1.0 Abstract

Title

Re-examination report for post-marketing surveillance (PMS) study of adalimumab (Humira®) for non-infectious intermediate, posterior, or panuveitis patients

Keywords

Panuveitis, adalimumab, Non-infectious intermediate, posterior and panuveitis (NIIPPU)

Rationale and Background

This study was conducted in accordance with the Korean Standard for Re-examination of New Drugs, etc. and the protocol of this study was created in accordance with the relevant standards and codes of law. In order to evaluate the consistency of the safety profile in the real-world clinical practice, the safety data of this study was compared and contrasted with the drug approval details.

Research Question and Objectives

What are the real-world safety and effectiveness data of originator adalimumab (Humira®) in Korea? The purpose of this study was to evaluate the safety as the primary objective and effectiveness as the secondary objective of originator adalimumab (Humira®) for the treatment of Non-infectious intermediate, posterior and panuveitis (NIIPPU) patients under a routine clinical practice.

Study Design

Non-interventional prospective, post-marketing surveillance

Setting

NIIPPU patients who had been prescribed with Humira® were registered to the study in accordance with the drug approval status as well as the investigator's clinical judgment.

; 'Patients who had started administration of Humira® before study initiation (contract date) and continued at study initiation' as well as 'patients who started administration of Humira® after study initiation (contract date)' were enrolled.

The study registered patients who were administered with Humira® for the treatment of NIIPPU as well as satisfying the selection criteria, and the patients were selected from a study institution under an agreement with AbbVie Ltd.

When the study agreement had been made after site IRB approval, the study institution began the study, and until the completion of subject registration, all patients (with consent) who were prescribed with Humira® for the treatment of NIIPPU and satisfied the Inclusion/Exclusion criteria were registered for the study during the re-examination period.

- **Inclusion Criteria**

1. Age ≥ 19 years at the time of the enrollment.
2. Patient had been diagnosed with Non-infectious intermediate, posterior, and panuveitis
3. Patients voluntarily signed a patient authorization & informed consent form.
4. Decision on the treatment with Humira® had been made prior to any decision to approach the patient to participate in this study.
5. Eligible to Humira® treatment indicated as per approved local label.

- **Exclusion Criteria**

Patient with any of the following could not be registered in this study:

1. A patient who was contraindications to originator adalimumab (Humira®) as listed on the approved local label.
2. A patient who was participating on other interventional clinical trials
3. Prior treatment with Humira®, including current course of Humira® had started prior to baseline visit assessments.

The participating physician referred to the approved local label for Selection Criteria.

The study was planned to allow all patients who had been administered with Humira® to be registered for the study until the planned number of cases were collected in order to obtain a significant data for the drug safety. Once the study began in the study institution, the research physician was recommended to include/collect all possible patients who had been administered with Humira® for the study during the re-examination period or the remaining period of re-examination period.

A patient eligible for evaluation was a patient who had been administered Humira® at least once, and made a visit for safety evaluation (or phone calls, or any written correspondence) afterwards.

Safety information was also considered for the safety evaluation, including for drop-out patients from follow-up visits.

For the participants who were not followed up, the reason for the failure was recorded.

- **Selection Criteria for Study Institution / Investigators**

This study was conducted in a medical facility in Korea. Medical facility included hospitals and clinics. The investigator had to satisfy the criteria below.

1. An investigator who worked at a hospital or a clinic, and had a patient population that was suitable for this study
2. An investigator who was capable of conduct the study according to the study plan

3. An investigator who was capable of commit a sufficient amount of time for conducting of the study including activities such as patient registration, patient follow-up, writing case report form, and so forth
4. An investigator who was capable of reporting all serious adverse events to AbbVie Ltd. in accordance with this study protocol

Study Duration

The study duration determined by the Ministry of Food and Drug Safety (MFDS) was four (4) years from the drug approval. This study commenced after the study drug for the treatment of NIIPPU was released, and the final report shall be submitted to the MFDS within three months of the end of the re-examination period. Interim reports were submitted to the MFDS once in six months for the first two years, and then were submitted once a year afterwards.

Subjects and Study Size, Including Dropouts

According to the local regulations, 600 subjects had to be enrolled in this study. However, it had been considered that it would have been difficult to enroll 600 subjects within this study period, so the protocol was changed to enroll at least 130 subjects, which was approved by MFDS.

Variables and Data Sources

The data below were collected if available in the medical chart:

- **Demographical Information:**

Basic demographic information including patient initials, age (birth year and month), gender, height, weight, family history, and name of study institution/investigator

- **Diagnosis and Medical History**

All diagnosis and medical history including previous treatment history of NIIPPU

Following items were included to evaluate the medical condition of the patient:

NIIPPU specific medical history

Date of onset of NIIPPU (date of first symptom appeared), date of first investigation by either a non-ophthalmologist or an ophthalmologist (date of diagnosis), eye(s) affected, anatomical and etiological type of uveitis underlying systemic and / or immune-mediated inflammatory disease if any; ocular complications (cataract, glaucoma etc.). number of flares within the past 12 months (including the current flare), date of last flare prior to current flare, prednisone dose at time of last flare (or equivalent prednisone dose, if subject was on another corticosteroid), and date of onset of current flare

Previous treatment for NIIPPU;

Presence/absence of previous drug treatment for NIIPPU, biologics, other drugs (3 months ago from start of Humira® injection): product name of oral glucocorticoids, dose of oral steroid, previous non-drug treatment including surgery for NIIPPU

- **Treatment using Humira®**

The patient was administered Humira® according to the approved drug use. Per approved label in Korea, patients were given subcutaneous injections of adalimumab 80 mg at Week 0, 40 mg at week 1 and 40 mg every 2 weeks starting at Week 3.

The dose, frequency and duration of treatment (start/end date) were recorded on the case report form (CRF). If the study drug was suspended or terminated during the treatment period, the reason was recorded. The information of compliance with the regimen was collected.

- **Concomitant medication including surgery**

Concomitant medications including tuberculosis (TB) prophylaxis regimen, antibiotics, and corticosteroids were recorded, and items recorded were the

followings: generic name (brand name if concomitant agent), daily dosage, duration (start/end date) and indication.

- **Safety**

  Adverse events (AEs); Regardless of results of causality assessment, presence of AE(s), type of AE(s), onset date, end date, severity, causality assessment by investigator on the AE(s), action taken, outcome were captured from all subjects over the study period (from the first administration to 70 days following 22 weeks from first dose of adalimumab or the last administration of adalimumab in case subjects stopped adalimumab administration before 22 weeks).

- **Effectiveness**

  From the subjects treated with Humira® for 22 weeks, these data were collected at baseline, week 6, week 14 and week 22 as below.

  For Anterior Chamber (AC) cell grade (SUN criteria) and Vitreous Haze grade (NEI/SUN criteria), the treatment response as improvement, no improvement and, aggravation were evaluated.

- **Data Sources**

  The data sources in this study were from institute's medical chart. Participant physicians in this study transcribed the data from medical chart to CRF which AbbVie Ltd. prepared. If the event had fulfilled the serious criterion (serious adverse vent, SAE), the "SAE Report" form was to be completed additionally.

  CRF was provided by AbbVie Ltd. The investigator submitted collected information within the study period using this form. The case report form had to include any background information of the research subjects such as gender, age, past medical history, and evaluation. CRF had to keep patient confidentiality; for an example, even patient name (patient initial was permissible) and the date of birth were not recorded (recording of patient age or birth year/month was permissible). The designated

investigator or a staff under the investigator had to record this CRF, and AbbVie Ltd. or any commissioned organization did not record the case report form in place of the investigators or designated personnel.

Results

This study was conducted in 17 sites in South Korea, from 25 January 2018 (First patient first visit, FPFV) to 16 July 2020 (Last patient last visit, LPLV). The objectives of this study were to evaluate the safety and effectiveness of adalimumab (Humira®) for the treatment of NIIPPU patients under a routine clinical practice. During the entire PMS period, CRFs were collected from a total of 158 subjects. Of these, 155 subjects were included in the safety analysis set and 148 subjects were included in the effectiveness analysis set.

The mean age of the 155 subjects in the safety analysis set was 45.94±12.77 years. Of 155 subjects included in the safety analysis set, 52.26% (81/155 subjects) were 'Male' and 47.74% (74/155 subjects) were 'Female'. The mean height was 166.46±8.68 and the mean weight was 66.11±12.65 kg. 63.87% (99/155 subjects) did not have family history of uveitis ('No'), and 36.13% (56/155 subjects) were 'Unknown', and there were no subjects in 'Yes'. There were no pregnant women, none of the subjects were under 19 years old, nor any subjects who had renal disorder while geriatrics made up 7.10% (11/155 subjects) and subjects who had hepatic disorder were in 1.29% (2/155 subjects). The mean duration of uveitis was 1,425.20±1,447.97 days. 70.97% (110/155 subjects) were diagnosed with 'Non-infectious panuveitis', 24.52% (38/155 subjects) were diagnosed with 'Non-infectious posterior uveitis', and 4.52% (7/155 subjects) were diagnosed with 'Non-infectious intermediate uveitis'. 84.52% (131/155 subjects) were affected 'Both' eyes, 9.03% (14/155 subjects) were affected 'Right' eye, and 6.45% (10/155 subjects) were affected 'Left' eye. For anatomical and etiological type of uveitis, 76.77% (119/155 subjects) were 'Systemic immune-mediated inflammatory disease' and 23.23% (36/155 subjects) were 'Others'. 57.42% (89/155 subjects) had ocular complications ('Yes'), 38.06% (59/155 subjects) did not have ocular complications ('No'), and 4.52% (7/155 subjects) were 'Unknown'. The mean number

of flares within the past 12 months was 2.50±1.31 times. For treatment of prednisone/another corticosteroid, 50.00% (60/120 subjects) were 'Prednisone', 42.50% (51/120 subjects) were 'Unknown', 5.00% (6/120 subjects) were 'Another corticosteroid' and 2.50% (3/120 subjects) were 'Prednisone + Another corticosteroid'. There were no subjects who had history of allergies while 12.26% (19/155 subjects) had past medical history and 25.16% (39/155 subjects) had concomitant disease(s). 86.45% (134/155 subjects) had previous treatment for NIIPPU, 8.39% (13/155 subjects) did not have previous treatment for NIIPPU, and 5.16% (8/155 subjects) were 'Unknown'. 84.52% of subjects (131/155 subjects) were reported at least one current concomitant medication. The mean total administration period of adalimumab was 157.06±65.30 days and the mean total administration dose of adalimumab was 489.33±175.03 mg. 92.90% (144/155 subjects) confirmed '≥ 80%' compliance, 5.16% (8/155 subjects) were 'Unknown', and 1.94% (3/155 subjects) confirmed '50-79%.

Of 155 subjects included in the safety analysis set, subjects who had discontinued before 22 weeks after the first adalimumab administration were in 21.94% (34/155 subjects).

The subjects were categorized into 'after the contract date' and 'before the contract date'. 'After the contract date' group is for the subjects who had been administered the first dose of adalimumab on the same date or after the study initiation (contract date). 'Before the contract date' group is for the subjects who had been administered the first dose of adalimumab before the study initiation (contract date). Of 155 subjects included in the safety analysis set, subjects who started adalimumab administration after the contract date were in 69.03% (107/155 subjects) and subjects who started adalimumab administration before the contract date were in 30.97% (48/155 subjects).

The incidence proportion of AEs was 8.39% (13/155 subjects, 25 events), ADRs was 3.23% (5/155 subjects, 6 events), SAEs was 1.94% (3/155 subjects, 3 events), unexpected AEs was 6.45% (10/155 subjects, 13 events), unexpected ADRs was 1.29% (2/155 subjects, 2 events), and unexpected SAEs was 1.29% (2/155 subjects, 2

events). Most frequently reported AEs were ′Macular oedema', 'Paraesthesia', and 'Myalgia' (1.29%, 2/155 subjects, 2 events, 3 events, 2 events) ADRs were 'Ocular discomfort', 'Injection site hypersensitivity', 'Injection site pain', 'Paraesthesia', 'Myalgia', and 'Eczema' (0.65%, 1/155 subject, 1 event) and reported SAE was 'Macular oedema' (1.29%, 2/155 subjects, 2 events). Most frequently reported unexpected AE was ′Macular oedema' (1.29%, 2/155 subjects, 2 events), unexpected ADRs were 'Ocular discomfort' and 'Injection site hypersensitivity' (0.65%, 1/155 subject, 1 event) and unexpected SAE was ′Macular oedema' (1.29%, 2/155 subjects, 2 events).

The incidence rate of AEs occurring during the observation period was 38.47 AEs per 100 PTYs, the incidence rate of ADRs was 9.32 ADRs per 100 PTYs, the incidence rate of SAEs was 4.62 SAEs per 100 PTYs, the incidence rate of unexpected AEs was 20.01 unexpected AEs PTYs, the incidence rate of unexpected ADRs was 3.08 unexpected ADRs per 100 PTYs, and the incidence rate of unexpected SAEs was 3.08 unexpected SAEs per 100 PTYs. The PTs of AE, ADRs, SAE, unexpected AE, unexpected ADRs, and unexpected SAE of the highest incidence rate were presented as follow. The incidence rate of AE occurring during the observation period was 'Paraesthesia' in 4.62 AEs per 100 PTYs. The incidence rate of ADRs occurring during the observation period were 'Ocular discomfort', 'Injection site hypersensitivity', 'Injection site pain', 'Paraesthesia', 'Myalgia', and 'Eczema' each in 1.54 ADRs per 100 PTYs. The incidence rates of SAEs, unexpected AEs and unexpected SAEs occurring during the observation period were 'Macular oedema' in 3.08 SAEs, unexpected AEs and unexpected SAEs per 100 PTYs. The incidence rate of unexpected ADRs occurring during the observation period were 'Ocular discomfort' and 'Injection site hypersensitivity' each in 1.54 unexpected ADRs per 100 PTYs.

Among the subjects excluded from the safety analysis set, there were no subjects who experienced any AEs.

During the PMS period, the difference in the incidence proportion of AEs according to 2 factors of Anatomical and etiological type of uveitis (p=0.0124), Concomitant disease (p=0.0008) was statistically significant.

Based on this result, logistic regression analysis was conducted to identify the specific factors that influence on the frequency of AE. As a result of the analysis anatomical and etiological type of uveitis (p=0.0491) and concomitant disease (p=0.0034) were the factors that affect the frequency of AE. More in detail, odds ratio with AEs incurred was 0.29 indicating that subjects with 'Systemic immune-mediated inflammatory disease' are less at risk than 'Others' and odds ratio with AEs incurred was 6.71 indicating that subjects with concomitant disease are more at risk than those without concomitant disease.

In effectiveness results, if any of the following criteria were met in at least one eye, it was considered as 'Ineffectiveness', otherwise it was considered as 'Effectiveness': a two-step increase relative to baseline or an increase from grade 3+ to grade 4+ in Anterior Chamber (AC) cell grade; a two-step increase relative to baseline or an increase from grade 3+ to grade 4+ in Vitreous Haze grade; worsening ≥3 lines from the best corrected visual acuity achieved after the first dose on visual acuity chart; or development of new active or inflammatory lesions. Of 148 subjects included in the effectiveness analysis set, 93.24% (138/148 subjects) were evaluated as 'Effectiveness' and 6.76% (10/148 subjects) were evaluated as 'Ineffectiveness'.

Discussion

The reported ADRs were 'Ocular discomfort', 'Injection site hypersensitivity', 'Injection site pain', 'Paraesthesia', 'Myalgia', and 'Eczema' each in 0.65% (1/155 subject, 1 event). All those 6 events were non-SADRs and 2 events ('Ocular discomfort', 'Injection site hypersensitivity') were unexpected ADRs. The reporting term of 'Ocular discomfort' in subject no.08-012 was 'eye discomfort, OD'. The severity of the ADR was 'Mild' and there was no action taken with adalimumab. The outcome of the ADR was 'Recovered/Resolved'. The reporting term of 'Injection site hypersensitivity' in subject no.17-010 was 'Injection site allergy'. The severity of the

ADR was ‘Mild’ and by the investigator’s decision, administration of adalimumab was permanently discontinued. The outcome of the ADR was ‘Recovered/Resolved’. ‘Ocular discomfort’ is one of the symptoms that can occur with uveitis, and ‘Injection site hypersensitivity’ can be seen as a more specific term of ‘Injection site reaction’ which is already listed in the approved local label. Therefore, although these unexpected ADRs are not listed in the approved local label, it has been considered as one of AEs that could be expected to occur among any patient who administers adalimumab including non-infectious intermediate, posterior, or panuveitis patients.

The difference in the AE incidence proportion by anatomical and etiological type of uveitis was statistically significant (p=0.0491). However, most of the details of ‘Others’ were ‘Unknown’ in 97.3% (36/37) and there was a large difference in the number of subjects in the two groups (119 subjects (76.8%) in ‘Systemic immune-mediated inflammatory disease’, 36 subjects (23.2%) in ‘Others’). Thus, this finding cannot be seen as clinically significant.

The difference in the AE incidence proportion by concomitant disease was statistically significant (p=0.0034). Of 9 subjects who had concomitant disease and experienced AE(s), 4 subjects had ‘Diabetes mellitus’, 2 subjects had ‘Hypertension’, and 2 subjects had ‘Retinitis pigmentosa’ as concomitant diseases. Generally, patients who had chronic disease such as diabetes mellitus or hypertension are at increased risk of complications. ‘Retinitis pigmentosa’ is an inherited disorder that results from harmful changes in any one of more than 50 genes. In summary, it is difficult to conclude that concomitant disease affects to AE incidence proportion.

Since the PMS depends on the data from the non-interventional real-world clinical practice, which may differ among clinicians, it is difficult to conclude that the result of this PMS are confirmative.

In conclusion, PMS on Humira® showed no significant factors that affect the safety and effectiveness of adalimumab. In terms of effectiveness, the results demonstrate adalimumab to be effective for non-infectious intermediate, posterior, and panuveitis.

There were no new safety signal or unexpected trend was identified for adalimumab. The safety profile is consistent with the known safety profile of adalimumab for the treated subject population. The safety of adalimumab will be continuously monitored after the submission of this report through collection of safety information from other solicited and unsolicited sources.

Marketing Authorisation Holder(s)

AbbVie Ltd.

Names and Affiliations of Principal Investigators

Refer to section 3.0 Investigators