1.0 Abstract

Title

Special Investigation (Long-term Treatment in Patients with Rheumatoid Arthritis)

Keywords

Adalimumab, Long-term Treatment, Rheumatoid Arthritis, Effectiveness, Safety

Rationale and Background

HUMIRA® is a fully human tumor necrosis factor (TNF)-alpha monoclonal antibody preparation and was approved in Japan for treatment of rheumatoid arthritis (RA) in patients showing an inadequate response to conventional therapy in April 2008. Since RA is a chronic autoimmune disease requiring long-term treatment, knowledge about long-term safety and effectiveness is important. However, no studies have been conducted to assess the long-term use of HUMIRA® in a large number of Japanese patients with RA. Also, as one of the conditions of approval of HUMIRA®, the Japanese regulatory authority (Health, Labour and Welfare Ministry (MHLW)) requested a large-scale Post-Marketing Observational Study (PMOS) to investigate the long-term safety of HUMIRA®, particularly associated with the development of infections and malignant tumors.

Research Questions and Objectives

Information on the safety and effectiveness of HUMIRA® was collected during a 3-year period for the treatment of RA to clarify the following:

1) Incidence of adverse drug reactions (ADRs*) in the clinical setting

2) Incidence of infections and malignant tumors in the clinical setting

3) Factors affecting the safety and effectiveness of HUMIRA®

*ADR: The causal relationship between HUMIRA and adverse event could not be ruled out.

Study Design

This was a single-cohort, non-interventional observational study. Patients were followed up from week 24 to 3 years of treatment. Information on the safety and effectiveness of HUMIRA® treatment was collected once every 6 months, using an electronic data capture system or printed case report forms (CRFs). For each patient who completed the all-case PMOS and met the inclusion criteria, the following were confirmed:

1) Presence/absence of HUMIRA® treatment at the beginning of the survey

2) Presence/absence of Health Assessment Questionnaire (HAQ) or Modified HAQ (MHAQ) evaluation at baseline

3) Presence/absence of history of anti-TNF therapy (including all treatment records, durations and doses of anti-TNF drugs) other than HUMIRA® treatment at baseline

Patients with "Presence" of the above items 1) and 2) were suitable for the study registration. Registered patients were those with filled out "Follow-up Case Confirmation Forms" during the registration period. The investigators then filled out the CRFs for each registered patient. When HUMIRA® treatment was discontinued during the observation period, the investigator filled out a "Questionnaire Form" once every 6 months until 3 years after the initiation of HUMIRA® therapy to record the presence/absence of malignant tumors, tuberculosis, serious infection, and death. Analysis was performed on the data obtained during the 3 years after the initiation of HUMIRA® treatment, including the data from the all-case survey.

Setting

This PMOS study was conducted in Japan. The survey took place from November 2009 to December 2013, and the enrollment period was from November 2009 to December 2010.

Subjects and Study Size, Including Dropouts

Based on the incidence (1%) of malignant tumors in patients enrolled in pre-approval clinical studies in Japan, a target sample size of 300 patients was set to ensure the detection of at least one patient with malignant tumor with a probability of 95%. The

target number of patients to be registered was set at 600 in anticipation of dropouts or discontinuations due to long term study.

Variables and Data Sources

Information was collected at the different time points as follows:

1) The history of anti-TNF therapy, HUMIRA® treatment, concomitant drug information, including disease-modifying antirheumatic drugs (DMARDs), biologics and glucocorticoids, surgical treatment of RA, effectiveness evaluation (Disease Activity Score 28 4 ESR (DAS28-4 ESR) and MHAQ), and adverse events were collected by CRF once every 6 months from 24 weeks to 3 years after the initiation of HUMIRA®.

2) After discontinuation of HUMIRA®, the presence or absence of malignant tumors, tuberculosis, serious infection and death were collected using the Follow-up Questionnaire Form every 6 months to 3 years after the initiation of HUMIRA®.

Results

Baseline characteristics

Of the 508 patients included in the safety analysis set, 81.9% (416/508) were female and 18.1% (92/508) were male. The patients had a mean ± SD age of 59.5 ± 13.4 years at administration and a mean body weight of 53.93 ± 11.55 kg. Mean disease duration was 10.370 ± 9.947 years; 27.0% (137/508) and 34.8% (177/508) of the patients were at Steinbrocker RA stages III and IV, respectively. Additionally, 61.4% (312/508) of the patients were at Steinbrocker functional class II. The previous treatment was ineffective for 97.6% (496/508) of the patients. The previous use of any biologics was noted in 131 patients (25.8%), any DMARDs in 97.2% of the patients and glucocorticoids (GCs) in 57.7% of the patients.

Safety

During the 3 year observation period, among 508 patients in the safety analysis set, 306 ADRs were reported by 169 patients {33.3% (169/508)}. With a total exposure in this study of 1248.2 patient-years (PY), the number of events per 100 PY was 24.5 for all

ADRs. The most common ADRs were coded to the MedDRA system organ class (SOC) "infections and infestations", with a total of 114 events (incidence rate of 9.1/100 PY) occurring in 82 patients {16.1% (82/508)}. 72 serious ADRs (SADRs) (incidence rate of 5.8/100 PY) were reported by 54 patients {10.6% (54/508)}. 37 SADRs in the SOC "infections and infestations"(incidence rate of 3.0/100 PY) were reported by 30 patients {5.9% (30/508)}. 6 malignant tumors (incidence rate of 0.5 /100 PY) were reported by 6 patients {1.2% (6/508)}. The causal relationship between 6 malignant tumors and HUMIRA® could not be ruled out. It was considered that all 6 events were serious by the reporting physicians.

7 patients died during the observation period. For 3 of the deaths, a causal relationship with HUMIRA® could not be ruled out. The cause of death reported for each of these 3 cases was pneumonia (n=1), peritonitis (n=1) and interstitial lung disease (n=1). Additionally, 2 patients died after the observation period. One of the two patients, a causal relationship with HUMIRA® could not be ruled out. The cause of death was interstitial lung disease.

Effectiveness

In the 429 patients in the effectiveness analysis set treated with HUMIRA®, DAS28-4ESR scores (mean ± SD) changed from 5.03 ± 1.21 at baseline (week 0) to 3.24 ± 1.14 at week 24, 3.12 ± 1.13 at 1 year, 3.08 ± 1.19 at 1.5 years, 3.11 ± 1.23 at 2 years, 3.11 ± 1.27 at 2.5 years, and 3.15 ± 1.27 at 3 years. The DAS28-4ESR scores at each evaluation were significantly decreased ($p < 0.001$, paired *t*-test, There are analyzed without multiplicity adjustment.) from the score at week 0.

The percentages of patient with achieving remission (DAS28-4ESR score< 2.6) was increased from week 0 (2.8%, 12/429) up to week 4(14.5%, 62/429) and 36.4% (156/429) of patients were achieving remission at 3 years.

MHAQ (mean ± SD) changed from 0.81 ± 0.70 at baseline (week 0), to 0.67 ± 0.70 at 24 weeks, 0.56 ± 0.68 at 1 year, 0.54 ± 0.67 at 1.5 years, 0.53 ± 0.68 at 2 years, 0.52 ± 0.67

at 2.5 years, and 0.53 ± 0.68 at 3 years. The changes in MHAQ at each evaluation were significantly decreased ($p < 0.001$, paired *t*-test) from the score at week 0.

The percentages of patient with achieving remission (MHAQ scores ≤ 0.5) was increased from week 0 (43.4%, 185/426) to week 24(53.5%, 228/426) and 66.2% (282/426) of patients were achieving remission at 3 years.

Discussion

The incident of any ADRs and SADRs were 33.3% (n = 169) and 10.6% (n=54), respectively. The most common ADRs and SADRs reported in this analysis were infection. The rate of ADR, SADR, infection and serious infection at each observation period were showed [redacted]

In this study, from week 0 to week 24 was the highest incidence rate of ADR (15.6%) and infection (5.7%) in 3 years. Since the patients could complete the preceding 24-week PMOS (all-case PMOS) were enrolled, it was lower than all case PMOS (ADR: 24.0%, infection: 7.0%). SADR and serious infection were increased after week 24. From year1 to year 1.5 was highest incidence rate of SADR (3.4%). From year2 to year 2.5 was highest incidence rate of serious infection (1.3%).

When HUMIRA® is administered to patients with risk factors for ADRs, the benefit and risks of HUMIRA® treatment should be thoroughly considered. Stepwise multiple cox regression analysis identified the following risk factors for ADR: previous or concurrent infectious respiratory disease, more advanced RA (Steinbrocker stage III and IV), infection: age ≥ 65 years and renal disorder, and serious infection: age ≥ 65 years and previous use of biologics. HUMIRA® should be used with caution in patients with these underlying risk factors.

Six malignant tumors were reported in 6 patients (1.2%, 0.5 events/100 PY). The causal relationship between 6 malignant tumors and HUMIRA® could not be ruled out. All of

them were considered SADRs. No trends in cancer type were detected because of limited cases [redacted]

The incidence rate of malignancy for this study did not higher than reported in the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) Japanese RA cohort study, in which incidence rate of malignancy was 676.7 (men, 1331.5; women 542.2) per 100,000 person-yeards.[1)]

Further, 7 patients died during the observation period. For 3 of the deaths, a causal relationship with HUMIRA® could not be ruled out. The cause of death was pneumonia (n=1), peritonitis (n=1) and interstitial lung disease (n=1). The Standardized mortality rates (SMR) 0.56 (95% CI= 0.23-1.15) for this study did not exceed that reported in IORRA, in which the SMR range was 1.46-1.90.[2)]

We also examined patients characteristics linked to successful HUMIRA® treatment. Background factors shown to contribute to the achievement DAS28-4ESR remission (score < 2.6) and MHAQ remission (score ≤ 0.5) in patients receiving HUMIRA® included male, age < 65 years, no previous administration of biologics, previous or concurrent infectious respiratory disease and pulmonary disease, less advanced RA (Steinbrocker stage I and II), and low disease activity (DAS28-4ESR ,MHAQ) at baseline. The response rate was higher in patients with less advanced RA (Steinbrocker stage I and II), and lower DAS28-4ESR and MHAQ at baseline. These results indicate that it is preferable to start HUMIRA® treatment in patients with less advanced RA to maximize clinical response. It was suggested that less advanced RA (Steinbrocker stage I and II) had a higher response rate and a lower risk for ADRs.

Marketing Authorisation Holder(s)

AbbVie GK

[redacted]

Names and Affiliations of Principal Investigators

Not applicable.