1.0 Abstract

Title

A Prospective Multi-Center study to observe the Effectiveness on Ulcerative Colitis and predictive factors of clinical REsponse in Korean Patients treated with Adalimumab (EUREKA study)

Keywords

Ulcerative Colitis, Adalimumab, Humira, Mayo Score, Korean, Prospective observational study

Rationale and Background

Ulcerative colitis (UC) is a chronic inflammatory bowel disorder characterized by a relapsing and remitting course. In Korea, the incidence and prevalence of CD (Crohn's Disease) and UC are low compared to that in Europe and the USA, but are increasing rapidly. According to a recent epidemiological survey of Inflammatory Bowel Disease (IBD) in Korea that extrapolated the national incidence from the actual measured incidence in a sample from an urban district in Seoul, the mean annual incidence of UC in Korea increased from 0.34 per 100,000 inhabitants in 1986 - 1990 to 3.08 per 100,000 inhabitants in 2001 - 2005.[(1)] The adjusted prevalence rate of UC per 100,000 inhabitants was 30.87 (95% CI, 27.47-34.27). Genotypic features and clinical characteristics of Korean IBD are somewhat different from those seen in Western countries. For example, the HLA-DRB1*1502 allele was shown to be positively associated with UC in Korea, whereas in Western populations this association is absent.[(2)] The clinical features of UC at diagnosis are reported to be similar in Koreans and Westerners,[(3)] however, the clinical course of UC in Korean patients seems milder than that in Western countries, as indicated by the lower rates of colectomy and better responses to pharmacological management.[(4)] In terms of drug toxicity, Korean patients with IBD who are treated with AZA/6-MP experience myelotoxicity more frequently than similarly treated Europeans. Among 133 IBD patients treated with azathioprine in Korea, leucopenia occurred in 75 cases (56.4%), which more frequent than the rates reported in Western studies.[(5)] In a retrospective study of infliximab in 134 Korean UC patients, the rates of clinical response and remission were 87% and 45% at week 8.[(6)] Long-term clinical response and remission rates were 71% and 52%, respectively, and mucosal healing was the only factor influencing long-term response. Recently (2013), adalimumab was already used in the treatment of CD, was approved treating moderately to severely active UC in adults with an inadequate response to conventional therapy or who are intolerant to or have medical contraindications for such therapies. To our best knowledge, there is no published data about the effectiveness and safety of adalimumab for

the treatment of UC in Korean patients. In addition, gut bacteria plays an important role in the onset and perpetuation of intestinal inflammation in IBD. Some dysbiosis have been found in UC as well as Crohn's disease, and also their relationship to the clinical course of IBD has been suggested. Composition of Fecal microbiota (16S rRNA gene sequencing) will be regarded as predictive factors of clinical response in this study.[7-9]
This study was the first prospective study to evaluate the effectiveness of adalimumab in Korean patients with UC in the real-life clinical setting and to explore clinical predictive factors of response.

Research Question and Objectives

To evaluate the real world effectiveness of adalimumab in Korean UC patients and to explore potential predictive factors of clinical response.

Primary Endpoint:
· Clinical response at week 8
· Clinical response at week 56 in week 8 responders

Secondary Endpoints:
· Clinical remission at week 8 and 56
· Steroid free remission at week 8 and 56
· Mucosal healing at week 8 and 56
· Change of full and partial Mayo score from baseline overtime
· The change of the composition of Fecal micro biota from baseline at week 56
· The mean change of Fecal calprotectin level from baseline at week 56

Study Design

This was a prospective, single country, multi-center study in UC patients treated with adalimumab.

Setting

Of the 150 subjects who enrolled in this study, 4 subjects were not included in ITT set because of not treated to study drug. Based on case report forms (CRFs), total 146 subjects were enrolled the study from 11 Jun 2015 to 17 Sep 2018, at 19 sites in Korea.

Subjects and Study Size, Including Dropouts

· Planned: about 147 subjects (including 5% dropouts)
· Enrolled: 150 subjects

· ITT (Intend-To-Treat) set: 146 subjects
· PP (Per-Protocol) set: 49 subjects

Variables and Data Sources

Variables and data sources included consisting of medical records containing demographic, UC-related medication, concomitant medication, adalimumab administration, Full and partial Mayo score, endoscopic sub-score for mucosal healing, general lab test including CRP, albumin and hemoglobin, adalimumab related test (trough level and antibody level), and stool examination (fecal calprotectin level and fecal microbiota).

Results

This study was conducted in 19 sites in South Korea, from 11 Jun 2015 to 18 Sep 2018. The primary objective of this study was to investigate the percentage of patient with clinical response at week 8 and clinical response at week 56 in week 8 responders. The secondary objectives were to observe the percentage of patients with clinical remission, steroid-free remission, mucosal healing at week 8 and 56, The change of partial Mayo score from baseline overtime and the composition of fecal micro biota and mean change of fecal calprotectin level from baseline at week 56 in routine clinical practice.

The baseline assessment performed prior to the first dose of adalimumab (Visit 1). Study visits were conducted at 8, 16, 24, 32, 40, 48 and 56 weeks after baseline. Subjects had one Follow-up approximately 30 days after the last dose of adalimumab.

Of the 150 subjects who enrolled in this study, 4 subjects were not included in ITT set. Subjects in the ITT set were evaluated to determine whether they were in the PP set.

The percentage of subjects with clinical response at week 8 and 56 in the ITT set was 52.05% (76/146 subjects)and 28.08% (41/146 subjects), respectively. .Of76 subjects in clinical responders at week 8, durable clinical response was 53.95% (41/76 subjects) at week 56.

For observing the effectiveness of adalimumab on UC disease in routine clinical practice, clinical remission, steroid-free remission, mucosal healing, Full and Partial Mayo score, composition of fecal micro biota and fecal calprotectin level was assessed.

The percentage of patients with clinical remission in the ITT set was 23.97% (35/146 subjects) and 21.92% (32/146 subjects) at week 8and 56, respectively. Of76 subjects in clinical responders at week 8, durable clinical remission was 35.53% (27/76 subjects) at week 56.

The percentage of patients with steroid-free remission in the ITT set was 12.33% (18/146 subjects) and 21.23% (31/146 subjects) at week 8 and 56, respectively. Of76 subjects in clinical responders at week 8, steroid-free remission was 34.21% (26/76 subjects) at week 56.

In ITT set, the percentage of patient with mucosal healing was 39.04% (57/146 subjects) and 30.14% (44/146 subjects) at week 8 and 56, respectively. Of76 subjects in clinical responders at week 8, mucosal healing was 46.05% (35/76 subjects) at week 56.

There was statistically significant decreased in the mean change of full and partial Mayo score from baseline overtime in subjects who had clinical response at weeks 56, showing lower in non-clinical responders at week 56.

The mean of the composition of fecal calprotectin level was decreased at baseline, week 8 and week 56. At week 8, there was a statistically significant decreased in the composition of fecal calprotectin level in clinical responders at week 8, showing lower than in non-clinical responders at week 8. Also, the subjects who were clinical response at week 56 showed lower levels of fecal calprotectin levels in the baseline and week 56 than subjects who were non-clinical responders.

The same evaluations were also performed in the PP set.

The percentage of patients with clinical response at week 8 and 56 in the PP set was 83.67% (41/49 subjects) and 89.80% (44/49 subjects), respectively. The percentage of patients with clinical response at week 56 in week 8 responders was 97.56% (40/41 subjects).

The percentage of patients with clinical remission at week 8 and 56 in the PP was 32.65% (16/49 subjects) and 59.18% (29/49 subjects), respectively. The percentage of patient with clinical remission at week 56 in week 8 clinical responders was 65.85% (27/41 subjects).

The percentage of patient with steroid-free remission at week 8 and 56 in the PP was 16.33% (8/49 subjects) and 57.14% (28/49 subjects), respectively. The percentage of patients with steroid-free remission at week 56 in week 8 responders was 63.41% (26/41 subjects).

The percentage of patient with mucosal healing at week 8 and 56 in the PP was 59.18% (29/49 subjects) and 79.59% (39/49 subjects), respectively. The percentage of patient with mucosal healing at week 56 in week 8 responders was 82.93% (34/41 subjects).

There was a statistically significant decreased in the mean change of full and partial Mayo score from baseline overtime in subjects who were clinical response at weeks 56, showing lower in non-clinical responders at week 56 ..

Alpha diversity of fecal bacteria has been decreased at 56 weeks compared to baseline and week 8.

The composition of fecal calprotectin levels decreased at baseline, week 8, week 56. At week 8, there was statistically significant decrease in the composition of fetal calprotectin levels in subjects who were clinical responders at week 8, rather than non-clinical responders at week 8. At baseline and week 56, the lower composition of fecal calprotectin level was found in subjects who were clinical response at Week 56 compared to subjects without clinical response.

During the study period, among AEs, ADRs, SAE, SADRs leading to discontinuation of adalimumab and were used as safety endpoint. The incidence of AEs and ADRs leading to discontinue adalimumab were 9.59% (14/146 subjects, 14 cases) and 6.16% (9/146 subjects, 9 cases). And the incidence of SAEs and SADRs leading to discontinue adalimumab were 6.16% (9/146 subjects, 9 cases) and 2.74% (4/146 subjects, 4 cases) respectively. Also, the incidence of SAEs during study period was 17.12% (25/146 subjects, 29 cases). Among them, there were 9 ADRs and SAEs leading to discontinue adalimumab in 9 subjects: ‘Haematochezia’ and ‘Colitis ulcerative’.

No new safety signals were observed. The known benefit-risk profile of adalimumab for UC remains unchanged.

Discussion

In this study, the primary endpoints in this study are clinical response at week 8 and at week 56 in week 8 responders.

For the percentage of clinical response at week 8 and 56 in the ITT set was 52.05% (76/146 subjects) and 37.67% (55/146 subjects). The result of PP set was opposite to the result of ITT set.

In the multi-center, observational, prospective study in Spain, of 53 patients with UC who were TNF-inhibitor-naïve and showed steroid resistant or steroid dependent, Clinical response at week 8 and 52 was observed in 84.9% and 69.8%, respectively. When comparing the percentage of clinical response in this study to multi-center, observational, prospective study in Spain, clinical response at week 8 was similar (49.1% vs. 52.05%) and clinical response at last visit was higher (60.3% vs. 37.67%) in Korean patients. Although

the last visit showed a higher clinical response than the study, the tendency to decrease in clinical response was similar.

In our observational study, the percentage of clinical remission at week 8 and 56 was 23.97% and 21.92%, respectively. The pivotal trials ULTRA I and ULTRA II showed a remission rate of 29.5% and 30.9% at week 52, respectively.

In this study, the mean score change of the partial mayo score in clinical response at week 56 from the baseline to week 56 sustained (-4.49±1.81, -4.54±2.04, -5.09±1.66, at week 8, 24, and 56, respectively). Also, the mean score change of the full mayo score in clinical response at week 56 from the baseline to week 56 was sustained (-5.78±2.49, -6.55±2.28, at week 8, and 56, respectively). The study by Anita Bálint et al, showed that the changes in partial Mayo subscore was decreased significantly from week 12 and keep decreased over time (16.3, 9.0, 7.8 7.1; at week 0, week 12, week 30, and week 52)..

Mucosal healing at week 8 and 56 was 39.04% (57/146 patients) and 30.14% (44/146 subjects), respectively. Also, the percentage of patients with mucosal healing in week 8 clinical responders was 46.05% (35/76 subjects) at week 56. In the real-life multicenter, observation study in Hungary, 48.1% of the 73 moderate active UC patients achieved mucosal healing at week 52, and this was higher than to this study. However, the study was enrolled moderate-to severe subjects.

On the other hand, general lab tests (ESR, CRP, hemoglobin, and albumin levels) were not statistically significant, but showed a tendency to decrease in ESR and CRP, and or increase in hemoglobin, and albumin levels in subjects who were clinical responses

There were statistically significant differences in fecal calprotectin level, CRP and ESR level in clinical responders at week 8 in ITT set. Also, there were statistically significant differences in full, partial Mayo score and CRP level in clinical responders at week 56 in ITT set. PP set was similar in ITT set.

However, albumin level was statistically significant different between clinical responder and non-clinical responder at week 8, but there was not statistically significant difference from baseline at week 56 in PP set. At week 8 and 56, level of hemoglobin was was statistically significant different between clinical responder and non-clinical responder, but there was not statistically significant difference in ITT set.

In conclusion, based on the findings of the study, the percentage of clinical response in moderate Korean UC patients were investigated. Also, adalimumab in Korean clinical practice was turned out to be effective in two or more aspects.

Clinical response observed in about 52.05% of subjectsat week 8. Durable clinical response, clinical remission and steroid-free clinical remission in clinical responders at week 8 increased from baseline at week 8 and 56.

For observing the effectiveness of change of mean Full Mayo score, Partial Mayo score and fecal calprotectin, were observed from baseline until the end of last follow up visit. In this study, the Full Mayo score, Partial Mayo score, fecal calprotectin were decreased from baseline to week 56 with gradually decreased until the end of last follow up visit.

Any different tendency in safety from the approved label of adalimumab was not observed. The safety and effectiveness of adalimumab will be continuously monitored.
Based on this study, further studies on the potential predictive factors of adalimiumab at 8 and 56 weeks in moderate to severe UC patients in Korea should be conducted.