

## 1.0 Abstract

### Title

An observational study of Fecal calprotectin as clinical tool in monitoring moderate-to-severe Crohn's disease on Adalimumab Induction therapy: a Korean experience (FAIR)

### Keywords

Adalimumab, Crohn's disease (CD), Mucosal healing, Fecal calprotectin (FC), ELISA, Observational Study

### Rationale and Background

Recently, mucosal healing has become a therapeutic target for the treatment of IBD, and mucosal healing has traditionally been assessed by endoscopy. However, performing endoscopy on a frequent basis has significant limitation and FC measurement has not been widely used in monitoring CD patients in Korean practice. In IBD, fecal calprotectin (FC) value correlates strongly with the excretion of indium-111-labeled granulocytes, considered to be the most sensitive marker of disease activity.<sup>10</sup> Furthermore, FC correlates closely with endoscopic and histological grading of disease activity in both UC and CD.<sup>11-14</sup>

The objective of this study was to monitor fecal calprotectin (FC) level in Korean patients with moderate to severe Crohn's disease (CD) received adalimumab induction therapy.

This study was not able to identify a correlation between the endoscopic findings and FC levels in adalimumab treated CD patients since colonoscopy was not required for all subjects. However, in several other studies in IBD patients, FC levels during or at completion of induction treatment were associated with mucosal healing.<sup>19,20</sup>

## **Research Question and Objectives**

The objective of this observational study was to monitor the fecal calprotectin as a clinical monitoring tool in patients with moderate to severe Crohn's disease (CD) who received adalimumab induction therapy.

## **Study Design**

Non-interventional, prospective, multi-centre, observational study.

## **Setting**

This study was approved by the Institutional Review Board (IRB) of each institution, and a written study agreement was documented with each institution before the initiation of the study.

Subjects were fully informed regarding this study, and written authorization for the use/disclosure of data was obtained. Subjects who met the eligibility criteria were invited to participate in the study. The prescription of adalimumab was at the discretion of the physician in accordance with clinical practice and label, was made independently from this study and precedes the decision to offer the patient the opportunity to participate in this study.

Participating subjects were followed up every 4 weeks for 12 weeks after baseline in accordance with standard follow-up schedule in Korea. At baseline, demographics, disease and medication related data were collected. On every follow-up visit, a stool sample was obtained and sent to a central lab for a quantitative analysis of fecal calprotectin using ELISA [REDACTED] CDAI scores were calculated by the investigators based on subjects' clinical symptoms (general wellbeing, abdominal pain, and number of liquid stools). If endoscopy was performed during study period, the findings were recorded.

In the event of adalimumab discontinuation, the reason for discontinuation was determined and summarized in the study report.

## **Subjects and Study Size, including Discontinuations**

Subjects were fully informed regarding this study, and written authorization for use/disclosure of data was obtained. Subjects who met the eligibility criteria were invited to participate in the study.

### Inclusion Criteria

1) Crohn's disease subjects:

Active luminal, moderate-to-severe Crohn's Disease with CDAI > 220, who were to start adalimumab treatment in normal clinical practice setting

Fecal Calprotectin (FC) 150 µg/g

Ileocolonic or colonic disease, with or without involvement of proximal gastrointestinal areas

2) Signed authorization form to use personal and/or health data prior to the entry into the study

### Exclusion Criteria

Disease restricted to proximal (small bowel, gastroduodenal) gastrointestinal tract

Subjects who had undergone colectomy other than ileocecal resection

Pregnancy or breast feeding

Contraindication to any anti-TNF agent

Any drug dependency

### Discontinuations

Subjects will be discontinued from the study:

if the subject or their legally acceptable representatives choose to withdraw from the study.

where ethical or practical conflicts hinder the procedure of the study, and such cases will be determined based on the investigator's judgment.

if adalimumab is discontinued at any point during study period.

In this study, 101 subjects were enrolled at 14 sites. Of the 101 enrolled subjects, 91 subjects completed the study and 10 subjects were discontinued from the study.

### **Variables and Data Sources**

Variables including demographics, medical characteristics related to Crohn's disease (month and year of diagnosis, lesion location, and fistula), previous Crohn's disease-related therapy, current Crohn's disease-related therapy, co-morbidity, CDAI score, Fecal Calprotectin ( $\mu\text{g/g}$ ), endoscopy finding (if available), the reason for discontinuation and safety variables were collected.

### **Results**

There were 99 subjects included in the safety set. This excludes 2 subjects who did not receive adalimumab treatment. Of 99 subjects enrolled in this study, 93 were included in the intention-to-treat (ITT) set, excluding 1 subject who did not have FC measured at baseline, and 5 subjects who did not measure FC level after adalimumab administration. In the ITT set, a total of 86 subjects completed the 12 week follow-up during the study period, excluding 3 subjects who violated inclusion/exclusion criteria. The 83 subjects who completed the 12 week follow up during the study period without violation of inclusion/exclusion criteria were in the per-protocol (PP) set.

After completion of adalimumab induction treatment, the percentage of subjects achieved  $\text{FC} < 150 \mu\text{g/g}$  at week 4 was 16.30% (15/92 subjects) in the ITT population and 13.25% (11/83 subjects) in the PP population.

In the ITT population, the percentage of subjects with  $\text{FC} < 150 \mu\text{g/g}$  was 21.84% (19/87 subjects) at week 8 and 18.82% (16/85 subjects) at week 12.

In the PP population, the percentage of subjects with FC < 150 µg/g was 20.25% (16/83 subjects) at week 8, 17.07% (14/83 subjects) at week 12.

In the ITT population, the mean ±SD of the percent changes of FC level from baseline to week 4, 8 and 12 were -34.60% ± 59.85, -43.14% ± 51.59 and -10.49% ± 147.38, respectively.

In the PP population, the mean ± SD of the percent changes of FC level from baseline to week 4, 8 and 12 were -39.28% ± 58.59, -45.08% ± 50.32 and -22.43% ± 88.76 respectively.

In the ITT population, the percentage of subjects with CDAI score < 150 was 66.30% (61/92 subjects) at week 4, 72.94% (62/85 subjects) at week 8 and 83.53% (71/85 subjects) at week 12. The percentage of subjects with clinical response of CR70 was 86.96% (80/92 subjects) at week 4, 89.41% (76/85 subjects) at week 8, 94.12% (80/85 subjects) at week 12, and that with clinical response of CR100 was 75.00% (69/92 subjects) at week 4, 85.88% (73/85 subjects) at week 8 and 90.59% (77/85 subjects) at week 12.

In the PP population, all the values for each variable at each time point were generally greater than the corresponding values in the ITT population.

In the safety set (99 subjects), 9 serious adverse events were reported in 6 subjects (6/99 subjects, 6.06%) that included 3 cases of abdominal pain (3/99 subjects, 3.03%) and 1 case of the followings; aphthous stomatitis (1/99 subjects, 1.01%), diarrhea (1/99 subjects, 1.01%), large intestinal stenosis (1/99 subjects, 1.01%), melaena (1/99 subjects, 1.01%), hand fracture (1/99 subjects, 1.01%), and rash (1/99 subjects, 1.01%).

Three adverse events leading to discontinuation of adalimumab were reported in 2 subjects (■■■■■ abdominal pain, large intestinal stenosis, ■■■■■ urinary tract infection).

## **Discussion**

The study was aimed to observe FC level in patients with moderate to severe Crohn's disease under routine clinical practice. As a result, after completion of 12 week follow up, the FC level significantly decreased at week 4 and patients with adalimumab showed clinical response defined by Crohn's Disease Activity Index (CDAI < 150) score as well. However, as it was an observational study conducted under routine clinical practice, colonoscopy was not required for all subjects from this study. Therefore, the study data was not able to identify a correlation between colonoscopic findings and FC level.

In conclusion, FC concentrations significantly decreased with adalimumab treatment, implying possible improvement of intestinal inflammation. However, FC levels remained higher than 150 µg/g in a considerable number of subjects who had symptomatic improvement as shown by the CDAI scores. A long-term follow up study is needed to explore the clinical significance of subclinical inflammation in adalimumab-treated Crohn's disease.

## **Marketing Authorisation Holder(s)**

AbbVie Korea Ltd.

## **Names and Affiliations of Principal Investigators**

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