1.0 Abstract

Title

Assessment of clinical effectiveness and safety of adalimumab and high dose methotrexate in routine clinical practice **(**Combo study; Adalimumab with high dose MTX)

Keywords

Adalimumab, high dose methotrexate

Rationale and Background

In Japan, Humira was approved on April 16, 2008 and launched in the market on June 18, 2008. The results of a recent retrospective data analysis of the all-case survey of Japanese subjects with RA suggested that the effectiveness of adalimumab in bio-naïve subjects with RA was more efficacious when they receive adalimumab in combination with MTX at a dose of ≥10 mg/week. Thus, we designed a prospective non-interventional study of ADA + MTX ≥12 mg/week in patients with early (≤2 years) RA without previous biological treatment to assess the effectiveness and safety in daily routine practice.

Research Question and Objectives

In daily clinical setting, subjects with RA who receive adalimumab (Humira®) and high-dose MTX (≥12 mg/week) were observed prospectively and the effectiveness was assessed by DAS28, HAQ and mTSS. In addition the safety was assessed in terms of the incidence and pattern of the occurrence of adverse events.

(1) The primary objective

Assess the clinical effectiveness of adalimumab in combination with high dose MTX (≥12 mg/week). This was measured by the percentage of subjects with the DAS28 score of <2.6 at week 52.

(2) The secondary objective

Assess the clinical effectiveness of adalimumab in combination with high dose MTX (≥12 mg/week) by assessing the proportion of subjects with a change in the following variables from baseline to week 104:

・Clinical Disease Activity Index (CDAI)

・Simplified Disease Activity Index (SDAI)

・The severity of functional impairment (HAQ)

・The health-related quality of life (EQ-5D)

・The inhibition of structural progression was assessed by measuring the modified van der Heijde Total Sharp Score (mTSS).

The safety profile was assessed by measuring the following variables:

・All serious adverse events (SAEs) and adverse events (AEs)

Study Design

This was a single-arm, multi-center, open labeled and prospective cohort study (post marketing observational study).

・Observation period
- 104 weeks (or discontinuation of this study)

・Discontinuation of this study

a. Patients within 52 weeks study period: When adalimumab treatment is discontinued.
b. Patients after 52 weeks study period: When any biologics other than adalimumab is administered.

Setting

This study was conducted from September 2012 to March 2017. This registration period of subjects was from September 2012 to December 2014.

Subjects and Study Size, Including Dropouts

＜Subjects＞

Adult subjects (≥16 years) with early (≤2 years), MTX (12mg/week) for at least 3 months before starting on adalimumab and DAS28-CRP >3.2, Bio Naive RA subjects

＜Study Size＞

350 subjects

(1) Inclusion Criteria

The subjects of this study are subjects with a diagnosis of RA and to whom adalimumab and methotrexate are prescribed as part of their normal treatment of RA. All subjects should be satisfying the following conditions.

1) Disease duration of RA ≤2 years

2) MTX administration ≥3 months prior to starting adalimumab

3) Dose of MTX ≥12mg/week

4) DAS28-CRP >3.2

(2) Exclusion Criteria

1) Patients who have been previously treated with biologics (including TNF inhibitors others)

Variables and Data Sources

[Variables]

Effectiveness;
DAS28-4CRP, HAQ, CDAI, SDAI, EQ-5D, mTSS

Safety;
Adverse events, Adverse drug reactions

[Data Sources]

Data sources in this study are from institute's medical charts. Participant physicians in this study transcribed the data from medical charts to Case Report Forms (CRF) provided by AbbVie.

Results

＜Safety＞

226 adverse events were observed in 124 subjects out of 300 subjects in the safety analysis set, and the incidence rate of adverse events was 41.33%(124/300). 35 serious adverse events were observed in 29 subjects, and the incidence rate of serious adverse events was 9.67% (29/300).

143 adverse drug reactions were observed in 92 subjects out of 300 subjects in the safety analysis set, and the incidence rate of adverse drug reactions was 30.67%(92/300). 31 serious adverse reactions were observed in 26 subjects, and the incidence rate of adverse reactions was 8.67% (26/300).

＜Effectiveness＞

The remission rate was 71.2% (208/292) in the last observation. The remission rate at week 52 was 77.1%（162/210）in 210 subjects with available data set to calculate DAS28 score out of 292 subjects in the efficacy analysis set. The remission rate at week 104 was 92.3%(120/130) in 130 subjects with available data set to assess the DAS28 score out of 292 subjects in the efficacy analysis set. The change of the DAS28 score from baseline was statistically significant at week 52 and the change of the score from baseline in 210 subjects at week 52. The score improved thereafter at week 104.

1. Significant differences of all other efficacy indexes (CDAI, SDAI, HAQ, and EQ-5D), was observed at any point from week 12 to weeks 52 and 104 compared to baseline. The change (≦ 0.5) at week 52 of mTSS and the change of mTSS (≦ 1.0) at week 104 were over 80 %.

Discussion

No new safety and efficacy concerns were observed and the known benefit-risk profile of humira remains unchanged.

Marketing Authorization Holder(s)

AbbVie GK

[redacted]

Names and Affiliations of Principal Investigators

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