1.0 Abstract

Title

Post-Marketing Surveillance of Humira® Injection in Korean JIA Patients under the "New-Drug Re-examination"

Keywords

Humira®, Juvenile Idiopathic Arthritis (JIA), Juvenile enthesitis-related arthritis, Post-Marketing Surveillance (PMS)

Rationale and Background

This surveillance was conducted in compliance with the New Drug Re-examination Guideline in Korea.

Research Question and Objectives

To evaluate the safety profile of Humira® for JIA patients in normal medical practice:

1. Serious adverse event•adverse drug reaction
2. Unexpected adverse event•adverse drug reaction
3. Already known adverse drug reaction
4. Non-serious adverse drug reaction
5. Adverse events resulting from drug misuse, drug abuse or drug interaction
6. Other information related to the product's safety and effectiveness (including the influence to the laboratory value)

Study Design

Post-Marketing Surveillance

Setting

Selection of Study Population

JIA patients to whom Humira® has been prescribed according to normal clinical judgment of the treating physician.

Inclusion Criteria

1. Patients from 2 years of age who were diagnosed with polyarticular juvenile idiopathic arthritis (JIA) or patients from 6 years of age who were diagnosed with enthesitis-related arthritis (ERA).
2. Polyarticular juvenile idiopathic arthritis (JIA) patients for whom the response to previous disease-modifying anti rheumatic drug therapy had been inadequate.
3. Patients who give written authorization form to use their personal and health data from legal parents or representative.

Exclusion Criteria

1. Patients with known hypersensitivity to Humira® or any of its excipients.
2. Patients who is participating on other clinical trials.

Physician referred to the product market authorization (label) for exclusion criteria.

Subjects and Study Size, Including Dropouts

This Post-Marketing Surveillance (PMS) was planned to recruit 600 subjects for 4 years to meet the local requirements for regulatory PMS. However, the number of subjects to be enrolled was adjusted to 26 subjects mainly because of the significantly low incidence and prevalence of polyarticular JIA, and the criteria for using biologics for JIA. The study actually enrolled 28 subjects from 9 study sites during the PMS study period (4 years, 10 Aug 2012 through 09 Aug 2016). All subjects were included in the safety analysis.

9 subjects were excluded from the effectiveness analysis because no values on efficacy parameters at baseline or Week 12 were available.

Variables and Data Sources

Variables

Demographics, Medical History, PPD Skin Test, Chest X-ray, Treatment with Humira®, Concomitant Medication, Safety, Active joint count, Physician's global assessment, Parent's global assessment

Data Sources

Paper Case Report Form

Results

Subject characteristics

Of 28 subjects in the safety population, 50.00% (14/28 subjects) were male and 50.00% (14/28 subjects) were female. The mean age was 17.68 (± 5.69) years, and ranged from 8 to 34 years.

The mean duration of JIA symptoms was 101.15 (± 96.85) months ranging from 4.00 months to 408.00 months. Prior to treatment with Humira®, 92.86% (26/28 subjects) had been treated with anti-rheumatic therapy. Among the anti-rheumatic therapies, biologic agents were Etanercept and Abatacept. Etanercept and Abatacept was administered to 15 patients and 4 patients respectively, and 3 patients administered both medications. There were 15 biologic-switcher patients, 11 biologic agent naive patients, and 2 anti-rheumatic therapy naive patients.

The subjects were categorized and presented into 'before participation' when Humira® has been administered for more than 12 weeks at participation, and had additionally collected past safety and effectiveness data. The other subjects were categorized as 'after

participation' otherwise. Effectiveness population was also divided in the same way reflecting the subjects excluded from safety population.

Among safety population (n = 28), the subjects who exceeded 12 weeks of Humira® administration at participation, additionally collected past safety and effectiveness data were 53.57% (15/28 subjects), and after participation were 46.43% (13/28 subjects). The mean length of Humira® treatment was 535.04 (± 438.33) days and ranged from 65.00 days through 1,971.00 days. Humira® treatment at the last administration was on-going for 92.86% (26/28 subjects) and 7.14% (2/28 subjects) discontinued/terminated Humira® administration. The reason for discontinue/termination of Humira® administration was 'Lack of drug effect.'

Safety

All adverse events (AEs) that occurred during the study period were reported regardless of the causal relationship with Humira®. 8 adverse events were reported in 6 subjects (6/28 subjects, 21.43%). The most frequently reported AE was influenza, with 3 cases in 3 subjects (3/28 subjects, 10.71%), remaining 5 AEs (back pain, joint swelling, erythema, urticaria, and pyrexia) were each reported by a single subject (1/28 subject, 3.57%).

Unexpected adverse events, 'joint swelling' that are not listed in the product label occurred in a single subject, which is 3.57% (1/28 subjects, 1 case). This AE with moderate severity recovered without action taken and reported to have 'Probably not' causal relationship with Humira®.

There was a single serious adverse event (3.57%, 1/28 subjects, 1 case) of 'erythema.' This SAE was classified as 'hospitalization or the prolongation of hospitalization' (hospitalized from [redacted]). Investigator reported the causality with Humira® as not related.

The relationships between various factors (i.e., demographic characteristics, medical background, and treatment with Humira®) and adverse events following Humira® were explored. As a result of conducting univariate analysis and logistic regression analysis on

demographic, medical, and treatment with Humira®, all factors were not statistically significant.

All AEs were mild or moderate in severity. 87.5% of AEs were recovered without sequelae. For all, no actions were taken.

Overall, the safety of Humira® observed during the course of this PMS study was not remarkably different than the previously documented safety profile of the product, as described in the label and periodic safety update reports.

Effectiveness

Effectiveness analyses were performed for the subjects who administrated Humira® for 12 (± 4) weeks with the record of effectiveness evaluation variable (i.e., Active joint status [0 – 68] data at inclusion and at 12 [± 4] weeks post-treatment Investigator's global assessment, and Parent's global assessment data at 12 [± 4] weeks post-treatment). For the subjects who had the administration period over 12 weeks at the time of participation, main analysis was suggested on effectiveness data collected after the date of obtaining ICF, and sub analysis was suggested on effectiveness evaluation result, collected between 12 weeks from subject's first administration date of Humira®. The main analysis of effectiveness evaluation was conducted on 19 effectiveness evaluation subjects except 9 subjects whose effectiveness data were missing. The sub-analysis was conducted on 10 subjects whose effectiveness data of 12 weeks post-Humira® were available before participation among 19 subjects.

Active Joint Count at Baseline and 12 Weeks Post-Humira® Treatment

Main Analysis

The mean active joint count at baseline visit was 9.63 (± 8.43) and following visit was 3.58 (± 6.28). The mean decrease from baseline visit to following visit was 6.05 (± 6.65) and it showed statistically significant result (p-value < 0.0001).

Sub-Analysis

The mean active joint count at baseline visit was 9.10 (± 4.84) and following visit was 2.10 (± 1.73). The mean decrease from baseline visit to following visit was 7.00 (± 5.01) and it showed statically significant result (p = 0.0020).

Parent's and Physician's Global Assessment at 12 Weeks Post-Humira® Treatment

Main Analysis

The assessment was evaluated in 4 scales which are 'Improved,' 'Not changed,' 'Aggravated,' and 'Not assessable.' Parent's global assessment after 12 (± 4) weeks of Humira® administration in 19 subjects was 100% (19/19 subjects) 'Improved,' and the Physician's global assessment was 94.74% (18/19 subjects) 'Improved' and 5.26% (1/19 subjects) 'Not changed.'

Sub-Analysis

Parent's global assessment and Physician's global assessment were all improved and none of the subjects were investigated to be 'Not improved' or 'Aggravated.'

Total Effectiveness Assessment at 12 Weeks Post-Humira® Treatment

Main Analysis

Total effectiveness assessment was classified as 'Improved' or 'Not improved' on 19 subjects and was investigated. If active joint count (50% decrease of active joint count is categorized as 'Improved'), Parent's global assessment and Physician's global assessment were all 'Improved,' it was categorized as 'Improved,' and the subjects were categorized as 'Not improved' otherwise. In total effectiveness assessment, 63.16% (12/19 subjects) were 'Improved' and 36.84% (7/19 subjects) were 'Not improved.'

Sub-Analysis

In total effectiveness assessment, 90.00% (9/10 subjects) were improved and 10.00% (1/10 subjects) were 'Not Improved.'

Effectiveness Evaluation by the Background Factors of Subjects

The relationships between various factors (i.e., demographic characteristics, medical background, and treatment with Humira®) and effectiveness results following Humira® were explored. As a result of conducting univariate analysis and logistic regression analysis on demographic, medical, and treatment with Humira®, all factors were not statistically significant.

Discussion

No new safety signals have been detected. The safety of Humira® observed during the course of this PMS study was not remarkably different than the previously documented safety profile of the product, as described in the label and periodic safety update reports. In terms of effectiveness, the results demonstrate Humira® to be highly effective. The safety of Humira® will continue to be monitored after the submission of this report through spontaneous reporting of adverse events and collection of safety information.

Marketing Authorisation Holder(s)

AbbVie Korea
[redacted] Seoul, 06182, Korea

Names and Affiliations of Principal Investigators

- [redacted]
- [redacted]
- [redacted]
- [redacted]