J Chin Med Assoc

ORIGINAL ARTICLE

Health-related quality of life improvement by adalimumab therapy in patients with rheumatoid arthritis in Taiwan: A nationwide prospective study

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Abstract

Background: To determine the effects of adalimumab on health-related quality of life (HRQoL) in Taiwanese patients with moderate-to-severe rheumatoid arthritis (RA) (NCT02616380).

Methods: During a 24-week observational period, 100 biologic-naive patients with RA received 40 mg adalimumab subcutaneously, every 2 weeks. The primary endpoint was a change in Health Assessment Questionnaire–Disability Index (HAQ-DI) score at 24 weeks. The secondary endpoints included change in HAQ-DI at week 12, number and percentage of patients achieving a meaningful improvement in HAQ-DI at weeks 12 and 24, and changes in the 36-Item Short Form Health Survey (SF-36), EuroQol 5-dimension 3-level version (EQ-5D-3L) index, and Work Productivity and Activity Impairment (WPAI) questionnaire scores at weeks 12 and 24.

Results: At weeks 12 and 24, mean changes in HAQ-DI from baseline were -0.34 ± 0.46 and -0.44 ± 0.59 (both $p < 0.001$), and clinically meaningful improvement in HAQ-DI was achieved by 60.4% and 59.6% of patients, respectively. SF-36, EQ-5D-3L index, and WPAI scores significantly improved ($p < 0.001$) from baseline to weeks 12 and 24. Exploratory analyses showed diabetes was significantly associated with changes in HAQ-DI, EQ-5D-3L, and WPAI scores whereas peptic ulcer correlated with changes in the SF-36 physical component summary T-score.

Conclusion: HRQoL improved after initiation of adalimumab therapy in Taiwanese patients with moderate-to-severe RA.

Keywords: Adalimumab; Health-related quality of life; Rheumatoid arthritis

1.INTRODUCTION

Rheumatoid arthritis (RA) is a debilitating, chronic autoimmune disease characterized by persistent synovial inflammation, articular damage, and cartilage breakdown in peripheral joints.[1] If inadequately treated, continual joint damage can have detrimental effects on patient function and quality of life.[2] Thus, controlling disease activity is important to lessen the disease-related burden on patients and healthcare systems. Current RA guidelines recommend a treat-to-target strategy with remission as primary therapeutic goal and low disease activity as an alternative.[3,4] In patients with newly diagnosed RA, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as methotrexate, sulfasalazine, and hydroxychloroquine, are the most widely used treatments. As disease advances, therapy with biologic DMARDs (bDMARDs) including adalimumab, golimumab, and certolizumab, is implemented stepwise.[3,4]

Since the early 2000s, bDMARDs have been used more frequently and started earlier in the disease course because of mounting evidence that the early use of biologics combined with csDMARDs provides greater radiographic and clinical improvements than the use of csDMARDs alone, especially in patients with high disease activity.[5–8] However, the high costs associated with bDMARDs and the chronic nature of RA have

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Conflicts of interest: Dr. Chang-Youh Tsai, an editorial board member at Journal of the Chinese Medical Association, had no role in the peer review process of or decision to publish this article. The other authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Journal of Chinese Medical Association. (2023) 86: 366-374.

Received March 16, 2022; accepted December 10, 2022.

doi: 10.1097/JCMA.0000000000000889.

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led stakeholders in countries with socialized healthcare systems, such as Taiwan, to scrutinize the cost-effectiveness of prolonged bDMARD therapy.[9–11] Hence, more evidence is being sought to ensure that utilization of health care resources benefits patients.[12]

The mainstay in evaluating treatment effects has been weighted composite indices combining objective measures, based on pathophysiology and disease/functional activity, and subjective measures, based on patient global assessment of health/disease, such as the American College of Rheumatology (ACR) response criteria and the Disease Activity Score in 28 joints (DAS28).[13] However, from a patient's perspective, changes in these indices have little meaning because personal treatment goals are mostly to improve quality of life and reduce pain and fatigue.[14,15] Therefore, a need arises for the evaluation of treatment effectiveness by integrating validated patient-reported outcomes (PROs) with physician-assessed measures.[16,17] PROs evaluate pain, physical function, well-being, sleep, fatigue, psychological distress, and ability to work and interact socially.[18,19] Eliciting responses directly from patients, these PROs truly reflect how patients perceive the effects of their current RA therapy and can thus be good indicators of disease activity.[20]

Adalimumab, a fully humanized monoclonal antibody against tumor necrosis factor (TNF)-α, is an efficacious anti-inflammatory agent in RA, psoriatic arthritis, ankylosing spondylitis, and Crohn's disease.[21] The combination of adalimumab and methotrexate is well tolerated and more effective than monotherapy with either agent at treating early RA.[6] To date, there have been few real-world studies investigating the effects of adalimumab on health-related quality of life (HRQoL) and the ability to work.[22] In Taiwan, reimbursement of bDMARDs is unique, in that it is strongly influenced by the National Health Insurance (NHI) program, wherein therapies are chosen based on available budget and patient preference, apart from treatment efficacy. Herein, we present the real-world outcomes of adalimumab therapy in terms of HRQoL among biologic-naive Taiwanese patients with moderate-to-severe RA.

2.METHODS

2.1. Study design and participants

We conducted a prospective, observational study (ROCKI; NCT02616380) assessing the clinical effects of adalimumab on HRQoL and work productivity in Taiwanese patients with moderate-to-severe RA. The study protocol was approved by the respective Institutional Review Boards of participating centers (Supplementary Table S1, http://links.lww.com/JCMA/A181). Study subjects were enrolled from October 10, 2015 to January 31, 2017 and recruited from regular clinic settings in rheumatology. Patients aged ≥18 years were eligible for study inclusion if they had moderate-to-severe RA (ie, DAS28–erythrocyte sedimentation rate or DAS28–C-reactive protein >3.2), were naive to bDMARDs and were willing to start adalimumab at the baseline visit. Patients were excluded if they had active hepatitis B or tuberculosis, an infection requiring anti-infectives in the 30 days (intravenous) or 14 days (oral) before the baseline visit, or a history of invasive infection (eg, human immunodeficiency virus, aspergillosis). All patients provided written informed consent before study entry. The decision to prescribe adalimumab for these patients was in line with the usual practice of participating clinics and not dictated by the need for study inclusion. Concurrent use of csDMARDs was allowed over the course of the study.

In total, 100 patients entered the study to receive 24 weeks of therapy with 40 mg of adalimumab every other week. We calculated this sample size to detect a clinically meaningful improvement of –0.22 in the Health Assessment Questionnaire–Disability Index (HAQ-DI) score, assuming an α of 0.05 and a power of 80% for a two-sided test.

2.2. Assessment instruments

Four PRO instruments were used to assess changes in HRQoL: HAQ-DI, 36-Item Short Form Health Survey (SF-36), EuroQol 5-dimension 3-level version (EQ-5D-3L) questionnaire, and Work Productivity and Activity Impairment (WPAI) questionnaire. The SF-36 included two components, the physical component summary (PCS) T-score and the mental component summary (MCS) T-score. Three additional instruments were used to measure the following: utilization of health care resources (health care resource use [HCRU] questionnaire), patient perception of changes in the disease (Patient Global Impression of Change [PGIC] questionnaire), and treatment satisfaction following therapy (Treatment Satisfaction Questionnaire for Medication [TSQM]). The Chinese versions of the SF-36,[23] EQ-5D-3L,[24] and WPAI[25] instruments have been previously validated. Permission to use the translated versions was acquired from their respective authors.

2.3. Outcome measures

Patient demographics and clinical characteristics, including age, sex, marital status, medical insurance type, DAS28 score, and comorbidities, were collected at the baseline visit. Data on quality of life, functioning, work productivity, treatment satisfaction, impression of change, and HCRU were collected at baseline, week 12, and week 24 with questionnaires.

The primary endpoint of the study was the change in HAQ-DI score at 24 weeks after starting adalimumab. Secondary endpoints of the study included change in HAQ-DI score at 12 weeks, the number and percentage of patients achieving a clinically meaningful improvement in HAQ-DI score (ie, reduction ≥0.22) at weeks 12 and 24, and change in SF-36 PCS and MCS T-scores, EQ-5D-3L index, and WPAI scores at weeks 12 and 24 following treatment initiation.

Exploratory data analyses evaluated HCRU, changes in treatment satisfaction and patient impression of disease change, associations between baseline DAS28 scores and PROs, associations between changes in DAS28 score and changes in PROs at weeks 12 and 24, and predictors of PRO changes.

2.4. Safety analysis

Adverse events (AEs) occurring over the course of the study were coded using the Common Terminology Criteria for Adverse Events. The incidence and percentage of AEs and serious AEs (SAEs) within each indication were summarized by System Organ Class, with a further summary by severity and relatedness (causality).

2.5. Statistical analysis

Statistical analysis was performed with SAS software v9.3 (SAS Institute, Cary, NC) via SAS Enterprise Guide v6.1. Unless otherwise specified, we provided results as descriptive statistics. We presented categorical data as frequencies and proportions and continuous variables as means with standard deviations.

Changes in HAQ-DI score at weeks 12 and 24 were assessed using paired *t* tests, without adjustment for baseline disease severity per DAS28 score in primary analyses and with adjustment in sensitivity analyses by analysis of variance. Mean changes in the SF-36 PCS and MCS T-scores, EQ-5D-3L index, and WPAI scores at weeks 12 and 24 were also assessed with paired *t* tests. Changes in treatment satisfaction at weeks 12 and 24 were assessed using the Wilcoxon signed-rank test. Treatment satisfaction was also dichotomized and analyzed over time using

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the Cochran-Armitage test of trends. All statistical tests were two-tailed with a significance level of 0.05.

Separate bivariate linear regression models were used to find associations between the baseline DAS28 score and each of the PROs (HAQ-DI score, SF-36 PCS and MCS T-scores, EQ-5D-3L index, and WPAI scores), as well as associations between changes in DAS28 score and changes in each of the PROs at 12 and 24 weeks. A multivariate, generalized linear model was used to assess the association between selected baseline parameters (ie, age, sex, DAS28 score, and comorbidities) and changes in PROs at 12 and 24 weeks.

3.RESULTS

3.1. Baseline patient characteristics

Table 1 summarizes the baseline characteristics of the study cohort. The study population (N = 100) had a mean age of 54.0 ± 12.2 years. Study subjects were mostly female (87%) with high disease activity, based on a mean DAS28 score of 6.3 ± 0.9.

Comorbidities were found in 22% of patients, including diabetes (9%), peptic ulcer disease (PUD; 6%), and peripheral vascular disease (6%). Nearly all participants (96%) concurrently used csDMARDs: 84% methotrexate, 57% hydroxychloroquine, and 36% sulfasalazine. The majority (57%) also used steroids while another 30% used nonsteroidal anti-inflammatory drugs (NSAIDs). Three patients were lost to follow-up before week 12.

Table 1

Summary of patient demographics and clinical characteristics at baseline

Characteristic	Participants (N = 100)
Age (y)	
Mean (SD)	54.0 (12.2)
Sex, n (%)	
Female	87 (87.0)
Male	13 (13.0)
Marital status, n (%)	
Married	87 (87.0)
Unmarried	13 (13.0)
Medical insurance type, n (%)	
National/public insurance	95 (95.0)
Private insurance	43 (43.0)
Employer benefits	2 (2.0)
Other	1 (1.0)
No insurance	2 (2.0)
DAS28 score	
Mean (SD)	6.3 (0.9)
DAS28 categorization, n (%)[a]	
Remission	0 (0.0)
Low disease activity	0 (0.0)
Moderate disease activity	9 (9.0)
High disease activity	91 (91.0)
Patients with comorbidities, n (%)	
Yes	22 (22.0)
No	78 (78.0)
Comorbidities, n (%)	
Congestive heart failure	1 (1.0)
Peripheral vascular disease	6 (6.0)
Peptic ulcer disease	6 (6.0)
Mild liver disease[b]	5 (5.0)
Diabetes	9 (9.0)

DAS28 = Disease Activity Score for 28 joints.

[a] DAS28 categorization is defined as follows: remission, ≤2.6; low disease activity, 2.6-3.2; moderate disease activity, 3.3-5.1; high disease activity, >5.1.

[b] As assessed and judged by the investigators.

3.2. Change in disease activity and PROs

Disease activity of the cohort significantly improved at 12 and 24 weeks after starting adalimumab therapy. The mean reductions in the DAS28 score from baseline were 1.96 ± 1.21 at 12 weeks and 2.52 ± 0.92 at 24 weeks (both $p < 0.001$).

Similarly, significant PRO improvements were observed at 12 and 24 weeks (Table 2). Mean reductions in HAQ-DI score from baseline were 0.34 ± 0.46 and 0.44 ± 0.59 at weeks 12 and 24, respectively (both $p < 0.001$). Aside from the HAQ-DI score, the SF-36 PCS and MCS T-scores, and EQ-5D-3L index significantly improved from baseline to weeks 12 and 24 (Fig. 1), as well as the WPAI scores.

Meanwhile, the proportion of patients achieving clinically meaningful improvement in HAQ-DI score, defined as a reduction of ≥0.22, was 60.4% at week 12 and 59.6% at week 24.

3.3. Exploratory analyses

3.3.1. PGIC and treatment satisfaction

After starting adalimumab therapy, 90.6% of patients at week 12 and 92.5% at week 24 perceived improvement in their disease, based on the PGIC questionnaire (Table 3). Likewise, based on the TSQM, patients were more satisfied with RA treatment at 12 and 24 weeks than they were at baseline, specifically in terms of how treatment had improved morning stiffness, mobility, and capability to perform activities of daily living (Supplementary Table S2, http://links.lww.com/JCMA/A181). Furthermore, the proportion of patients who were very or somewhat satisfied with their treatment was only 28.8% at baseline but became 80.3% at week 12 and 86.2% at week 24.

3.3.2. HCRU after the initiation of adalimumab

In the 24 weeks after starting adalimumab therapy, patients primarily visited their rheumatologist for checkups; only one emergency department visit was recorded (Supplementary Table S3, http://links.lww.com/JCMA/A181). The most common procedures they underwent during these checkups were blood tests and chest radiography, which were part of routine clinical practice after starting biologics. None of the subjects underwent surgery, and only one subject had ≥1 hospitalization.

3.3.3. Predictors of disease activity among PROs

Table 4 presents results from the bivariate models for assessing the association between PROs and DAS28 scores. Generally, the DAS28 score had a positive correlation with the HAQ-DI score and WPAI scores but had a negative correlation with the SF-36 PCS and MCS T-scores and EQ-5D-3L index. At baseline, the HAQ-DI score, SF-36 PCS T-score, EQ-5D-3L index, and WPAI activity impairment score were each significantly predictive of the DAS28 score. At week 12, change in SF-36 PCS T-score also significantly predicted change in DAS28 score (p = 0.044). A 1-point increase in SF-36 PCS T-score corresponded to a 0.94-point reduction in DAS28 score. Meanwhile, at week 24, change in DAS28 score was significantly predicted by changes in SF-36 PCS T-score (p = 0.004), WPAI work productivity impairment score (p = 0.034), and WPAI activity impairment score (p = 0.012). A 1-point increase in each of the SF-36 PCS T-score, WPAI work productivity impairment score, and WPAI activity impairment score corresponded respectively to a 2.17-point decrease, 0.075-point increase, and 0.071-point increase in DAS28 score.

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Table 2

Mean changes in PROs from baseline to week 12 and week 24

PROs	Mean (SD)	95% CI	Evaluable subjects, n	Subjects with missing data, n (%)[a]	*p*[b]
HAQ-DI					
Baseline	1.06 (0.72)	0.92 to 1.20	100	0 (0.0)	–
Change at week 12	–0.34 (0.46)	–0.43 to –0.25	96	1 (1.0)	<0.001
Change at week 24	–0.44 (0.59)	–0.56 to –0.32	94	3 (3.1)	<0.001
SF-36 PCS T-score					
Baseline	39.05 (7.82)	37.50 to 40.60	100	0 (0.0)	–
Change at week 12	5.72 (5.78)	4.54 to 6.90	95	2 (2.1)	<0.001
Change at week 24	8.09 (7.13)	6.63 to 9.56	93	4 (4.1)	<0.001
SF-36 MCS T-score					
Baseline	38.88 (7.81)	37.33 to 40.43	100	0 (0.0)	–
Change at week 12	3.67 (7.94)	2.05 to 5.29	95	2 (2.1)	<0.001
Change at week 24	5.85 (7.99)	4.21 to 7.50	93	4 (4.1)	<0.001
EQ-5D-3L					
Baseline	0.35 (0.33)	0.29 to 0.42	100	0 (0.0)	–
Change at week 12	0.23 (0.30)	0.17 to 0.30	96	1 (1.0)	<0.001
Change at week 24	0.33 (0.38)	0.26 to 0.41	94	3 (3.1)	<0.001
WPAI work productivity impairment (%)					
Baseline	55 (26)	47.4 to 63.5	44	56 (56.0)	–
Change at week 12	–18.2 (23.3)	–25.7 to –10.8	40	57 (58.8)	<0.001
Change at week 24	–19.3 (22.6)	–26.7 to –12.0	39	58 (59.8)	<0.001
WPAI activity impairment (%)					
Baseline	57 (25)	51.8 to 61.7	99	1 (1.0)	–
Change at week 12	–14.3 (22.0)	–18.8 to –9.8	95	2 (2.1)	<0.001
Change at week 24	–24.2 (25.1)	–29.4 to –19.0	92	5 (5.2)	<0.001

CI = confidence interval; EQ-5D-3L = EuroQol 5-dimension 3-level version; HAQ-DI = Health Assessment Questionnaire–Disability Index; MCS = mental component summary; PCS = physical component summary; PRO = patient-reported outcome; SD = standard deviation; SF-36 = 36-Item Short Form Health Survey; WPAI = Work Productivity and Activity Impairment.

[a] Denominators for percentages are N = 100 at baseline and n = 97 at 12 and 24 weeks.

[b] *p* from paired *t* test for mean change from baseline.

3.3.4. Predictors of PRO change

The effects of baseline patient characteristics, including age, sex, DAS28 score, and comorbidities, on changes in PROs at weeks 12 and 24 after adalimumab initiation are presented in Table 5. Age, baseline DAS28 score, and presence of either PUD or diabetes were independent predictors of change in at least one set of PROs. The presence of diabetes significantly predicted greater improvements in the following PROs at 12 and 24 weeks: HAQ-DI score (week 12: $p = 0.034$; week 24: $p < 0.001$), EQ-5D-3L index (week 12: $p = 0.009$; week 24: $p < 0.001$), and WPAI activity impairment (week 12: $p = 0.018$; week 24: $p = 0.009$). Meanwhile, presence of PUD was a significant predictor of greater worsening in SF-36 PCS T-score at 12 weeks ($p = 0.034$) and 24 weeks ($p = 0.031$).

3.4. Safety

One SAE and one AE were each reported in unique patients during the study period. Both events occurred during the initial visit after the drug administration. The SAE resulted in hospitalization but was deemed unrelated to adalimumab. The AE reported as "allergy on skin" did not lead to any change in the patient's adalimumab dosage.

4.DISCUSSION

Randomized controlled trials (RCTs) have established that adalimumab therapy significantly reduces the signs and symptoms of active RA in patients with either inadequate response or intolerance to csDMARDs.[6,21] In addition to these previously reported clinical benefits, our real-world cohort study shows that over 24 weeks of adalimumab therapy, PROs significantly improved from baseline, including physical functioning (HAQ-DI score), overall HRQoL (SF-36 scores and EQ-5D-3L index), and work and activity performance (WPAI scores) in biologic-naive Taiwanese patients with moderate-to-severe RA. Furthermore, the improvements in SF-36 PCS T-score and WPAI scores significantly predicted the improvements in disease activity (DAS28 score) after 24 weeks of adalimumab treatment.

Functional impairment and inability to participate in daily activities have significantly reduced the HRQoL in RA.[2] Therefore, restoring physical function has been a crucial treatment outcome sought by RA patients.[26,27] Using the HAQ-DI questionnaire, we demonstrate that at 12 and 24 weeks from adalimumab initiation, the improvement in patient perception of physical function was significant not only statistically but also clinically, based on the high proportion of patients achieving the clinically meaningful score improvement. Along with the recovery of physical function, we illustrate significant improvements in other HRQoL domains and treatment satisfaction at weeks 12 and 24. However, because 84% of our cohort received methotrexate therapy at baseline, the observed PRO improvements may reflect the known benefits of combination therapy with adalimumab and methotrexate. Accordingly, the magnitude of PRO change over 24 weeks of adalimumab monotherapy in our real-world, community-based study is comparable to those described for adalimumab plus background methotrexate therapy in multiple RCTs, such as PREMIER, OPTIMA, MONARCH, RA-BEAM, and ORAL Standard, as well as real-world studies.[6,22,28–32]

Previous studies have reported a correlation between improvements in PROs and improvements in disease activity. In a cross-sectional study, RAPID3, RADAI RAPID4, RAPID5, and VAS-global moderately correlated with the DAS28 score.[33] In the phase 3 PREMIER trial, HAQ-DI, SF-36 PCS, SF-36 MCS, SF-6D, FACIT-F, and HUI3 scores were significantly

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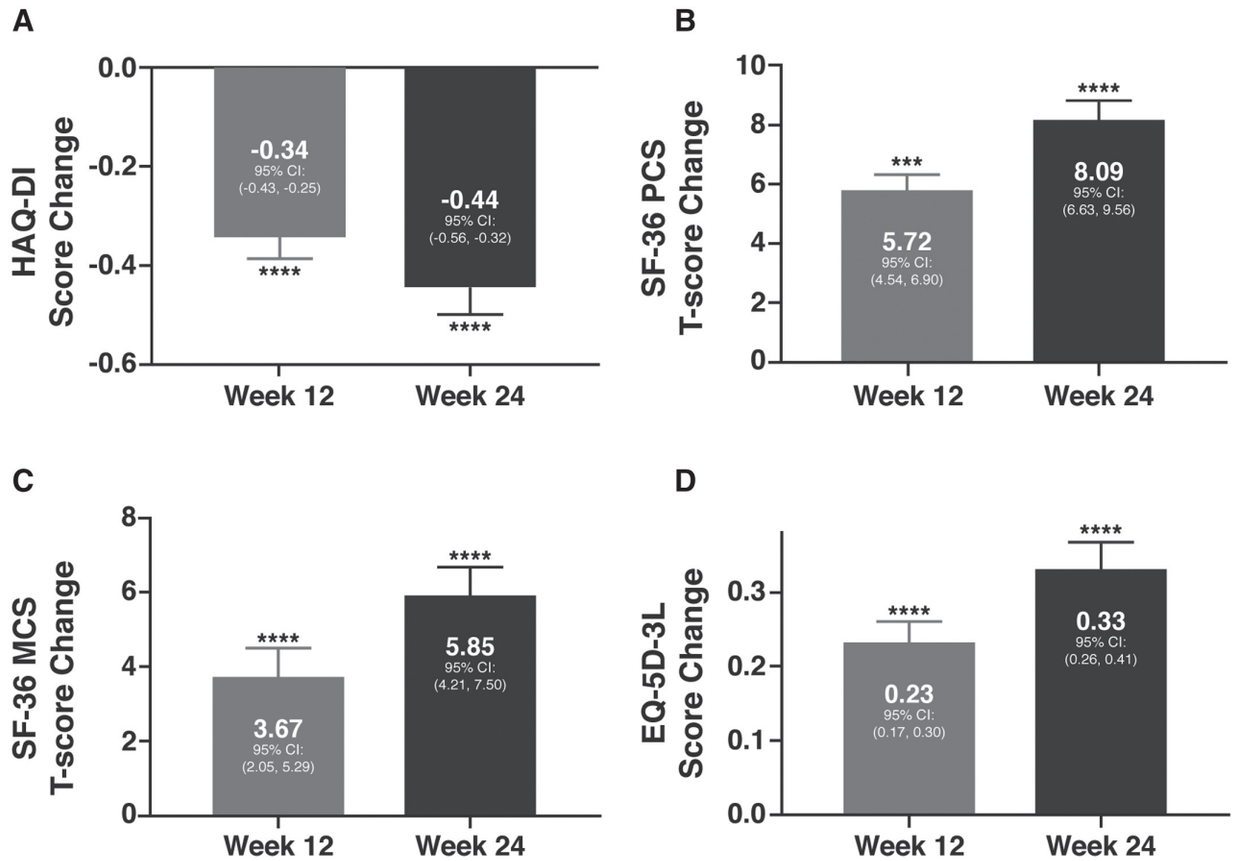

Fig. 1 Mean ± SEM changes from baseline in (a) HAQ-DI, (b) SF-36 PCS, (c) SF-36 MCS, and (d) EQ-5D-3L scores at 12 and 24 weeks after initiation of adalimumab therapy (n = 97). Change from baseline: $^{***}p < 0.001$, $^{****}p < 0.0001$. CI = confidence interval; EQ-5D-3L = EuroQol 5-dimension 3-level version; HAQ-DI = Health Assessment Questionnaire–Disability Index; SF-36 MCS = 36-Item Short Form Health Survey, Mental Component Summary; SEM = standard error of the mean; SF-36 PCS = 36-Item Short Form Health Survey, Physical Component Summary.

Table 3

Patient Global Impression of Change at 12 and 24 weeks after initiation of adalimumab (n = 97)

PGIC in RA since initiation of adalimumab	Observed population, n (%)
At 12 wks	
Very much better	0 (0.0)
Much better	41 (42.7)
A little better	46 (47.9)
No change	8 (8.3)
A little worse	1 (1.0)
Much worse	0 (0.0)
Very much worse	0 (0.0)
Missing	1 (1.0)
At 24 wks	
Very much better	11 (11.7)
Much better	55 (58.5)
A little better	21 (22.3)
No change	6 (6.4)
A little worse	1 (1.1)
Much worse	0 (0.0)
Very much worse	0 (0.0)

PGIC = Patient Global Impression of Change; RA = rheumatoid arthritis.

associated with a clinical response by ACR response criteria.[27] Our present study demonstrates that improvements in HRQoL after adalimumab initiation also significantly correlated with improvements in DAS28 score. The strongest predictive effects were observed with the SF-36 PCS T-score and WPAI activity impairment score while the HAQ-DI score, ED-5D-3L index, and WPAI work productivity impairment score exhibited moderate effects. The ability of these PROs to predict clinical response over the course of adalimumab therapy highlights their value in complementing clinician-driven instruments for routine monitoring of patient well-being and therapeutic response. Moreover, attaining acceptable scores in these PROs may become an alternative goal during adalimumab therapy for RA.

Baseline clinical and demographic characteristics have influenced RA remission rates and DAS28 scores,[34–38] as well as HRQoL changes,[33,39,40] in previous reports. In our study, baseline DAS28 score, age, sex, presence of PUD, and presence of diabetes influenced several PRO scores. Generally, a higher baseline DAS28 score predicted a greater decrease in HAQ-DI score while increased age predicted greater reductions in SF-36 MCS T-score and EQ-5D-3L index.

Comorbidities influenced PROs in our cohort despite their low prevalence. Based on prior literature, the presence of coexisting diseases has led to worse PROs in RA, possibly due to the limited ability of subjective indices to discriminate between similar painful or prostrating conditions.[41]

In our study, the presence of PUD was predictive of a greater decrease in SF-36 PCS T-score and a greater increase in WPAI activity impairment score. The reported incidence of PUD in

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Table 4

Association between PROs and DAS28 score

	Association with DAS28 score at baseline			Association with DAS28 change at week 12			Association with DAS28 change at week 24		
PROs	**Parameter[a] (SE)**	**95% CI**	***p***	**Parameter[a] (SE)**	**95% CI**	***p***	**Parameter[a] (SE)**	**95% CI**	***p***
HAQ-DI	0.352 (0.070)	0.214 to 0.489	<0.001	0.003 (0.037)	–0.070 to 0.076	0.929	0.073 (0.063)	–0.051 to 0.196	0.251
SF-36 PCS T-score	–3.167 (0.794)	–4.722 to –1.611	<0.001	–0.941 (0.467)	–1.856 to –0.025	0.044	–2.171 (0.757)	–3.655 to –0.686	0.004
SF-36 MCS T-score	–0.487 (0.852)	–2.156 to 1.182	0.567	–0.977 (0.669)	–2.289 to 0.335	0.145	–0.941 (0.885)	–2.676 to 0.794	0.288
EQ-5D-3L	–0.102 (0.034)	–0.169 to –0.035	0.003	–0.025 (0.025)	–0.075 to 0.024	0.316	–0.079 (0.042)	–0.162 to 0.004	0.061
WPAI work productivity impairment	–0.067 (0.049)	–0.164 to 0.029	0.171	–0.020 (0.031)	–0.080 to –0.040	0.522	0.075 (0.035)	0.006 to 0.144	0.034
WPAI activity impairment	0.068 (0.027)	0.015 to 0.121	0.012	0.011 (0.018)	–0.025 to 0.046	0.555	0.071 (0.028)	0.016 to 0.127	0.012

CI = confidence interval; DAS28 = Disease Activity Score for 28 joints; EQ-5D-3L = EuroQol 5-dimension 3-level version; HAQ-DI = Health Assessment Questionnaire–Disability Index; MCS = mental component summary; PCS = physical component summary; PRO = patient-reported outcome; SE = standard error; SF-36 = 36-Item Short Form Health Survey; WPAI = Work Productivity and Activity Impairment.
[a] Parameters shown are β-coefficients from bivariate regression analyses.

RA has been three to four times that of the general population,[42] suggesting that RA patients may be more susceptible to PUD, irrespective of the effects of RA therapy.[43] We speculate that in our cohort, HRQoL improvements among RA patients with PUD were dampened due to possible NSAID use, which may delay the healing of peptic ulcers.[44,45] Almost one-third of our participants were concurrently taking NSAIDs while others may have been taking these medications before study entry. Additionally, in our study, adalimumab was administered for a duration (24 weeks) that may not have sufficiently overcome this dampening effect of PUD on specific PROs. However, because of the limited number of patients with PUD in the current study, any association between its presence and PRO changes following adalimumab treatment should be interpreted with caution. Notwithstanding this caveat, our findings still suggest that in most patients, PRO improvements may be seen as early as 24 weeks after adalimumab initiation.

Interestingly, in contrast to PUD, the presence of diabetes was a predictor of PRO improvement in this study, resulting in a greater decrease in HAQ-DI and WPAI activity impairment scores and a greater increase in SF-36 PCS T-score and EQ-5D-3L index. Insulin resistance (IR), a hallmark of diabetes, may be driven by chronic inflammation.[46] Hence, evidence has been emerging on the increased risk of IR, and possibly diabetes, in inflammatory arthritides such as RA, particularly during active disease, wherein circulating levels of proinflammatory cytokines such as TNF-α may be high.[47] Correspondingly, a growing number of clinical studies have evaluated the use of TNF-α inhibitors, including adalimumab, to treat IR and diabetes among patients with inflammatory arthritides.[47] In our study, the association between PRO improvements and diabetes may be a reflection of this potential antidiabetic effect of adalimumab.

This study provides valuable PRO profiles of RA patients receiving adalimumab in a real-world setting in Taiwan. Our results are comparable to those of the adalimumab arms in RCTs as well as adalimumab-treated RA cohorts in real-world studies from Western countries, which have demonstrated improvements in HRQoL and work productivity.[48,49] A previous cohort study by Chen et al. (2018) involving 330 RA patients in Taiwan has also shown statistically significant and clinically meaningful improvements in SF-36 PCS and MCS scores, as well as the global quality of life scores, after treatment with bDMARDs.[22] Furthermore, significant deterioration of HRQoL was observed following treatment reduction or discontinuation in this study, wherein adalimumab constituted 30.6% of biologic therapy.[22]

The costs attributable to RA in Western nations have been well characterized.[50] Despite its clinical benefits, adalimumab therapy entails higher costs than conventional RA therapies and may add to the significant financial burden of RA, especially for patients requiring continuous treatment. In Taiwan, the NHI program substantially reduces this burden through the provision of universal health care coverage for Taiwanese citizens, thus increasing adherence to adalimumab therapy. The NHI program also helps in controlling the comorbidities of RA patients by covering other prescription drugs, dental services, Chinese medicines, home nurse visits, hospitalizations, and preventive medical services. These factors, albeit unquantified, may have contributed to the improvements in disease activity and PROs in our study.

Several limitations should be considered when interpreting the results of this study. The lack of a control group limits our ability to attribute the reported improvements to adalimumab therapy. The use of PROs may have introduced bias if patients had expected improvement with a new treatment. The observational design of our study and the exploratory nature of the subgroup analyses restrict the interpretation of the effects of comorbidities on HRQoL and any implications for clinical practice. Due to the study's length of follow-up, the sustainability of the reported improvements over the longer term is unknown. Nonetheless, because several well-established PRO instruments were applied to evaluate multiple health domains, our community-based study represents a comprehensive evaluation of patient-perceived effects of initiating adalimumab therapy for RA.

PROs are increasingly being used in combination with clinician-driven assessments to provide a more complete view of RA, including the effects of therapies on patient function and well-being. In the present study, we report improvements in HAQ-DI score, SF-36 PCS and MCS T-scores, EQ-5D-3L index, and WPAI scores among biologic-naive RA patients following initiation of adalimumab therapy in accordance with Taiwanese routine clinical practice. These findings show that PROs can complement clinician-reported outcomes and assist clinicians in delivering optimal therapy for RA patients.

ACKNOWLEDGMENTS

This study was funded by AbbVie Biopharmaceuticals GmbH Taiwan Branch. Editorial and writing support for the preparation of this manuscript was provided by MIMS Pte. Ltd., Taiwan Branch, and funded by AbbVie Biopharmaceuticals GmbH Taiwan Branch. AbbVie also participated in the interpretation, review, and approval of the publication. The content of this article and the opinions expressed within are those of the authors, and it was the decision of the authors to submit this manuscript for publication. The authors would like to acknowledge Daniel Furtner (AbbVie Pty Ltd., Sydney, Australia) and Jessie Chang (AbbVie Biopharmaceuticals GmbH Taiwan Branch) who helped manage the editorial support for this manuscript.

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Table 5

Association between baseline characteristics and changes in PRO scores

Baseline characteristic by PRO instrument	Association with change in PRO at week 12			Association with change in PRO at week 24		
	Parameter[a] (SE)	95% CI	*p*	Parameter[a] (SE)	95% CI	*p*
HAQ-DI score						
Age, continuous	0.002 (0.004)	–0.006 to 0.009	0.668	0.007 (0.005)	–0.002 to 0.016	0.140
Female sex (reference: male)	0.08 (0.137)	–0.189 to 0.349	0.560	0.115 (0.167)	–0.213 to 0.442	0.492
Baseline DAS28 score, continuous	–0.07 (0.052)	–0.173 to 0.033	0.182	–0.178 (0.062)	–0.298 to –0.057	0.004
With the comorbidity (reference: without)						
Congestive heart failure	–0.286 (0.508)	–1.282 to 0.711	0.574	0.421 (0.591)	–0.738 to 1.58	0.476
Peripheral vascular disease	0.261 (0.192)	–0.114 to 0.637	0.173	0.199 (0.223)	–0.238 to 0.637	0.372
Peptic ulcer disease	0.309 (0.205)	–0.093 to 0.711	0.132	0.502 (0.239)	0.034 to 0.97	0.036
Mild liver disease[b]	–0.002 (0.202)	–0.397 to 0.394	0.993	–0.027 (0.235)	–0.488 to 0.434	0.910
Diabetes	–0.359 (0.169)	–0.69 to –0.027	0.034	–0.889 (0.197)	–1.275 to –0.503	<0.001
SF-36 PCS T-score						
Age, continuous	0.031 (0.05)	–0.066 to 0.128	0.533	0.006 (0.06)	–0.112 to 0.123	0.925
Female sex (reference: male)	–0.451 (1.744)	–3.869 to 2.968	0.796	–0.035 (2.14)	–4.23 to 4.159	0.987
Baseline DAS28 score, continuous	0.119 (0.667)	–1.189 to 1.426	0.859	0.897 (0.789)	–0.651 to 2.444	0.256
With the comorbidity (reference: without)						
Congestive heart failure	11.026 (6.337)	–1.393 to 23.446	0.082	10.895 (7.573)	–3.947 to 25.737	0.150
Peripheral vascular disease	–1.531 (2.386)	–6.208 to 3.147	0.521	–1.258 (2.857)	–6.857 to 4.342	0.660
Peptic ulcer disease	–5.425 (2.557)	–10.436 to –0.413	0.034	–6.601 (3.058)	–12.595 to –0.607	0.031
Mild liver disease[b]	1.075 (2.516)	–3.856 to 6.006	0.669	2.963 (3.012)	–2.94 to 8.866	0.325
Diabetes	2.485 (2.11)	–1.651 to 6.62	0.239	6.446 (2.522)	1.503 to 11.39	0.011
SF-36 MCS T-score						
Age, continuous	–0.163 (0.068)	–0.296 to –0.029	0.017	–0.112 (0.07)	–0.248 to 0.024	0.108
Female sex (reference: male)	3.296 (2.387)	–1.383 to 7.974	0.167	2.872 (2.48)	–1.989 to 7.732	0.247
Baseline DAS28 score, continuous	0.894 (0.913)	–0.895 to 2.684	0.327	–0.744 (0.915)	–2.537 to 1.049	0.416
With the comorbidity (reference: without)						
Congestive heart failure	6.941 (8.673)	–10.056 to 23.939	0.423	3.624 (8.775)	–13.574 to 20.823	0.680
Peripheral vascular disease	–0.309 (3.266)	–6.711 to 6.092	0.925	–2.762 (3.31)	–9.25 to 3.726	0.404
Peptic ulcer disease	5.538 (3.5)	–1.322 to 12.397	0.114	–2.382 (3.544)	–9.328 to 4.563	0.501
Mild liver disease[b]	–0.945 (3.443)	–7.694 to 5.804	0.784	–5.907 (3.49)	–12.747 to 0.933	0.091
Diabetes	3.18 (2.888)	–2.481 to 8.84	0.271	3.905 (2.923)	–1.824 to 9.633	0.182
EQ-5D-3L score						
Age, continuous	–0.005 (0.003)	–0.01 to 0.00	0.050	–0.007 (0.003)	–0.014 to –0.001	0.020
Female sex (reference: male)	0.035 (0.088)	–0.137 to 0.207	0.688	0.056 (0.114)	–0.168 to 0.280	0.623
Baseline DAS28 score, continuous	0.04 (0.033)	–0.026 to 0.105	0.234	0.068 (0.042)	–0.014 to 0.151	0.104
With the comorbidity (reference: without)						
Congestive heart failure	0.322 (0.325)	–0.314 to 0.958	0.321	0.022 (0.405)	–0.772 to 0.816	0.957
Peripheral vascular disease	–0.06 (0.122)	–0.299 to 0.180	0.626	0.014 (0.153)	–0.285 to 0.314	0.925
Peptic ulcer disease	0.101 (0.131)	–0.155 to 0.358	0.439	–0.011 (0.164)	–0.332 to 0.310	0.946
Mild liver disease[b]	0.091 (0.129)	–0.162 to 0.344	0.480	–0.033 (0.161)	–0.349 to 0.282	0.836
Diabetes	0.284 (0.108)	0.072 to 0.496	0.009	0.474 (0.135)	0.210 to 0.739	<0.001
WPAI work productivity impairment score						
Age, continuous	0.003 (0.004)	–0.005 to 0.011	0.444	0.004 (0.004)	–0.003 to 0.012	0.267
Female sex (reference: male)	–0.008 (0.108)	–0.219 to 0.203	0.942	–0.022 (0.106)	–0.23 to 0.186	0.837
Baseline DAS28 score, continuous	0.05 (0.045)	–0.038 to 0.138	0.266	–0.004 (0.044)	–0.09 to 0.083	0.929
With the comorbidity (reference: without)						
Congestive heart failure	0.329 (0.22)	–0.102 to 0.76	0.135	0.172 (0.217)	–0.253 to 0.596	0.428
Peripheral vascular disease	–	–	–	–	–	–
Peptic ulcer disease	–0.083 (0.223)	–0.519 to 0.354	0.710	0.15 (0.219)	–0.28 to 0.58	0.494
Mild liver disease[b]	–0.086 (0.13)	–0.341 to 0.17	0.511	–0.114 (0.128)	–0.366 to 0.137	0.374
Diabetes	–0.337 (0.308)	–0.94 to 0.266	0.274	–	–	–
WPAI activity impairment score						
Age, continuous	0 (0.002)	–0.004 to 0.003	0.882	–0.001 (0.002)	–0.005 to 0.003	0.689
Female sex (reference: male)	–0.015 (0.065)	–0.143 to 0.114	0.824	0.022 (0.079)	–0.133 to 0.176	0.784
Baseline DAS28 score, continuous	0.007 (0.026)	–0.044 to 0.057	0.798	–0.036 (0.03)	–0.095 to 0.023	0.231
With the comorbidity (reference: without)						
Congestive heart failure	0.128 (0.24)	–0.344 to 0.599	0.595	0.212 (0.277)	–0.331 to 0.755	0.444
Peripheral vascular disease	0.097 (0.091)	–0.080 to 0.275	0.284	0.012 (0.104)	–0.193 to 0.216	0.911
Peptic ulcer disease	0.09 (0.097)	–0.100 to 0.280	0.352	0.248 (0.112)	0.029 to 0.467	0.027
Mild liver disease[b]	–0.189 (0.095)	–0.377 to –0.002	0.047	–0.089 (0.110)	–0.305 to 0.127	0.418
Diabetes	–0.189 (0.08)	–0.346 to –0.032	0.018	–0.239 (0.092)	–0.42 to –0.059	0.009

CI = confidence interval; DAS28 = Disease Activity Score for 28 joints; EQ-5D-3L = EuroQol 5-dimension 3-level version; HAQ-DI = Health Assessment Questionnaire–Disability Index; MCS = mental component summary; PCS = physical component summary; PRO = patient-reported outcome; SE = standard error; SF-36 = 36-Item Short Form Health Survey; WPAI = Work Productivity and Activity Impairment.

[a] Parameters shown are β-coefficients from multivariate regression analyses.

[b] As assessed and judged by the investigators.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A181.

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