

1.0 Abstract

Title: Real-World Outcome of Adalimumab on Rheumatoid Arthritis Patients in China

Keywords: Adalimumab, Rheumatoid Arthritis, HCRU, WPAI

Rationale and background:

Rheumatoid arthritis (RA) is a chronic, progressive autoimmune disease associated with a substantial comorbidity burden. Patients with RA have poorer survival experience and can lead to the deterioration of their health-related quality of life (HRQoL).

Given the requirement to keep a balance between effectiveness and cost containment to ensure that the available health resources are used in a cost-effective manner, there is an increasing demand for real-world evidence (RWE) from policy makers, regulators, providers and payers in the region to optimize spending and patient outcomes.

So far, there are no prospective study data available regarding adalimumab's impact on patients' quality of life (QoL) and healthcare resource utilization (HCRU) in China.

The goal of this study is to determine the QoL, HCRU and costs of the patients care in subjects with RA who are treated with adalimumab in China.

Research question and objectives:

The objective of this observational study is to assess the impact of adalimumab on HRQoL and work productivity in patients with RA in China.

Study design:

This was a prospective observational study involving 55 subjects enrolled at 8 different sites and observed for 12-week baseline and 24 weeks after initiation to assess the effect of adalimumab on HRQoL and work productivity in patients with RA in China.

To assess health and disability outcomes, the Health Assessment Questionnaire – Disability Index (HAQ-DI) at baseline, Week 12 and Week 24 after treatment initiation with adalimumab will be collected. In addition,

other patient-reported outcomes (PRO) of work activity and well-being, including the Work Productivity and Activity Impairment Questionnaire (WPAI), EuroQoL 5-Dimension (EQ-5D), and Short form-36 (SF-36), will also be collected.

Setting:

Clinical settings are preferred by the participating rheumatologists.

Subjects and study size, including dropouts:

Fifty-five patients diagnosed with RA were enrolled on 8 different sites in China.

Inclusion Criteria:

Patients meeting all of the following inclusion criteria at baseline were included:

1. Subject has a diagnosis of RA as defined by the 1987 revised American College of Rheumatology (ACR) classification criteria and/or the ACR/the European League against Rheumatism (EULAR) 2010 classification criteria (any duration since diagnosis)
2. Male or female subjects ≥ 18 years of age (local definition according to adalimumab label) who is in compliance with eligibility for adalimumab based on the local label
3. Patients with moderate to severe RA defined as Disease Activity Score in 28 Joints (DAS28) (erythrocyte sedimentation rate) or DAS28 (C-reactive protein) >3.2
4. Biologically treatment naïve and initiated adalimumab at baseline visit
5. Availability of clinical data of the previous 12 weeks prior to baseline
6. Ability to self-complete patient questionnaires
7. Subject must be able and willing to provide written informed consent and comply with the requirements of this study protocol

Exclusion Criteria:

Patients meeting any of the following exclusion criteria at baseline were excluded:

1. Patients who are pregnant or breast feeding at enrolment or wish to become pregnant in the next 24 weeks
2. Participation in any RA-related clinical trial at the time of enrolment, at baseline or at any point during the past 24 weeks prior to baseline

3. Patients, who in the clinician’s view, may not be able to accurately report their QoL or prior resource utilization
4. Patients, who in the clinician’s view, may not be able to adhere to adalimumab therapy over 24 weeks

Variables and data sources:

Primary Variable

- Change in HAQ-DI score at week 24 from baseline

Secondary Variable

- Change in other PROs (SF-36 domain scales, EQ-5D Index, Work Productivity and Activity Impairment Questionnaire [WPAI]) from baseline to weeks 12 and 24
- Change in HAQ-DI score at week 12 from baseline
- Number and percent of patients achieving a clinically meaningful improvement on the HAQ-DI, from baseline to weeks 12 and 24
- Healthcare resource utilization (HCRU) at baseline, 12 and 24 weeks

Exploratory Variable

- Difference of the change in HAQ-DI score from baseline to 24 weeks between as observed population and withdrawal population
- Change in patient satisfaction questions from baseline to weeks 12 and 24
- Patient’s impression of change at weeks 12 and 24 from baseline
- Association between disease severity and PROs
- Association between change in disease severity and change in PROs

Case Report Forms (CRFs) and patient questionnaires (PROs)

Collection of data includes but not limited to subject demographics, clinical history, comorbidities, spontaneous adverse events (AEs), and concomitant medications. The following questionnaires will be utilized to collect data directly from participating subjects:

- EQ-5D
- SF-36
- HAQ-DI

- WPAI
- HCRU
- Patient Global Impression of Change (PGIC)
- Patient Treatment Satisfaction Questions

Results:

- **Patient Demographics**

Mean age in RA patients was 50 years old (standard deviation (SD) \pm 13.4) with majority of patients in the age group of 55-64 and 45-54 years. Only 2% were RA elderly patients (75+ years old). Most RA patients in China were female (78.2%).

- **Clinical Characteristics**

Mean DAS28 was found to be 6.0 (SD \pm 1.4), with majority of patients comprising of high disease activity (69.1%). The proportion of comorbidities was low, with only mild liver disease (12.7%) reported in more than 10% of the population while peptic ulcer disease and cerebrovascular disease (5.5%, each) were the only comorbidities reported in more than 5% of the patient population.

- **Change in Health Assessment Questionnaire – Disability Index (HAQ-DI) at Weeks 24 and 12 after Initiation of Adalimumab**

Mean HAQ-DI scores change from baseline were -0.5 at week 24 and -0.4 at week 12 (p=0.0002 and p=0.0006, respectively). Clinical improvement in HAQ-DI, defined as improvement from baseline greater than -0.21, was achieved in 51.3% patients at week 24 and 50% patients at week 12.

- **Change in SF-36 Domain Scales at Weeks 24 and 12 after Initiation of Adalimumab**

Mean PCS T score change from baseline improved to 6.63 at 24 weeks and 5.99 at 12 weeks (p<.0001 vs baseline, respectively). Mean change from baseline in MCS T score improved to 6.91 at 24 weeks and 3.73 at 12 weeks (p=0.0017 vs baseline and p=0.0497 vs baseline, respectively).

- **Change in EQ-5D-3L Index at Weeks 24 and 12 after Initiation of Adalimumab**

Mean EQ-5D-3L index change from baseline were 0.22 (SD \pm 0.20) at 24 weeks and 0.16 (SD \pm 0.21) at 12 weeks (p<0.001, respectively).

- **Change in WPAI at Weeks 24 and 12 after Initiation of Adalimumab**

Significant mean changes from baseline in percentage of overall work impairment ($p=0.0137$) and activity impairment ($p=0.0001$) at 24 weeks was observed. The significant mean change from baseline at 12 weeks, was observed only for activity improvement ($p=0.0047$).

- **Patient Satisfaction Questions at Weeks 24 and 12 after Initiation of Adalimumab**

Approximately 39% of patients were “very satisfied” on how RA treatment improved morning stiffness in and around the joints at both 24 weeks (39.5%) and 12 weeks (39.1%) . Regarding satisfaction on how RA treatment improved mobility, more patients felt “somewhat satisfied” at week 24 than week 12 (52.6% vs. 50%, respectively) compared to “very satisfied” (34.2% vs. 32.6%, respectively), demonstrating improvement in this domain. At 24 weeks and 12 weeks, around 34.2% and 34.8%, respectively, were “very satisfied” how RA treatment improved the ability to perform daily living requiring fine motor skills. A lower number of patients were “somewhat satisfied” at week 24 compared to 12 weeks (50% vs. 41%).

Regarding the question on overall satisfaction with RA treatment, 42.1% patients at week 24 and 32.6% patients at week 12 were “very satisfied”.

- **Patients’ Global Impression of Change at Weeks 24 and 12 after Initiation of Adalimumab**

Approximately 10% patients felt “very much better” at 24 weeks; and one (2.2%) RA patient felt “very much better” at 12 weeks from baseline. 59% felt “much better” at 24 weeks after the initiation of adalimumab whereas approximately 61% RA patients felt “much better” at 12 weeks. Also, none of the patient felt “no change” at 24 weeks whereas one (2.2%) patient felt there was “no change” at 12 weeks after the initiation of adalimumab.

- **Post-Index Healthcare Resource Utilization**

Overall, around 98% of patients consulted healthcare professional more than once. The majority of patients, around 94%, visited a rheumatologist. Overall 93.6% of patients received one or more than one procedure.

Blood samples (93.6%), liver function test (76.6%), urine test (53.2%) and electrocardiogram (ECG) (21.3%) were most common procedures patients underwent. Two patients (4.3%) received one or

more than one surgery. Four (8.5%) patients had more than one hospitalization. Around 98% of patients used Disease-Modifying Antirheumatic Drugs (DMARD), mainly methotrexate (62.2%), leflunomide (33.3%), and hydroxychloroquine (24.4%). Also, 53.3% of patients used anti-inflammatory drugs (NSAIDs), mainly celecoxib (13.3%). Among other medications, steroids were used by 22.2% of patients.

- **Associations between Disease Severity and patient-reported outcomes (PRO)**

Among the various PROs studied in this study, HAQ-DI ($p=0.0283$), PCS T score ($p=0.0103$), EQ-5D-3L ($p=0.0485$) and percent overall work impairment ($p=0.0055$), were found to be significantly associated with disease severity at baseline using regression of PROs on DAS28 at baseline. Change in PCS T-score ($p=0.0454$) and percent overall work impairment on change in DAS28 at 12 weeks ($p=0.0146$) were found to be significantly associated with change in disease severity using regression of change in PROs on change in DAS28.

- **Generalized linear model (GLM) - Modifying Effects on Changes in patient-reported outcomes (PRO)**

Based on the significance level of 0.05: Chronic pulmonary diseases showed a significant correlation with HAQ-DI and MCS T-scores at 24 weeks ($p=0.0041$ and 0.0030 , respectively) and 12 weeks ($p=0.0072$ and 0.0004 , respectively). Peptic ulcer disease showed a significant correlation with HAQ-DI scores and change in percentage activity impairment at 12 weeks ($p=0.0420$ and 0.0238). “Any tumor” showed a significant correlation with PCS T score, change in EQ-5D-3L index, and change in percentage activity impairment at 12 weeks ($p=0.0064$, 0.0008 and 0.0489 , respectively). In addition to that, “any tumor” also showed a significant correlation with change in EQ-5D-3L index at 24 weeks ($p=0.0225$). Connective tissue disease showed a significant correlation with change in EQ-5D-3L index at 24 and 12 weeks ($p=0.0432$ and 0.0194 , respectively). Mild liver disease showed a significant correlation with change in % overall work impairment at 24 weeks ($p<0.001$). Cerebrovascular disease showed significant correlation with change in percentage of overall activity impairment at 12 weeks ($p=0.0367$) and in EQ-5D-3L index at 12 weeks ($p=0.0347$).

Discussion

The results of the present study in China demonstrate that adalimumab was effective in producing clinically important and statistically significant reductions in the signs and symptoms of disease at 24 weeks. These findings on the Chinese patients was further validated in other Asian populations where the results from similar studies which took place in Taiwan and Korea.