1.0 Abstract

Title

A Prospective, Mono-Country and Multi-center study to Observe safety and effectiveness in KoREan intestinal Behcet's disease (BD) patients treated with adalimumab (AMORE study)

Rationale and Background

This non-interventional, observational study was conducted to investigate safety and effectiveness of adalimumab in Korean intestinal Behcet's disease (BD) subjects as a commitment for indication approval of intestinal BD.

Research Question and Objectives

The primary and secondary objectives of this study were to obtain the following information of safety profile of adalimumab in Korean intestinal BD subjects in routine clinical practice.

Primary Objectives:

1) All adverse event
2) Serious adverse event
3) Unexpected adverse event

Secondary Objectives:

1) All adverse drug reaction
2) Serious adverse drug reaction
3) Unexpected adverse drug reaction

Exploratory Objectives:

The exploratory objectives of this study were to obtain the following information to observe effectiveness of adalimumab in Korean intestinal BD subjects in routine clinical practice.

1) The percentage of subjects who achieved ≥20 points of reduction in Disease Activity Index for Intestinal Behcet's Disease (DAIBD) score from adalimumab baseline at week 4, 8, 12, 28 and 56
2) The mean measured value change of C-reactive protein (CRP) level from baseline at week 4, 8, 12, 28 and 56
3) The mean score change of endoscopic improvement from baseline at week 28 and 56

Study Design

Post-marketing observational study

Setting

Selection of Study Population

All subjects who met the inclusion/exclusion criteria and received treatment with adalimumab due to intestinal BD from the date of study initiation and during the study at the sites where the study contract was signed were eligible to participate in the study. They were enrolled in the study using this precedent survey.

Inclusion Criteria

1) Subjects must be an adult ≥19 years
2) Subjects who are eligible to be treated with adalimumab for intestinal BD in accordance with the approved label in Korea
3) Subjects provide written authorization form for use/disclose of personal health data prior to participating in this study

Exclusion Criteria

1) Subjects who are contraindicated to any anti-Tumor Necrosis Factor (TNF) agent
2) Female subjects who are pregnant or breast feeding
3) Subjects who are participating in other interventional clinical trials

Subjects and Study Size

In Korea, Intestinal BD subjects are managed in limited number of hospitals. Therefore, this study was conducted in major 10 hospitals where intestinal BD subjects treated with adalimumab. Sites not initially included in this study but prescribed adalimumab to intestinal BD subjects during study period were added.
This study was planned to be conducted with 3-year enrollment period and approximately 50-60 subjects were expected to be enrolled. Actually, this study was conducted with 4-year enrollment period and a total of 59 subjects were enrolled. The sample size was not calculated according to statistical method, but it was based on estimated number of subject who will be treated with adalimumab due to intestinal BD during study period.

Variables and Data Sources

Variables

1) Demographics and subject characteristics
2) Concomitant medication/therapy
3) Previous intestinal BD-related medication
4) Administration of adalimumab
5) Tuberculosis (TB) related information
6) DAIBD score
7) CRP value
8) Endoscopic improvement
9) Evaluation of non-Gastrointestinal (GI) BD symptoms
10) Adverse events

Data Sources

Paper based Case Report Forms (CRFs)

Results

Subject Characteristics

Of 59 subjects whose CRFs were retrieved during the study period, 50 subjects were included in the safety evaluation set, 44.00% (22/50 subjects) were male and 56.00% (28/50 subjects) were female. The mean age was 47.52 (±14.83) years old ranged from 21.00 to 78.00 years old. Twenty six percent (13/50 subjects) were between the age of 40 and 49 years old, and 22.00% (11/50 subjects) were between 50 and 59 years old. Eighteen percent (9/50 subjects) were between the age of 60 and 69 years old and 16.00% (8/50 subjects) were between 19 and 29 years old and 14.00% (7/50 subjects) were between 30 and 39 years old and 4% (2/50 subjects) were more than 70 years old. None of the subjects were under 19 years old.

The mean duration of intestinal BD was 57.12 (±55.13) months ranging from 0.00 months to 216.00 months. About Non-GI BD symptom, oral ulcer had been the most commonly reported as 60.00% (30/50 subjects), followed by 26.00% (13/50 subjects) with skin lesion, 22.00% (11/50 subjects) with arthralgia, 16.00% (8/50 subjects) with eye lesion, 12.00% (6/50 subjects) with genital ulcer and etc. Thirty percent (15/50 subjects) had past medical history, 72.00% (36/50 subjects) had 1 or more co-morbidities at the time of study participation and 92.00% (46/50 subjects) had concomitant medication(s) during the study period.

Prior to the treatment with Humira®, 92.00% (46/50 subjects) had been treated with non-biologics - 84.00% (42/50 subjects) with 5-ASA/sulfasalazine, 80.00% (40/50 subjects) with systemic steroids, 54.00% (27/50 subjects) with immunomodulator of azathioprine, 40.00% (20/50 subjects) with other non-biologics (colchicine, rebamipide, and etc.), and so

on. Twenty percent (10/50 subjects) had been treated with biologics, and all of the biologics were infliximab.

The subjects were categorized into 'before enrollment' and 'after enrollment'. 'Before enrollment' group is for the subjects who had been administered the first dose of Humira® before enrollment into this study. 'After enrollment' group is for the subjects who had been administered the first dose of Humira® on the same date or after they signed the informed consents form for this study.
Of 50 subjects in the safety evaluation set, the subjects included in 'before enrollment' were 38.00% (19/50 subjects), and 'after enrollment' were 62.00% (31/50 subjects). Among all subjects in safety evaluation set, the mean of total dose of administration was 1,508.80 (±370.42) mg ranged from 240.00 mg to 2,320.00 mg. The mean of total dosing frequency was 33.76(±9.24) times ranged from 2.00 times to 54.00 times. Humira® treatment status at the last administration in this study was ongoing for 88.00% (44/50 subjects) and discontinuation for 12.00% (6/50 subjects). The reasons for discontinuation of Humira® administration were others (e.g., PI's judgement) in 60.00% (3/5 subjects) and inadequate response and adverse event in 20.00% (1/5 subjects) each.

Safety

The safety evaluation set includes all subjects who have received at least one administration of Humira® following the initiation of study and have completed follow up for the safety information. Among 59 enrolled subjects, 50 subjects were included in the safety evaluation set, excluding 9 subjects either who did not use the drug according to the approved indication or dosage, or who with eligibility violation, or who failed to follow up or who were not administered Humira®. Five subjects whose administration schedule was delayed based on PI's medical judgement were included in safety evaluation set.
All adverse events collected among subjects during this study period were reported regardless of causality to Humira® administration.

A total of 122 adverse events in 72.00% (36/50 subjects) were reported from 50 safety evaluation subjects during this study period. Of them, 24.00% (12/50 subjects) had 28 adverse events which were evaluated as adverse drug reactions.

The most frequently reported adverse event was arthralgia occurred in 28.00% (14/50 subjects) with 15 cases. Mouth ulceration was reported in 22.00% (11/50 subjects) with 13 cases. Skin lesion was reported in 20.00% (10/50 subjects) with 10 cases. These were cases in which non-GI BD symptoms evaluated as 'aggravated' or 'newly occurred' was reported as AEs. Behcet's syndrome was reported in 18.00% (9/50 subjects) with 16 cases. Among all Behcet's syndrome reported as AE, the 15 cases were aggravation of Behcet's disease and 1 case was BD-related operative treatment (Behcet's disease laparoscopic ileocecectomy). The most frequently reported adverse drug reactions were mouth ulceration, cough and pyrexia occurred in 4.00% (2/50 subjects) with 2 cases each.
Psoriasis was reported in 2.00% (1/50 subjects) with 2 cases, Behcet's syndrome (aggravation of Behcet's disease), diarrhoea, abdominal pain, abdominal pain upper, constipation, gastrooesophageal reflux disease, nausea, dermatitis, dermatitis contact, pruritus, rash, pyelonephritis acute, disseminated tuberculosis, fungal infection, pharyngitis, injection site induration, sleep disorder, hypophagia, cytopenia and haematuria was reported in 2.00% (1/50 subjects) with 1 case each.

A total of 37 serious adverse events in 26.00% (13/50 subjects) were reported from 50 safety evaluation subjects. Of these adverse events, 11 serious adverse events which occurred in 8.00% (4/50 subjects) were considered as serious adverse drug reactions. The most frequently reported adverse event was Behcet's syndrome occurred in 10.00% (5/50 subjects) with 12 cases. Among all of Behcet's syndrome reported as SAE, the 11 cases were aggravation of Behcet's disease and 1 case was BD-related operative treatment (Behcet's disease laparoscopic ileocecectomy). Pyrexia was reported in 6.00% (3/50 subjects) with 3 cases. Intestinal obstruction, pyelonephritis acute, hypophagia was reported in 4.00% (2/50 subjects) with 2 cases each. The most frequently reported serious adverse drug reaction were pyrexia occurred in 4.00% (2/50 subjects) with 2 cases. Abdominal pain,

abdominal pain upper, diarrhoea, nausea, pyelonephritis acute, disseminated tuberculosis, pharyngitis, hypophagia, and cough was reported in 2.00% (1/50 subjects) with 1 case each.

A total of 55 unexpected adverse events in 54.00% (27/50 subjects) were reported from 50 safety evaluation subjects. Of these adverse events, 9 unexpected adverse events which occurred in 14.00% (7/50 subjects) were considered as unexpected adverse drug reactions. The most frequently reported unexpected adverse event was mouth ulceration occurred in 22.00% (11/50 subjects) with 13 cases. Behcet's syndrome was reported in 18.00% (9/50 subjects) with 16 cases. Among all Behcet's syndrome reported as AE, 15 cases were aggravation of Behcet's disease and 1 case was BD-related operative treatment (Behcet's disease laparoscopic ileocecectomy). Genital ulceration was reported in 6.00% (3/50 subjects) with 3 cases. The most frequently reported unexpected adverse drug reaction was also mouth ulceration occurred in 4.00% (2/50 subjects) with 2 cases. Behcet's syndrome (aggravation of Behcet's disease), abdominal pain upper, constipation, sleep disorder, hypophagia, injection site induration and dermatitis contact were reported in 2.00% (1/50 subjects) with 1 case each.

Intestinal BD is a chronic, relapsing, multisystem inflammatory disorder of unknown etiology classified among the vasculitides [7]. Clinical presentation is characterized by recurrent ulcers [8]. So, the aggravation of intestinal BD was common symptoms of progression of disease. In this study, the only one AE, aggravation of Behcet's disease (08-003 subject) was evaluated ADR and the event was mild and recovered.

The relationships between various factors (i.e., demographics, medical characteristics, and treatment with Humira®) and the adverse events / adverse drug reactions following Humira® were explored. Univariate analysis and logistic regression analysis were conducted on demographics, medical characteristics, and treatment with Humira®. And then, multivariable logistic regression analysis was conducted in factors which showed $p \leq 0.2$ in univariate analysis (Chi-square test or Fisher's exact test) and univariate logistic regression analysis and used stepwise selection. For adverse event, it was found that multivariable logistic regression analysis on the incidence of adverse events was not statistically

significant.
For adverse drug reaction, it showed statistically significant result according to duration of intestinal BD (p=0.0418). For a month increase in duration of intestinal BD, the odds of adverse drug reaction occurrence decease by a factor of 0.9757 (95% C.I.: [0.9528, 0.9991]). This result can be interpreted that the incidence rate of ADRs was decreased as the duration of intestinal BD was longer. However, this interpretation required attention because the frequency of Humira® administration and total dosage of Humira® did not affect to incidence of ADRs. From the results of the previous observation study in Japan that analyzed 462 subjects, the duration of intestinal BD did not influence to incidence of ADRs [9]. The sample size of the previous study was larger than this study so the data was considered representation of real world.
It was found that multivariable logistic regression analysis on the incidence of adverse drug reactions was not statistically significant in other factors.

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

Effectiveness

The effectiveness analyses were performed using effectiveness evaluation set including the subjects who administered Humira® for intestinal BD with any effective data (DAIBD score, CRP value, endoscopic improvement) among the safety evaluation set. Among 50 safety evaluation subjects, 50 subjects were included in the effectiveness evaluation set, excluding 0 subjects. The two subjects, whose effectiveness evaluation was not properly conducted because their data from evaluation parameters were missing, were already excluded from the safety analysis set for other reasons. Five subjects whose administration schedule was delayed based on PI's medical judgement were included in safety evaluation set.

The effectiveness assessment of Humira® therapy was presented by the number and percentage of the subjects with clinical response. The DAIBD score was used to assess

disease activity of intestinal BD and the change scores of DAIBD that corresponded to no change, slightly improvement, significant improvement, slightly worsening, and significant worsening were (-9 to 10), (10–19), (≥20), (-14 to -11), and (≤-15), respectively [6]. Also, the Korea Health Insurance Review & Assessment Service approves continuous administration only if the DAIBD decreases by ≥20 points within 12 weeks after the first administration of adalimumab. Accordingly, clinical response was defined as decrease in DAIBD score from baseline by ≥20 points within 12-weeks post-treatment.

The results of the analysis on the DAIBD score for therapy showed that the mean DAIBD score at baseline visit was 109.27 (±32.53) ranged from 0.00 to 170.00. The mean DAIBD score at 4 weeks visit was 50.30 (±39.13) ranged from 0.00 to 170.00. The mean decrease from baseline to 4 weeks visit was 57.27 (±46.74) and it showed statistically significant result (p<0.0001). The mean DAIBD score at 8 weeks visit was 39.25 (±36.10) ranged from 0.00 to 175.00. The mean decrease from baseline visit to 8 weeks visit was 70.13 (±38.52) and it showed statistically significant result (p<0.0001). The mean DAIBD score at 12 weeks visit was 47.55 (±43.72) ranged from 0.00 to 169.00. The mean decrease from baseline visit to 12 weeks visit was 59.73 (±43.23) and it showed statistically significant result (p<0.0001). The mean DAIBD score at 28 weeks visit was 35.83 (±37.09) ranged from 0.00 to 135.00. The mean decrease from baseline visit to 28 weeks visit was 70.50 (±42.17) and it showed statistically significant result (p<0.0001). The mean DAIBD score at 56 weeks visit was 33.45 (±29.28) ranged from 0.00 to 100.00. The mean decrease from baseline visit to 56 weeks visit was 72.07 (±39.99) and it showed statistically significant result (p<0.0001). The mean DAIBD score at early discontinuation visit was 110.00 (±21.21) ranged from 95.00 to 125.00. The mean increase from baseline visit to early discontinuation visit was 15.00 (±7.07) and it did not show statistically significant result (p=0.5000).

The results of the analysis on the DAIBD improvement at 4, 8, 12, 28, 56 weeks post-treatment showed below. DAIBD improvement was defined as decrease in DAIBD score from baseline by ≥20 points.

Eighty one point eighty two percent (27/33 subjects) reported DAIBD improvement in 4 weeks. Eighty seven point fifty zero percent (35/40 subjects) reported DAIBD improvement in 8 weeks. Ninety point ninety one percent (30/33 subjects) reported DAIBD improvement in 12 weeks. Ninety percent (27/30 subjects) reported DAIBD improvement in 28 weeks. Eighty nine point sixty six percent (26/29 subjects) reported DAIBD improvement in 56 weeks. There were 2 subjects with early discontinuation of the treatment. Both did not show DAIBD improvement. The results showed that clinical response rate was 90.91%.

The relationships between various factors (i.e., demographics, medical characteristics, and treatment with Humira®) and effectiveness results following Humira® were explored. Univariate analysis and logistic regression analysis were conducted on demographics, medical characteristics, and treatment with Humira®. And then, multivariable logistic regression analysis was conducted in factors which showed $p \leq 0.2$ in univariate analysis (Chi-square test or Fisher's exact test) and univariate logistic regression analysis and used stepwise selection. It was found that multivariable logistic regression analysis on the clinical response rate was not statistically significant.

Discussion

There were no specific findings in this post-marketing observational study with adalimumab for intestinal BD. In terms of effectiveness, the results demonstrate Humira® to be effective for intestinal Behcet's disease. In conclusion, no new safety signal or unexpected trend is identified for adalimumab. The safety profile is consistent with the known safety profile of adalimumab for the treated subject population. 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.

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