

1.0 Abstract

Title

HUMIRA® 40 mg Syringe 0.8 mL for Subcutaneous Injection Protocol for Special Investigation (Long-term treatment for Crohn's Disease patients)

Keywords

Adalimumab, Crohn's Disease

Rationale and Background

Background

It was indicated that administration of Adalimumab at 160 mg (Week 0)/80 mg (Week 2)/40 mg (from Week 4 onward) improves disease activity and Quality of Life (QOL) in Japanese patients with moderate to severe Crohn's disease. This postmarketing observational study (PMOS) was requested by the Pharmaceuticals and Medical Device Agency (PMDA), as part of the approval for Crohn's disease indication.

Rationale

The purpose of this study was to examine the safety (especially profile of malignant tumors and serious infections) and efficacy of Humira in Japanese patients with moderate to severe Crohn's disease under the condition of daily medical.

Research Questions and Objectives

This special investigation of Humira 40 mg/0.8 mL for Subcutaneous Injection was to be conducted to obtain information on the safety (especially profile of malignant tumors and serious infections) and effectiveness in patients with Crohn's disease who are receiving Humira for an extended period of time.

Primary Endpoints

Number of patients with adverse events [Time Frame: Up to Year 3]

Number of patients with adverse events with evaluation beginning upon administration of Humira

Secondary Endpoints

1. Crohn's Disease Activity Index (CDAI) [Time Frame: Up to Year 3]
2. Work Productivity and Activity Impairment Questionnaire (WPAI) [Time Frame: Up to Year 3]
3. C-reactive Protein [Time Frame: Up to Year 3]
4. Endoscopy [Time Frame: Up to Year 3]

Study Design

Patients were to be observed for a period of 3 years after administration of Humira started (although the treatment could be continued beyond 3 years, the CRF was completed at the time point of 3 years). This surveillance study was to include patients of all ages, not only adult patients. For patients who were lost to follow-up during the observation period*, their last available data prior to study discontinuation were to be used.

* A patient who suspended Humira treatment for 2 months or more was to be regarded as having discontinued the survey.

Subjects and Study Size, Including Dropouts

Subjects

Patients with moderate to severe active Crohn's disease insufficiently treated with conventional therapy who were prescribed Humira by their treating physician were surveyed.

Study Size

Planned sample size: 500 patients (Actual number enrolled: 511)

Inclusion Criteria

1. Patients with Crohn's disease indicated for Humira treatment with the recommended dosage regimen
2. Patients with no past- or present malignant tumors
3. Patients who have not ever been to administer of Humira.

Surveillance Schedule

This PMOS study was conducted in Japan, and the duration of the survey and registration periods was as follows:

Duration of the survey: November 2011 to March 2017

Duration of enrolment: November 2011 to October 2013

Variables and Data Sources

Patient characteristics, hospitalization, treatment, drug use, and AEs were collected through CRF forms.

Results

Safety

A total of 511 patients were enrolled. Among the enrolled patients, case report forms were not collected from 7 patients, and there were 504 patients whose data in case report forms were assessable. The reasons for the 7 patients whose case report forms were not collected were as follows:

- 6 patients: "Uncooperative"
- 1 patient: "The investigator transferred to another institute."

389 patients were evaluable for the safety analysis, after the exclusion of a total of 115 patients ("safety assessment impossible"). Among 389 patients included in the safety analysis set, 157 adverse reactions were noted in 105 patients, the percentage of patients who experienced adverse reactions was 26.99%.

Common adverse reactions by system organ class of adverse reactions (MedDRA SOC: ≥ 10 patients) and their incidence rates were:

"Infections and infestations" (9.51%, 37/389)

"Gastrointestinal disorders" (6.94%, 27/389)

"General disorders and administration site conditions" (3.86%, 15/389)

"Skin and subcutaneous tissue disorders" (3.60%, 14/389)

"Lab tests" (3.60%, 14/389)

Common adverse reactions by preferred term (MedDRA PT: ≥ 5 cases) and their incidence rates were:

"Crohn's disease" (2.57%, 10/389)

"Upper respiratory tract inflammation"

"Nasopharyngitis" (1.54%, 43/389)

"C-reactive protein increased" (1.54%, 43/389).

Possible factors having an impact on the occurrence of adverse reactions were examined. As a result, there was no factor requiring special actions. Important investigation items did not exhibit any new risk.

Efficacy

CDAI Remission Rate at the Final Assessment (CDAI < 150)

The efficacy analysis set consisted of 310 patients after 79 patients ("efficacy assessment impossible") were excluded from the 389 patients who made up the safety analysis set. Among the 310 patients of the efficacy analysis set, the remission rate (CDAI < 150) at the final assessment was 68.4% (212 patients).

Change in WPAI

In the 310 patients of the efficacy analysis set, mean "Percent overall work impairment due to Crohn's Disease (OWI)" before administration was 42.68 ± 34.71 . Mean OWI at 1 year after the start of administration was 23.89 ± 30.43 , and a statistically significant difference was observed ($p = 0.0040$, paired t test). After this, statistically significant improvement continued, and mean OWI at 3 years after the start of administration was 14.27 ± 25.06 ($p = 0.0094$, paired t test).

Results of Endoscopic Test

The administration of Humira resulted in sustained improvement as evidenced by endoscopy of the small and large intestine.

Change in C-Reactive Protein (CRP) Levels

CRP levels were significantly decreased compared to the start of Humira administration. The mean CRP level at the start of treatment was 0.74 mg/dL (median), the mean level at Year 1 of treatment was 0.10 mg/dL (median), the mean level at Year 2 of treatment was 0.10mg/dL (median), and the mean level at Year 3 of treatment was 0.10 mg/dL (median).

Discussion

No new safety and efficacy issues were observed in this PMOS and specific actions were therefore not considered necessary.

Marketing Authorization Holder(s)

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Names and Affiliations of Principal Investigators

Not applicable.