1.0 Abstract

Title

HUMIRA® 40 mg syringe 0.8 mL for Subcutaneous Injection

Special investigation (All-case survey) in patients with Crohn's disease

Keywords

HUMIRA®, adalimumab, All-case, PMOS, Crohn's Disease, Crohn's Disease Activity Index (CDAI), Remission

Rationale and Background

Rationale

Adalimumab, a fully human anti-human TNFα monoclonal antibody, is verified effective not only for the treatment of patients with Crohn's disease (CD) who are unresponsive to conventional drug therapy or who have not achieved clinical remission, but also for patients in which infliximab has lost its effect or is not well tolerated. Safety and effectiveness of adalimumab for CD patients in Western study have already established by Study M02-403 as the induction therapy and Study M02-404 as the maintenance therapy. Similar results were obtained in Japanese clinical studies (induction therapy: Study M04-729, maintenance therapy: Study M06-837). This investigation was performed after approval for the purpose of evaluating the safety and effectiveness of HUMIRA® under actual clinical practice.

Background

Treatment of Crohn's disease differs depending on the expansion of the lesion area and disease activities. Since it is impossible to achieve complete halt of inflammatory processes with presently available therapies, the purpose of treatment is to induce clinical remission. Surgical treatment may be necessary for patients who have persistent intestinal obstruction or who have abscess or fistula.

In Japan, nutrition therapy or drug therapy are generally used as basic therapy for the treatment of active Crohn's disease. Enteral nutrition or complete venous nutrition are effective for patients who need temporary special nutrition, who need to rest their intestine, and who are unable to obtain adequate nutrition from the small intestine. In particular, complete venous nutrition may be effective when the patient has inflammation in the small intestine or broad area of intestinal tract.

Meanwhile, 5-aminosalycilates (5-ASA) is most generally used in mild cases in combination with other drug therapies. In moderate and severe cases, corticosteroids are used, but gradual dose reduction and withdrawal is necessary because of adverse reactions such as infections, osteoporosis, or glucose intolerance. When it is difficult to discontinue corticosteroids, immunomodulators such as azathioprine or mercaptopurine are used. When clinical remission is not achieved with those existing therapies, anti-TNFα agents such as adalimumab or infliximab are used for induction therapy and maintenance therapy for Crohn's disease.

Research Question and Objectives

To clarify the following information regarding the use of HUMIRA® 40 mg Syringe 0.8 mL for Subcutaneous Injection (referred to as "HUMIRA®" hereinafter) in CD patients, which was recently approved as an additional indication of HUMIRA®.

1. Unknown adverse drug reactions (ADRs)
2. Incidence of ADRs in the clinical setting
3. Factors that might affect the safety and effectiveness of HUMIRA®

Study Design

The investigation was performed as a single cohort non-interventional observational study, as instructed by the regulatory authorities, for the purpose of evaluating the safety and effectiveness of HUMIRA® in patients with active Crohn's disease under

actual clinical practice. The approval condition was to perform all-cases of CD patients with HUMIRA®.

In this investigation, each patient was followed for 24 weeks. Patients with moderate or severe active Crohn's disease not responding well to conventional therapies. The approved dose of HUMIRA® is administered fortnightly by subcutaneous injections at the starting dose of 160 mg, and subsequent doses of 80 mg at Week 2 and 40 mg at Week 4 and subsequently.

When HUMIRA® was discontinued due to the occurrence of an adverse event or attenuation of effects, etc. during the follow-up period, the safety and effectiveness were evaluated as of the time of discontinuation.

In the effectiveness evaluation, reduction of CDAI below 150 as a result of adalimumab therapy was treated as "clinical remission."

Setting

This PMOS was conducted in only Japan, and the duration is as follows:

Duration of surveillance:	From 27 October 2010 to 29 October 2012
Duration of registration:	From 27 October 2010 to 30 April 2012

Subjects and Study Size, Including Dropouts

Target sample size: 600

All the patients treated with HUMIRA® after approval for the indication were enrolled and tabulations/analyses were performed when data from 600 subjects were obtained and reported to the regulatory authorities.

This investigation is for all cases of CD patients with Humira. Six hundred (600) patients as the interim report to regulatory were enrolled at the end of February 2011, but all CD patients had to be enrolled for a required period. As a result of continuous

enrollment of CD patients for a required period, a size became 1693. From October 27, 2010, (date of addition of Crohn's disease to the indications of adalimumab) to October 29, 2012, 1716 patients were enrolled in the investigation. Excluding 21 patients who were transferred to other institutions during the surveillance period and 2 patients who made no visit after the first administration, 1,693 patients were included in the safety analysis set. Excluding 3 patients treated with adalimumab off-label and 23 patients who did not receive adalimumab after the first administration, 1,667 patients were included in the effectiveness analysis set.

Variables and Data Sources

The following information is to be collected using the registration sheet and CRF.

Results

Safety

During the observation period, among 1693 patients in the safety analysis set, 527 events of adverse drug reactions were reported by 360 patients (frequency: 21.3%, 360/1693), and 542 events of adverse drug reactions were reported by 711.8 patients per year (incident rate : 76.1/100PY). One hundred twenty-six (126) events reported from 96 patients were assessed as serious adverse drug reactions (frequency: 5.7%, 96/1693), and 130 events of serious adverse drug reactions were reported by 711.8 patients per year (incident rate: 18.3/100PY).

Effectiveness

As for the changes in CDAI scores from baseline to Week 24 in 1667 patients in the effectiveness analysis set, CDAI scores (mean ± SD) changed from 204.3 ± 105.7 at Week 0 to 142.9 ± 90.4 at Week 4, 142.7 ± 93.8 at Week 8, and 149.1 ± 100.9 at Week 24. CDAI scores at each evaluation time point were significantly lower than the score on at Week 0 ($p < 0.0001$, paired t-test). Mild patients are including in this average of CDAI scores. Because patients who switched from infliximab or IM included. CDAI of these patients is lower than bio naive patients. And as this

investigation is non-intervention observational study and all-cases with Humira have to enroll in this investigation, mild patients included naturally. Meanwhile, the remission rate at each evaluation time point was calculated for the patients whose CDAI scores at Week 0 of adalimumab therapy were not less than 150. The remission rate using Observed Case (OC) was 46.8% (284/607) at Week 4, 48.0% (260/542) at Week 8, and 46.8% (304/649) at Week 24 of adalimumab therapy.

Discussion

In this investigation, the most common adverse reaction was "infections and infestaions" according to the System Organ Class. And these events were similar to other all-cases investigations conducted for Japanese patients with rheumatoid arthritis, and Japanese patients with psoriasis vulgaris and/or psoriatic arthritis. Events such as rhinopharyngitis, bronchitis, and pharyngitis reported and classified as "infections and infestations" were also reported in conventional clinical trials and post-marketing observational study and are not unique to adalimumab. In addition, the patients had alleviation and recovery as a result of receiving routine therapy, not special treatment; those events can be treated under the routine clinical practice.

Regarding effectiveness, CDAI scores decreased significantly in observational period. In the patients with CDAI scores of 150 or higher at Week 0, the remission rates at Week 4, Week 8, and Week 24 were maintained approximately at slightly below 50%. Those were similar to the results of remission rate obtained in the clinical studies.

Marketing Authorisation Holder(s)

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Names and Affiliations of Principal Investigators

Not applicable.