

## **1.0 Abstract**

### **Title**

The documentation of the effects on Quality of Life (QOL) and Working Productivity and Activity Impairment (WPAI) in patients with rheumatoid arthritis (RA) under HUMIRA® (Adalimumab) in routine clinical practice.

### **Keywords**

Adalimumab, rheumatoid arthritis, work productivity, WPAI, clinical practice

### **Rationale and Background**

Rheumatoid arthritis (RA) is a chronic inflammatory disease of the joints that often results in progressing joint destruction and lead to substantial functional losses, impairment, and reduced quality of life. On the social level, disease-related costs (due to lack of functionality) to be paid by social security systems are increasingly gaining priority.

Several clinical trials have shown that adalimumab both reduces the clinical symptoms of RA and decelerates the structural destruction of the joints, thus significantly improving health-related quality of life. This study at first time in Japanese RA patients will put added emphasis on data concerning work productivity and work ability as well as data concerning health related quality of life.

### **Research Question and Objectives**

The objectives of this study were to investigate followings;

(1) The primary objective;

Situation of work productivity using the Work Productivity and Activity Impairment/Rheumatoid Arthritis questionnaire (WPAI-RA) and functional

impairment (daily life activity) using the Health Assessment Questionnaire (HAQ) when adalimumab treatment

(2) The secondary objective;

- Clinical observation and improvement of the EuroQol Questionnaire 5 Dimensions (EQ-5D), Clinical Disease Activity Index Score (CDAI) and Disease Activity Score 28 (DAS28; number of tender and swollen joints, CRP and ESR, respectively, total score) when adalimumab treatment.
- Situation of the occurrence of adverse events definition during the course of the observation period while adalimumab treatment
- Factors considered to affect the safety and effectiveness

### **Study Design**

This was a single-arm, multi-center, prospective cohort study (Post-Marketing Observational Study). The observation period for each subject was 48 weeks.

### **Setting**

This study was conducted from May 2011 to January 2015 in Japan. The registration period of subjects was from May 2011 to October 2013.

### **Subjects and Study Size, Including Dropouts**

[Subjects]

(1) Inclusion Criteria

RA patients treated with adalimumab who satisfied the following conditions;

1. Paid worker (PW)

RA patients who are engaged in paid work for more than 35 hours per week

2. Home worker (HW)

- Category 1 unpaid workers; RA patients who are engaged in paid work for less than 35 hours per week
- Category 2 unpaid workers; RA patients who perform basic activities of daily life (household duties, shopping, child caring, exercise, study, etc.) other than PW

(2) Exclusion Criteria

1. RA patients showing lowered basic activities of daily life, such as hospitalization and being bedridden
2. RA patients with a history of previous treatment with adalimumab

[Study Size]

2,000 subjects

It was confirmed that the necessary number of subjects for analysis of work productivity and of functional impairment in persons who are engaged in PW, HW is approximately 500 cases each. To ensure this sample size, the number of patients to be enrolled is 1,000 cases each for PW and HW, because the rate of withdrawal during the period from the start of treatment to 48 weeks was assumed 50% by using dropout-rate of the all-case survey for adalimumab in Japanese RA patients. Therefore, the sample size of this study was set at 2,000 including PW and HW.

Since the dropout-rate of this study was approximately 40% as of September 2014, the actual sample size statistically needed was 1,700. Therefore, the recruitment period was closed as planned at October 2014 when 1,968 subjects were enrolled.

## **Variables and Data Sources**

[Variables]

Effectiveness;

WPAI: RA, HAQ-DI, DAS28, CDAI, EQ-5D

Safety;

Adverse events, Adverse drug reactions

[Data Sources]

Data sources in this study are from institute's medical chart. Participant physicians in this study transcribe the data from medical chart to Case Report Form (CRF) which AbbVie prepares.

## **Results**

A total of 2,088 registration forms were obtained, and 1,998 patients were registered after duplicate registrations were removed. Case report forms (CRFs) were retrieved from 1,973 patients, and could not be retrieved from 25 patients. Among the 1,973 patients with retrieved CRFs, 1,968 patients were eligible for safety analysis, and 1,808 patients were eligible for efficacy analysis in at least one item of efficacy evaluation.

[Effectiveness]

In 771 patients in whom percent overall work impairment due to RA was confirmed, the score improved significantly from  $41.06 \pm 29.58$  at baseline by a change of  $17.08 \pm 27.60$  at week 12. The score improved thereafter, and the change from baseline was  $19.77 \pm 29.99$  at the final evaluation. The change from baseline was statistically significant at all time points during the treatment period other than the time of discontinuation of adalimumab therapy.

In 1,546 patients in whom percent activity impairment due to RA was confirmed, the score improved significantly from  $48.42 \pm 28.11$  at baseline by a change of  $19.42 \pm 25.86$  at week 12. The score improved thereafter, and the change from baseline was  $22.36 \pm 29.44$  at the final evaluation. The change from baseline was statistically significant at all time points during the treatment period.

HAQ-DI was confirmed in 1,595 patients. At baseline, HAQ-DI was high in 326 patients (20.4%), moderate in 253 patients (15.9%), low in 416 patients (26.1%), remission in 411 patients (25.8%), and 0 in 189 patients (11.8%). At the time of final assessment, disease activity was "remission" in 421 patients (26.4%), and 0 in 583 patients (36.6%). The test result in patients with remission was statistically significant at all time points during the treatment period.

[Safety]

A total of 597 adverse events of which causal relationship with adalimumab could not be ruled out, i.e., adverse drug reactions (ADRs), were reported in 451 patients. The reporting rate was 22.92%.

A total of 87 serious ADRs of which a causal relationship with adalimumab could not be ruled out were reported in 79 patients. The incidence rate was 4.01%.

## **Discussion**

A total of 1,968 patients were included in the safety analysis set, and 1,808 patients in the efficacy analysis set.

During the study period, 35.9% of the patients discontinued adalimumab therapy. The duration of treatment was  $265.2 \pm 110.9$  days (mean  $\pm$  SD), ranging from 1 to 835 days. The most common reason for discontinuing adalimumab therapy was insufficient efficacy reported in 290 patients (14.7%).

[Safety]

Among 1,968 patients included in the safety analysis set, 451 patients experienced 597 ADRs. The reporting rate of ADRs was 22.92%. A total of 87 serious ADRs were reported in 79 patients. The reporting rate was 4.01%. The factors that were found to affect the incidence were age, employment status, comorbidity (cardiovascular disorders, respiratory disorders, and others), presence/absence of past illness, presence/absence of history of allergy, grade/stage of RA, previous treatment (biologics and steroids), and concomitant medications [non-MTX csDMARDs and steroids]. The factors that were found to affect the incidence and type of ADRs in the present study were similar to those in the drug-use results survey of adalimumab. The safety profile did not differ substantially between this survey and the drug-use results survey, in which the reporting rate of ADRs was 23.4% (1,847/7,739 patients) and that of serious ADRs was 4.5% (349/7,739 patients).

[Efficacy]

1. Changes over time in WPAI: RA scores indicate that adalimumab significantly improved the percent work time missed due to RA (absenteeism), percent impairment while working due to RA (presenteeism), percent overall work impairment due to RA (OWI), and percent activity impairment due to RA (AI) at week 12 and all time points (except the time point of the discontinuation) until the final assessment.
2. In the analysis of overall patients, measures of effectiveness, i.e., DAS28-4CRP, DAS28-4ESR, CDAI, SDAI, HAQ-DI and EQ-5D scores, improved significantly at week 12 and all time points until the final assessment. The percentage of patients with remission by category of DAS28-4CRP, DAS28-4ESR, CDAI, SDAI and HAQ-DI also significantly increased at week 12 and all time points until the final assessment.

#### **Marketing Authorisation Holder(s)**

AbbVie GK