

## 1.0 Abstract

### Title

Assessment of the safety of adalimumab in rheumatoid arthritis (RA) patients showing rapid progression of structural damage of the joints, who have no prior history of treatment with disease-modifying antirheumatic drugs (DMARDs) or biological agents (P13-983)

### Keywords

Adalimumab, Rheumatoid Arthritis, Effectiveness, Safety

### Rationale and Background

Adalimumab, a fully human anti-tumor necrosis factor (TNF)-alpha monoclonal antibody, was approved in Japan in April 2008 for the treatment of RA in patients inadequately responding to existing treatments (treatment-resistant patients). At the request of the Japanese regulatory authority (Pharmaceuticals and Medical Devices Agency [PMDA]), Abbott Japan (currently AbbVie GK) conducted a postmarketing double-blind controlled study (Study M06-859; HOPEFUL-I) to evaluate the protective effect of adalimumab against progression of structural joint damage. In Study M06-859, adalimumab plus methotrexate (MTX) was shown to be more effective than MTX alone in preventing the progression of structural joint damage assessed in terms of modified total Sharp score in MTX-naïve patients with early RA. Based on the results, PMDA approved an additional indication for use of adalimumab, in August 2012, for the prevention of structural joint damage in RA patients.

This approval offered DMARD-naïve patients at risk of early structural joint damage a chance to receive adalimumab as an upfront RA treatment. PMDA requested AbbVie GK to conduct a postmarketing observational study (PMOS) to compare the safety profiles of adalimumab between DMARD-naïve patients and those treatment-resistant patients (n=7,740) included and analyzed in a completed all-case PMOS (Study P10-559). Thus, AbbVie GK designed the present PMOS to determine the real-world

safety profile of adalimumab plus MTX and to establish the real-world effectiveness of this combination on disease activity in DMARD-naïve patients at risk of early structural joint damage, i.e., the new indication for adalimumab in RA.

### **Research Question and Objectives**

The objectives of this PMOS were as follows:

Primary Objective:

To examine the safety profile in daily clinical practice of adalimumab in rheumatoid arthritis patients showing rapid progression of structural damage of the joints, who have no prior history of treatment with DMARDs or biological agents.

Secondary Objective:

To clarify the effectiveness (Disease Activity Score(DAS)28, Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI)) in daily clinical practice of adalimumab in rheumatoid arthritis patients showing rapid progression of structural damage of the joints, who have no prior history of treatment with DMARDs or biological agents.

### **Study Design**

This was a multicenter, prospective, observational study of adalimumab conducted in the postmarketing phase of the drug. Each eligible patient was to be enrolled centrally when initiating adalimumab treatment and to be followed up for 24 weeks or until discontinuation of the drug use. For each patient who met the inclusion criteria, the following were confirmed:

- High disease activity, with poor prognostic factors (e.g., rheumatoid factor [RF]-positive, anti-cyclic citrullinated peptide [CCP] antibody-positive, or bone erosion)
- Combination of adalimumab and MTX was to be started
- No prior history of treatment with DMARDs
- No prior history of treatment with biological agents

## **Setting**

This PMOS was conducted in Japan and the study schedule was as follows:

Duration of registration: February 2013 to October 2014;

Duration of the survey: February 2013 to April 2015.

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

The study population consisted of DMARD- and biologic-naïve Japanese RA patients at risk of rapid progression of structural joint damage who were scheduled to start combination treatment with adalimumab and MTX. A total of 150 eligible patients were planned to be enrolled in the study.

Rationale for the planned sample size: In the completed all-case PMOS analyzing 7,740 treatment-resistant RA patients treated with adalimumab (Study P10-559),<sup>4</sup> the overall incidence of adverse events (AEs) was 27.8% and that of serious AEs (SAEs) was 6.1%. The most frequent SAEs by system organ class (SOC) were “infections and infestations” (2.4%). In that PMOS, serious infections and infestations occurred in 90 (2.15%) of 4,129 patients who received adalimumab concomitant with MTX only, i.e., a cohort similar to that studied in the present study. From this incidence rate, the least number of patients needed to be treated with this combination for 24 weeks in order to detect one patient experiencing a serious infection or infestation with a power of 95% was calculated to be 138.

## **Variables and Data Sources**

At weeks 0, 4, 12 and 24 or at visit at discontinuation of adalimumab, data on the following variables were obtained from paper-based case report forms (CRFs): adalimumab and MTX administration status, concomitant pharmacologic treatments (e.g., DMARDs other than MTX, corticosteroids, antituberculous drugs, and folic acid), disease activity (assessed by Disease Activity Score in 28 joints [DAS28], Clinical Disease Activity Index [CDAI], and Simplified Disease Activity Index [SDAI]), and AEs.

## Results

### Baseline characteristics

Of 163 patients enrolled, 157 were evaluated for safety. The 6 patients were excluded from the safety analysis set since they had DMARDs or biological agents prior treatment of adalimumab. Their demographic and baseline characteristics were as follows: 65.6% females; mean (SD) age of 56.5 (13.9) years; mean (SD) body weight of 57.77 (13.02) kg; mean (SD) RA duration of 9.5 (34.4) months; 64.3% patients having a baseline DAS28-4ESR score  $>5.1$ ; 73.2% and 66.9% patients positive for RF and anti-CCP antibody, respectively; 87.3% patients in Steinbrocker RA stage I or II; and 80.9% patients in Steinbrocker functional class I or II.

All 157 patients evaluated for safety were treated with adalimumab for their RA for a mean (SD) duration of 147.6 (51.5) days. All patients were concomitantly treated with MTX at  $\leq 8$  mg/week (63.1% patients) or  $>8$  mg/week (36.9% patients).

### Safety

A total of 37 treatment-related AEs (adverse drug reactions [ADRs]) occurred in 29 patients (18.47%), including 5 serious ones (pyelonephritis, *Pneumocystis jiroveci* pneumonia, pericarditis, interstitial lung disease, and pleurisy) reported in 4 patients (2.55%). The most common ADRs by SOC were “investigations” (6.37%), “infections and infestations” (5.73%), and “general disorders and administration site conditions” (2.55%).

### Effectiveness

Adalimumab plus MTX significantly decreased disease activity assessed by DAS28-4ESR, SDAI, and CDAI at all specified times as compared to baseline. At the endpoint, 51.9%, 47.6%, and 47.9% patients achieved clinical remission defined as DAS28-4ESR  $<2.6$ , SDAI  $\leq 3.3$  and CDAI  $\leq 2.8$ , respectively, and 90.1% patients showed a good or moderate DAS28-based European League against Rheumatism (EULAR) response.

## **Discussion**

In DMARD- and biologic-naïve RA patients at risk of early structural joint damage, adalimumab plus MTX had a safety profile similar in ADR type and frequency to that previously reported in treatment-resistant RA patients and consistent with the known safety profile of adalimumab monotherapy. Pericarditis, reported as a serious ADR, was the only ADR unexpected from the current Japanese label for adalimumab. More than 90% of the patients receiving the combination therapy showed a good or moderate DAS28-based EULAR response at the endpoint, confirming the efficacy findings of the phase III study in early RA patients.

## **Marketing Authorization Holder(s)**

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## **Names and Affiliations of Principal Investigators**

Not applicable.