 46]. Significant decreases in DAS28CRP obtained in this real-world setting were consistent with those reported in clinical trials of 24- to 52-week duration, as well as a 24-week post-marketing surveillance study conducted in Japan [27, 39, 47, 48]. Importantly, in the present large-scale study, improvements in WPAI/RA showed a weak to moderately strong positive linear correlation with improvement in disease activity, extending the findings from a previous small-scale study assessing the effects of TNF-α antagonists on DAS28ESR and work productivity in 42 patients [15].

Presenteeism and OWI in PWs significantly improved at weeks 12 and 24 compared to PTWs (Fig. 1). At baseline, RA duration was shorter and MTX dose was higher in PWs (compared to PTWs or HMs; Table 1). Since shorter RA duration and higher MTX dose are associated with increased ADA efficacy [39], such baseline differences may in part explain better outcomes in WPAI scores (especially in presenteeism and OWI) in PWs over PTWs.

Table 3 Association between change in WPAI/RA domain scores and baseline characteristics in PW group

WPAI/RA domains vs. clinical characteristics at week 48 in PWs ($n = 825$)		Biologic naïve/exposed		MTX combination (+)/(−)		MTX dose (mg/week)		RA duration (years)		Age (years)	
		Naïve ($n = 687$)	Exposed ($n = 138$)	MTX+ ($n = 761$)	MTX− ($n = 64$)	≤8 ($n = 342$)	>8 ($n = 419$)	≤2 ($n = 354$)	>2 ($n = 431$)	<50 ($n = 357$)	≥50 ($n = 468$)
Absenteeism (percentage of work time missed due to RA)	Baseline vs. week 48[a]	$p < 0.0001$	$p = 0.2122$	$p < 0.0001$	$p = 0.1729$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
	Changes from baseline[b]	−3.9	−1.4	−3.5	−3.6	−4.1	−3.1	−4.7	−2.7	−2.2	−4.6
		$p = 0.0262$		$p = 0.9805$		$p = 0.1158$		$p = 0.1293$		$p = 0.2432$	
Presenteeism (percentage of impairment while working due to RA)	Baseline vs. week 48[a]	$p < 0.0001$	$p = 0.0003$	$p < 0.0001$	$p = 0.0007$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
	Changes from baseline[b]	−20.5	−8.0	−19.1	−9.8	−19.5	−18.9	−20.7	−17.7	−18.6	−18.2
		$p < 0.0001$		$p = 0.0139$		$p = 0.8641$		$p = 0.1615$		$p = 0.9302$	
OWI (percentage of overall work impairment due to RA)	Baseline vs week 48[a]	$p < 0.0001$	$p = 0.0004$	$p < 0.0001$	$p = 0.0078$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
	Changes from baseline[b]	−20.7	−7.4	−19.4	−7.5	−20.0	−19.0	−21.3	−17.4	−19.1	−18.0
		$p < 0.0001$		$p = 0.0063$		$p = 0.6330$		$p = 0.1089$		$p = 0.6746$	

Table 3 continued

WPAI/RA domains vs. clinical characteristics at week 48 in PWs ($n = 825$)		Biologic naïve/exposed (+)/(−)		MTX combination (+)/(−)		MTX dose (mg/week)		RA duration (years)		Age (years)	
		Naïve ($n = 687$)	Exposed ($n = 138$)	MTX+ ($n = 761$)	MTX− ($n = 64$)	≤8 ($n = 342$)	>8 ($n = 419$)	≤2 ($n = 354$)	>2 ($n = 431$)	<50 ($n = 357$)	≥50 ($n = 468$)
AI (percentage of activity impairment due to RA)	Baseline vs. week 48[a]	$p < 0.0001$	$p = 0.0016$	$p < 0.0001$	$p = 0.0023$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$
	Changes from baseline[b]	−24.4	−7.8	−22.4	−12.9	−24.7	−20.5	−24.8	−19.4	−21.6	−21.7
		$p < 0.0001$		$p = 0.0302$		$p = 0.1228$		$p = 0.0173$		$p = 0.8930$	

AI activity impairment, *MTX* methotrexate, *OWI* overall work impairment, *PW* paid worker, *RA* rheumatoid arthritis, *WPAI/RA* RA-related work productivity and activity impairment

[a,b] The Wilcoxon signed-rank test was used to compare baseline and 48-week results, and the Wilcoxon rank sum test was used to compare the difference of the changes between two groups. Data were analyzed using the last observation carried forward method

In our evaluation of the relationship between baseline characteristics of PWs and WPAI/RA, we identified biologic-naïve status as a factor associated with improvement in all aspects of work productivity, including absenteeism, presenteeism, and OWI, as well as AI. Use of biologics has been shown to reduce absenteeism and improve presenteeism in previous studies [4, 49]. In the present study, estimated missed work days per year in PWs decreased significantly from 13.34 ± 38.89 days at baseline to 5.35 ± 23.44 days at week 48. These results are within the range presented in a systematic literature review evaluating randomized controlled trials showing the effect of biologics on the reduction in days of sick leave (ranging from 2.1 days in 4 weeks to 18.7 days in 2 years) [49]. A favorable effect of biologics on daily work-related productivity has been reported in Japan [15]. Concomitant use of MTX was also a factor associated with presenteeism, OWI, and AI, and shorter disease duration was another factor associated with AI for HMs in the present study. These factors were also identified as contributing to the effectiveness of ADA in the 24-week post-marketing surveillance study conducted in Japan. All subgroups in that study showed significant improvement, particularly biologic-naïve patients and those receiving concomitant MTX [39, 41]. Even in Western countries, treatment with ADA + MTX has been shown to reduce the risk of work impairment as exhibited by the improvement in presenteeism, OWI, and AI scores [50].

Although RA is known to be associated with increased cardiovascular morbidity and mortality [51], anti-TNF-α drugs have been suggested to reduce the cardiovascular burden in RA, possibly due to their potent anti-inflammatory effects [52]. The low incidence of cardiac disorders in the present study (one case) is consistent with these prior studies, although other biologics, such as abatacept (a selective inhibitor of T cell co-stimulation), may have a greater impact on decreasing cardiovascular risk [53].

This was a large, real-world study; nevertheless, it had some limitations. The

Table 4 Safety

Serious adverse event (MedDRA system organ class)[a]	Number of cases	Number of events (%)
Infections and infestations	31	37 (1.9)
Respiratory, thoracic, and mediastinal disorders	11	14 (0.7)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	14	17 (0.9)
General disorders and administration site conditions	4	5 (0.3)
Gastrointestinal disorders	3	3 (0.2)
Hepatobiliary system disorders	4	6 (0.3)
Injury, poisoning, and procedural complications	12	12 (0.6)
Skin and subcutaneous tissue disorders	3	4 (0.2)
Ocular disorders	4	4 (0.2)
Musculoskeletal and connective tissue disorders	2	2 (0.1)
Blood and lymphatic system disorders	2	2 (0.1)
Vascular disorders	2	2 (0.1)
Ear and labyrinth disorders	1	1 (0.1)
Cardiac disorders	1	1 (0.1)
Nervous system disorders	6	6 (0.3)
Psychiatric disorders	1	1 (0.1)
Reproductive and breast disorders	1	1 (0.1)
Clinical laboratory test	1	1 (0.1)

MedDRA Medical Dictionary for Regulatory Activities

[a] Total serious adverse event incidence rate: 5.23% (103/1968 cases)

differences in baseline HAQ-DI, EQ-5D-3L, and AI scores could be attributed to activity associated with employment status, as the dose of prednisolone, clinical disease activity measured by DAS28ESR, and SDAI were comparable at baseline between groups. Additionally, baseline characteristics of the patient population in this real-world study were heterogeneous in comparison to those of clinical trials in Japan [23, 26, 27, 39, 47, 48, 54]. Moreover, this study did not evaluate patients on the basis of comorbidity [54] and stage of disease, which could potentially impact the effectiveness of ADA.

CONCLUSIONS

ADA demonstrated significant, sustained improvements in RA-related WPAI in Japanese patients with RA. Further studies are needed to evaluate whether improved WPAI/RA scores are associated with a decreased risk of potential unemployment and financial impairment.

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Compliance with Ethics Guidelines. This study was a multi-institutional, prospective, noninterventional, observational study that conformed to the Good Post-marketing Study Practice (GPSP; Ministry of Health, Labour and Welfare ordinance). The study protocol was reviewed and approved in advance by the Pharmaceuticals and Medical Devices Agency, Japan. For this reason, no ethical review by the individual facilities participating in the study was conducted. Because informed consent is not required for post-marketing observational studies that are conducted under the GPSP in Japan, the present study did not solicit informed consent from the patients.

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

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