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Clinical outcomes and predictors of response for adalimumab in patients with moderately to severely active ulcerative colitis: a KASID prospective multicenter cohort study

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Background/Aims: This study assessed the efficacy and safety of adalimumab (ADA) and explored predictors of response in Korean patients with ulcerative colitis (UC). **Methods:** A prospective, observational, multicenter study was conducted over 56 weeks in adult patients with moderately to severely active UC who received ADA. Clinical response, remission, and mucosal healing were assessed using the Mayo score. **Results:** A total of 146 patients were enrolled from 17 academic hospitals. Clinical response rates were 52.1% and 37.7% and clinical remission rates were 24.0% and 22.0% at weeks 8 and 56, respectively. Mucosal healing rates were 39.0% and 30.1% at weeks 8 and 56, respectively. Prior use of anti-tumor necrosis factor-α (anti-TNF-α) did not affect clinical and endoscopic responses. The ADA drug level was significantly higher in patients with better outcomes at week 8 ($P<0.05$). In patients with lower endoscopic activity, higher body mass index, and higher serum albumin levels at baseline, the clinical response rate was higher at week 8. In patients with lower Mayo scores and C-reactive protein levels, clinical responses, and mucosal healing at week 8, the clinical response rate was higher at week 56. Serious adverse drug reactions were identified in 2.8% of patients. **Conclusions:** ADA is effective and safe for induction and maintenance in Korean patients with UC, regardless of prior anti-TNF-α therapy. The ADA drug level is associated with the efficacy of induction therapy. Patients with better short-term outcomes were predictive of those with an improved long-term response. **(Intest Res 2022;20:350-360)**

Key Words: Inflammatory bowel disease; Tumor necrosis factor inhibitors; Treatment outcome

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INTRODUCTION

Ulcerative colitis (UC) is a chronic, idiopathic inflammatory bowel disease (IBD) characterized by relapsing abdominal pain and bloody diarrhea with or without mucus.[1] The incidence and prevalence of UC have been reported as high in Northern Europe and North America and low in Asian countries.[2-5] However, researchers recently observed an increased number of UC patients in Asian countries including Korea, Japan, China, and Taiwan.[6-8] The incidence of UC in Asia has been rising in relation to rapid urbanization and a westernized lifestyle.[9,10] A population-based study performed in Korea showed that the incidence and prevalence of UC have been gradually increasing.[10,11] Furthermore, the genetic and clinical characteristics of IBD patients from Asia and Western countries are slightly different.[12,13]

Adalimumab (ADA) is a fully human immunoglobulin G1 monoclonal antibody directed against tumor necrosis factor-α (TNF-α) that inhibits the activity of the cytokine by blocking the interaction of TNF-α with its p55 and p75 cell surface receptors.[14] In Korea, ADA has been administered to patients with UC since 2013, and a nationwide population-based study showed that 27.6% were treated using ADA among patients who received anti-TNF-α therapy.[10]

Till date, little information regarding the clinical outcomes of the use of ADA in the Korean population is available. Most published studies of clinical outcomes in IBD have been conducted on Western patients. Investigating the clinical outcomes of biologic agents in Korean IBD patients will enable a better understanding and optimal management of this condition. Therefore, we conducted a prospective, observational, multicenter study to evaluate the real-world efficacy and safety of ADA and predictors of response in Korean patients with UC.

METHODS

1. Patients

This prospective, observational, multicenter study was conducted at 17 academic hospitals in Korea from June 2015 to September 2018. The study protocol was approved by the institutional review board at each center (IRB No. C2015020) and registered at clinicaltrials.gov (study identifier: NCT02499263). All patients provided written informed consent. All work was carried out in compliance with the Ethical Principles for Medical Research Involving Human Subjects outlined in the Helsinki Declaration in 1975 (revised in 2000). All authors had access to the study data and reviewed and approved the final manuscript.

Eligible patients were aged >18 years and had moderately to severely active UC defined as a Mayo score[15] between 6 to 12, with an endoscopic subscore of at least 2, despite concurrent therapy with 5-aminosalicylic acid, corticosteroids, and azathioprine/6-mercaptopurine. Previous use of anti-TNF-α agents other than ADA was permitted if the patient had discontinued its use owing to primary nonresponse, loss of response, or intolerance to the agent. Exclusion criteria were contraindications for using ADA including malignancy; severe infection such as active tuberculosis, invasive fungal infection, and opportunistic infection; being enrolled in other clinical trials; and pregnancy or breastfeeding. Patients were excluded if they chose to withdraw from the study or if the investigator discontinued ADA because of ethical or practical conflicts. Baseline assessment performed before administration of ADA, and details can be found in supplementary section.

2. Study Design

Patients received subcutaneous injections of ADA: 160 mg at week 0, 80 mg at week 2, and 40 mg every alternate week from week 4. Patients were evaluated at weeks 0 (baseline), 8, 16, 24, 32, 40, 48, and 56 in accordance with clinical practice. The window period was permitted as ±1 week for every visit. All participants underwent safety evaluations ≤30 days after the last administration of ADA.

Analysis of Mayo scores, including endoscopic subscore, and fecal calprotectin (FC) levels and laboratory tests, were performed at weeks 8 and 56. ADA trough level was evaluated at week 8 and at loss of response, even if ADA dose escalated to weekly injection. Patients with inadequate response to ADA (40 mg every 2 weeks) were permitted to escalate the dosage to 40 mg every week. Patients with inadequate response to dose escalation discontinued the drug based on their physician's judgement. Inadequate response was defined in supplementary section.

3. Outcomes

The primary outcomes were clinical response rates at weeks 8 and 56. Clinical response was defined as a decrease in Mayo score from baseline by ≥3 points and ≥30% with an accompanying decrease in rectal bleeding subscore of ≥1 point or an absolute rectal bleeding subscore of 0 or 1. Secondary outcomes were proportion of patients with clinical remission, steroid-free remission, and mucosal healing at weeks 8 and 56. Clinical remission was defined as a Mayo score ≤2 with no in-

dividual subscore exceeding 1 point. Steroid-free remission was defined as a clinical remission status with no use of systemic corticosteroids for 12 weeks before the date of investigation. Mucosal healing was defined as an endoscopy subscore of 0 or 1. Endoscopic remission was defined as an endoscopic subscore of 0. Predictors of response at weeks 8 and 56 were evaluated based on clinical characteristics at baseline and week 8. Safety evaluation was performed according to the recent version of the Medical Dictionary for Regulatory Activities version 20.0. Physical examination, investigation of vital signs, and laboratory tests were performed from baseline to week 56 and after 30 days from the last administration.

4. Statistical Methods

Analyses were performed with the intent-to-treat set. Missing or incomplete data were handled using the nonresponder imputation method, i.e., patients with missing or incomplete data were assumed to have not achieved the endpoint. Continuous variables are described with the number of subjects, arithmetic mean, and standard deviation. For categorical variables, the frequency and proportion are presented. For all the statistical tests, two-sided tests were conducted at the 0.05 significance level using the independent or paired *t*-test and the chi-square test. To identify factors associated with clinical response at weeks 8 and 56, variables that were significant in univariate analysis were subsequently tested in multivariate logistic regression analysis and expressed as odds ratios (ORs) with 95% confidence intervals (CIs). The Kaplan-Meier method was used to evaluate the drug persistence rate. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

1. Primary Endpoint

A total of 146 patients from 17 academic hospitals in Korea were enrolled and included in the analysis. Table 1 summarizes the baseline clinical characteristics of the participants.

Clinical response was achieved in 52.1% (76/146) of the patients at week 8 and 37.7% (55/146) of the patients at week 56 (Fig. 1A). Clinical response rate at week 56 in week 8 responders was 54.0% (41/76). Clinical response rate was not significantly different between patients who received anti-TNF-α and those who did not (Fig. 1B and C). The combination therapy with azathioprine/6-mercaptopurine in baseline was not associated with clinical response rate at both weeks 8 and 56 (Fig. 1D).

Table 1. Baseline Demographic and Clinical Characteristics of Participants

Characteristics	Participants (n = 146)
Age (yr)	44.9 ± 14.9
Male sex	50 (34.5)
Body weight (kg)	63.2 ± 12.2
BMI (kg/m^2)[a]	22.5 ± 3.6
Age at diagnosis (yr)	39.4 ± 15.5
Duration of disease (mo)[b]	52.8 ± 49.6
Mayo score	8.7 ± 1.4
Endoscopic subscore	2.5 ± 0.5
Disease location	
Proctitis	26 (17.8)
Left-sided colitis	65 (44.5)
Extensive colitis	50 (34.3)
Others	5 (3.4)
Fecal calprotectin (mg/kg)	
Mean ± SD	894.6 ± 630.4
Median	906.0
C-reactive protein (mg/dL)	
Mean ± SD	4.7 ± 11.4
Median	0.9
Albumin (g/dL)	
Mean ± SD	3.8 ± 0.6
Median	3.9
Concomitant medication (overlapped)	
5-Aminosalicylates	133 (94.3)
Methotrexate	3 (2.1)
Azathioprine/6-mercaptopurine	79 (56.0)
Cyclosporine/tacrolimus	0
Systemic corticosteroid	59 (41.8)
20 mg and above (daily dose)	43 (72.9)
Less than 20 mg (daily dose)	33 (55.9)
Prior anti-TNF therapy	36 (24.7)
One medication	34 (94.4)
Two medications and above	2 (5.6)

Values are presented as mean ± standard deviation or number (%).
[a]Data on BMI were available for 144 patients.
[b]Data on duration of disease were available for 80 patients.
BMI, body mass index; TNF, tumor necrosis factor.

2. Secondary Endpoints

At week 8, 24.0% (35/146) of patients were in clinical remission, and 22.0% (32/146) of patients achieved clinical remission at week 56. Steroid-free clinical remission was achieved in 12.3% (18/146) of patients at week 8 and 21.2% (31/146) of

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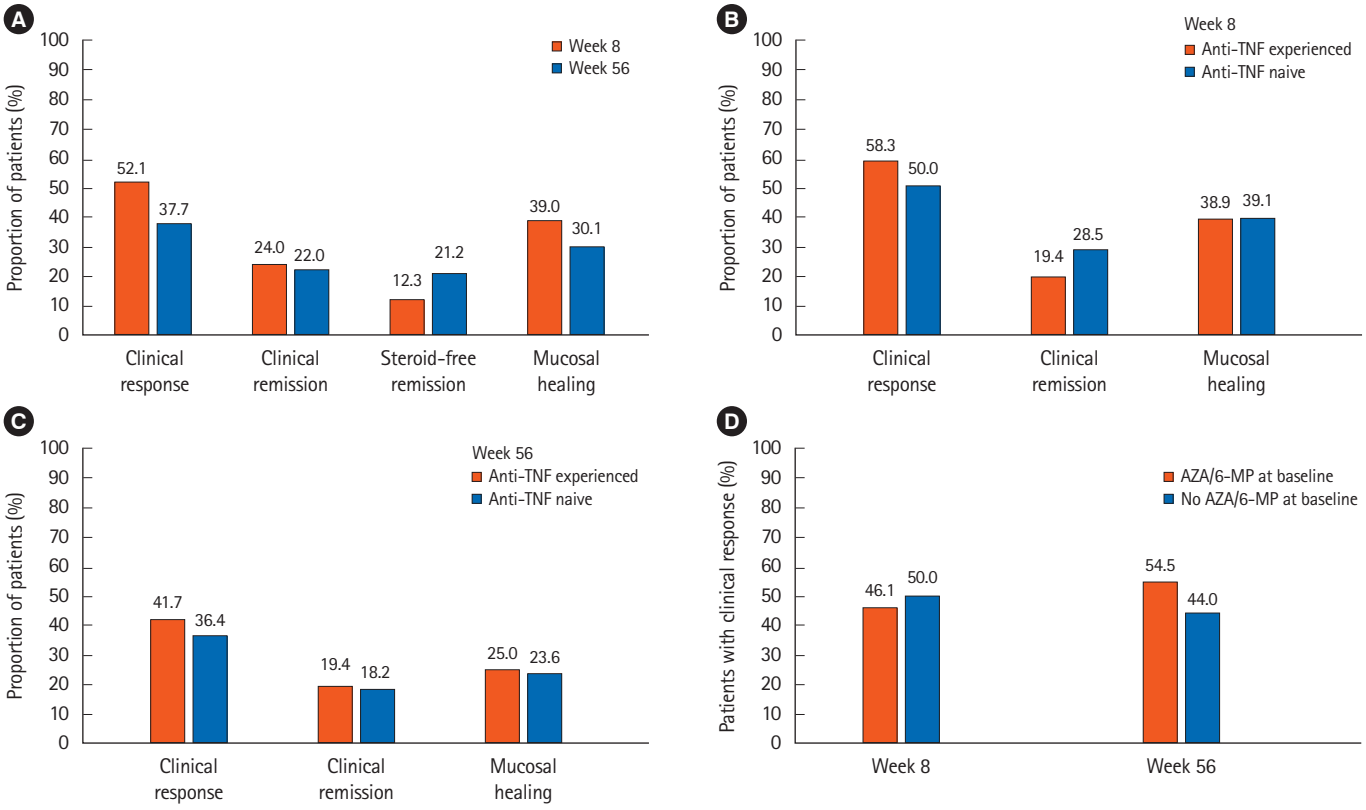

Fig. 1. Clinical response, remission, steroid-free remission, and mucosal healing rates according to the Mayo score at week 8 and 56 (A). Clinical outcomes according to prior anti-TNF-α therapy at week 8 (B) and at week 56 (C). Clinical response rates according to the use of immunomodulator at baseline (D). Clinical outcomes did not differ whether the patients had experienced anti-TNF therapy or not, and concomitant use of immunomodulator did not affect clinical response rate. TNF, tumor necrosis factor; AZA, azathioprine; 6-MP, 6-mercaptopurine.

patients at week 56. Mucosal healing was achieved in 39.0% (57/146) of patients at week 8 and 30.1% (44/146) at week 56 (Fig. 1A). Rates of clinical remission and mucosal healing were not significantly different between patients who received anti-TNF-α and those who did not (Fig. 1B and C). Twenty-five patients (17.1%) experienced dose escalation, and 40% and 20% of these achieved clinical response and remission at week 56, respectively.

3. Comparison of Clinical Characteristics between Clinical Responders and Nonresponders

A comparison of clinical characteristics between clinical responders and nonresponders can be found in Tables 2 and 3. Higher body mass index (BMI) ($P=0.034$) and serum albumin level ($P=0.019$), and less severe endoscopic findings ($P=0.002$) at baseline were associated with clinical response at week 8. Higher baseline BMI ($P=0.017$), and clinical response ($P<0.001$) and mucosal healing ($P=0.008$) at week 8 were associated with clinical response at week 56. Mayo score ($P=0.026$) and serum C-reactive protein (CRP) level ($P=0.035$) at week 8 were significantly lower in clinical responders than in nonresponders at week 56. In the multivariate analysis, baseline non-severe endoscopic finding (OR, 2.951; 95% CI, 1.365–6.382; $P=0.006$) and clinical response (OR, 10.456; 95% CI, 1.903–57.458; $P=0.007$) at week 8 were independent predictive factors for clinical responses at week 8 and week 56, respectively (Table 4).

4. Exploratory Outcomes

Treatment persistence rate and causes of discontinuation can be found in Supplementary Fig. 1 and Supplementary Table 1. Clinical response rates according to the partial Mayo score can be found in Supplementary Fig. 2.

Mean serum ADA concentration (trough level, μg/mL) was significantly higher in patients who achieved clinical response (10.8 vs. 8.0, $P=0.004$), remission (11.7 vs. 8.3, $P=0.007$), and mucosal healing (11.0 vs. 8.5, $P=0.010$) than in those with no clinical response at week 8. Mean serum ADA level was 7.5±6.4 μg/mL (range, 0.1–17.7 μg/mL) in patients who stopped ADA

Table 2. Comparison of Baseline Clinical Characteristics between Clinical Responders and Nonresponders at Week 8 Following Adalimumab Administration

Baseline clinical characteristics	Responder (n = 76)	Non-responder (n = 70)	*P*-value
Age (yr)	44.1 ± 14.9	45.9 ± 15.0	0.459
Male sex	46 (60.5)	50 (71.4)	0.165
Body mass index (kg/m^2)	23.1 ± 3.9	21.8 ± 3.2	0.034
Mayo Clinic score	8.7 ± 1.4	8.8 ± 1.4	0.582
Partial Mayo score	6.2 ± 1.2	6.1 ± 1.3	0.558
Endoscopic finding			0.002
Moderate	44 (57.9)	23 (32.9)	
Severe	32 (42.1)	47 (67.1)	
Disease location			0.903
Proctitis	14 (18.4)	12 (17.1)	
Left-sided colitis	33 (43.4)	33 (47.1)	
Extensive colitis	29 (38.2)	25 (35.7)	
Fecal calprotectin (mg/kg)	853.7 ± 620.9	950.2 ± 645.3	0.414
C-reactive protein (mg/dL)	3.3 ± 6.7	6.5 ± 15.0	0.109
Albumin (g/dL)	3.9 ± 0.6	3.7 ± 0.6	0.019
Concomitant medication (overlap)			
5-Aminosalicylates	68 (89.5)	54 (77.1)	0.072
Azathioprine/6-MP	35 (46.1)	35 (50.0)	0.633
Systemic corticosteroid	25 (32.9)	19 (27.1)	0.449

Values are presented as mean ± standard deviation or number (%).
6-MP, 6-mercaptopurine.

Table 4. Multivariate Analysis for Predictive Factors of Clinical Response to Adalimumab at Weeks 8 and 56

Predictive factor	OR (95% CI)	*P*-value
Clinical response at week 8		
Baseline		
BMI ≥ 23 kg/m^2	1.218 (0.578–2.567)	0.604
Non-severe endoscopic finding	2.951 (1.365–6.382)	0.006
Albumin ≥ 4.0 g/dL	1.497 (0.697–3.214)	0.301
Clinical response at week 56		
Week 8		
Clinical response	10.456 (1.903–57.458)	0.007
Mucosal healing	0.777 (0.185–3.260)	0.731
Mayo score ≤ 3	2.046 (0.268–15.641)	0.490
Partial Mayo score ≤ 2	0.296 (0.040–2.189)	0.233
C-reactive protein ≤ 1 mg/dL	1.748 (0.479–6.375)	0.398

OR, odds ratio; CI, confidence interval; BMI, body mass index.

Table 3. Comparison of Clinical Characteristics between Clinical Responders and Nonresponders at Week 56 Following Adalimumab Administration

Clinical characteristics	Responder (n = 55)	Non-responder (n = 91)	*P*-value
Baseline characteristics			
Age (yr)	43.8 ± 14.9	45.7 ± 14.9	0.460
Male sex	33 (60.0)	63 (69.2)	0.255
Body mass index (kg/m^2)	23.4 ± 3.9	22.0 ± 3.3	0.017
Mayo Clinic score	9.0 ± 1.3	8.6 ± 1.4	0.096
Partial Mayo score	6.4 ± 1.1	6.0 ± 1.3	0.094
Endoscopic finding			0.671
Moderate	24 (43.6)	43 (47.3)	
Severe	31 (56.4)	48 (52.7)	
Disease location			0.304
Proctitis	7 (12.7)	19 (20.9)	
Left-sided colitis	24 (43.6)	42 (46.2)	
Extensive colitis	24 (43.6)	30 (33.0)	
Fecal calprotectin (mg/kg)	850.4 ± 617.1	920.8 ± 640.9	0.559
C-reactive protein (mg/dL)	3.1 ± 5.9	5.9 ± 15.0	0.109
Albumin (g/dL)	3.8 ± 0.6	3.8 ± 0.6	0.546
Concomitant medication (overlap)			
5-Aminosalicylates	49 (89.1)	73 (80.2)	0.161
Azathioprine/6-MP	30 (54.5)	40 (44.0)	0.215
Systemic corticosteroid	17 (30.9)	27(29.7)	0.874
Characteristics at week 8			
Clinical response	41 (74.5)	35 (38.5)	< 0.001
Mucosal healing	29 (52.7)	28 (30.8)	0.008
Mayo score	3.2 ± 2.3	4.4 ± 3.1	0.026
Partial Mayo score	1.9 ± 1.6	3.0 ± 2.3	0.001
C-reactive protein (mg/dL)	0.9 ± 1.3	2.2 ± 4.9	0.035
Fecal calprotectin (mg/kg)	422.5 ± 505.7	317.7 ± 435.8	0.187
Albumin (g/dL)	4.2 ± 0.5	4.0 ± 0.5	0.139
Adalimumab trough level (μg/mL)	9.3 ± 5.0	9.9 ± 5.4	0.550
Concomitant use of azathioprine/6-MP	27 (49.1)	31 (34.1)	0.072

Values are presented as mean ± standard deviation or number (%).
6-MP, 6-mercaptopurine.

administration because of inadequate response (Fig. 2). FC and CRP levels associated with the clinical and endoscopic outcomes can be found in Fig. 3.

A total of 246 FC levels were collected at the 3 points, and the correlation with endoscopic findings was investigated by

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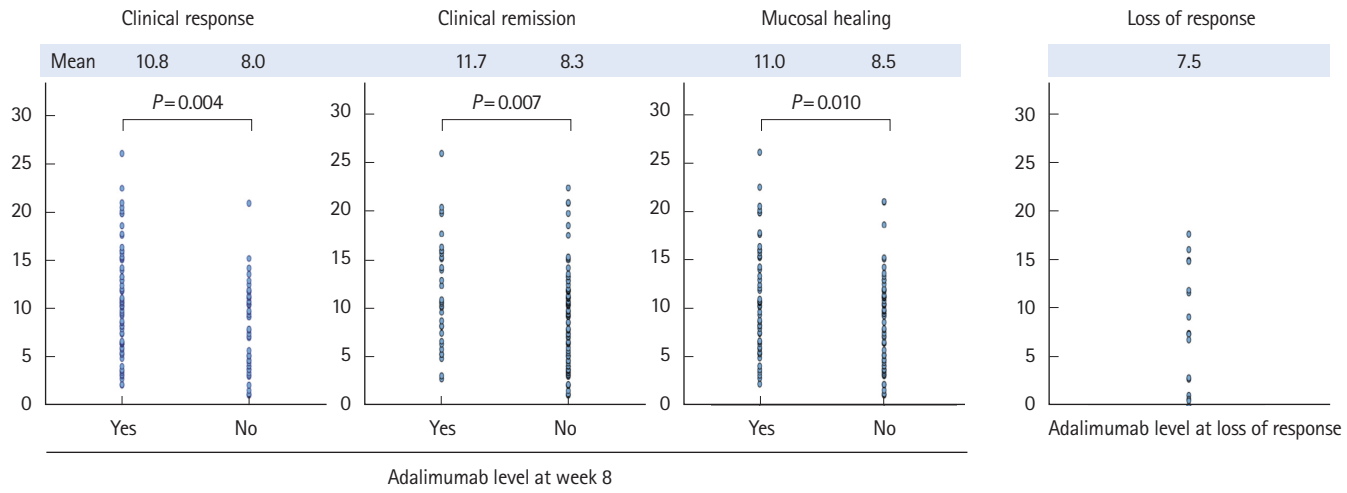

Fig. 2. Serum adalimumab concentration (μg/mL) according to clinical outcomes at week 8. Mean serum adalimumab levels were significantly higher in patients who achieved clinical response, remission, and mucosal healing than in those without clinical response, remission, and mucosal healing, respectively, at week 8.

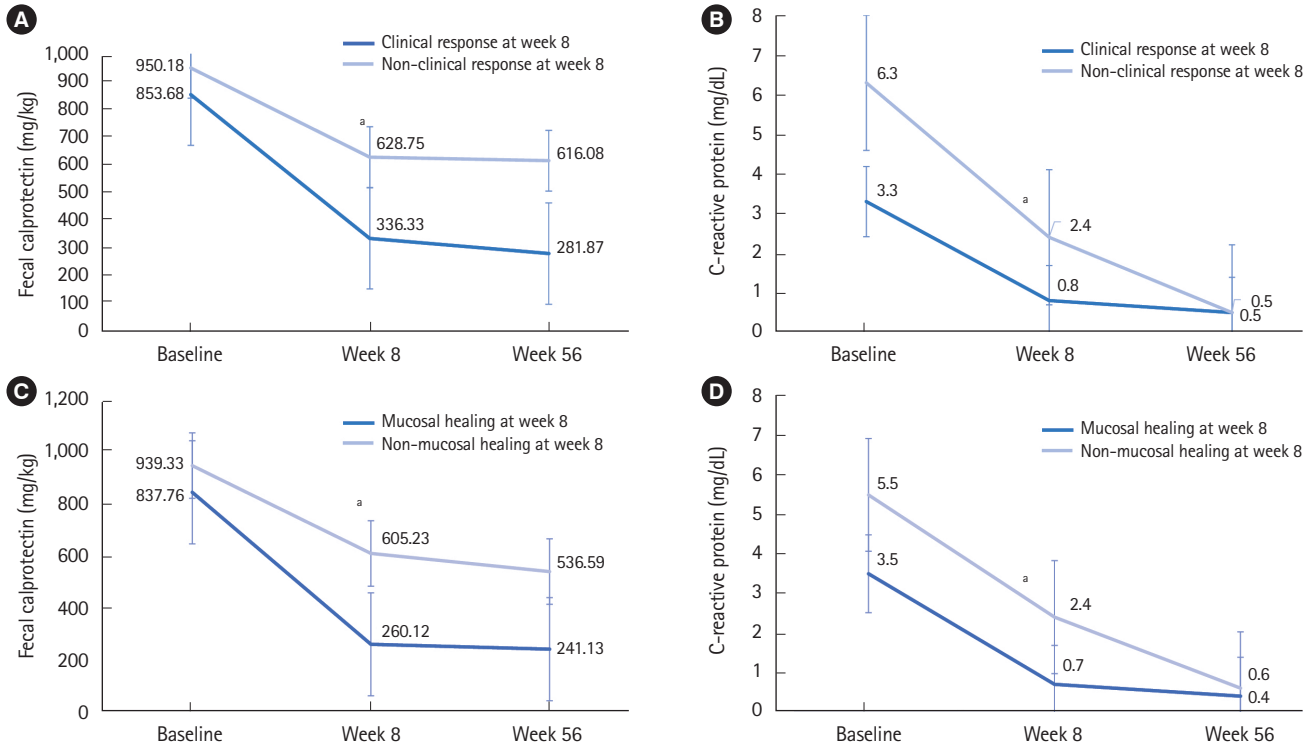

Fig. 3. Changes in mean fecal calprotectin and C-reactive protein levels from baseline in clinical responders and nonresponders at week 8 (A, B) and in patients with and without mucosal healing at week 8 (C, D). Fecal calprotectin and C-reactive protein levels significantly improved in patients achieving clinical response and mucosal healing compared with patients without clinical response and mucosal healing, respectively, at week 8. [a]$P<0.05$.

integrating them (Fig. 4). The FC level to predict mucosal healing was 274.7 mg/kg, with a sensitivity of 72.2% and specificity of 71.3% on the receiver operating curve (area under the curve, 0.771). The predictive level for endoscopic remission (Mayo subscore 0) was 87.9 mg/kg, with a sensitivity of 73.6% and specificity of 73.5% on the receiver operating curve (area under the curve, 0.774).

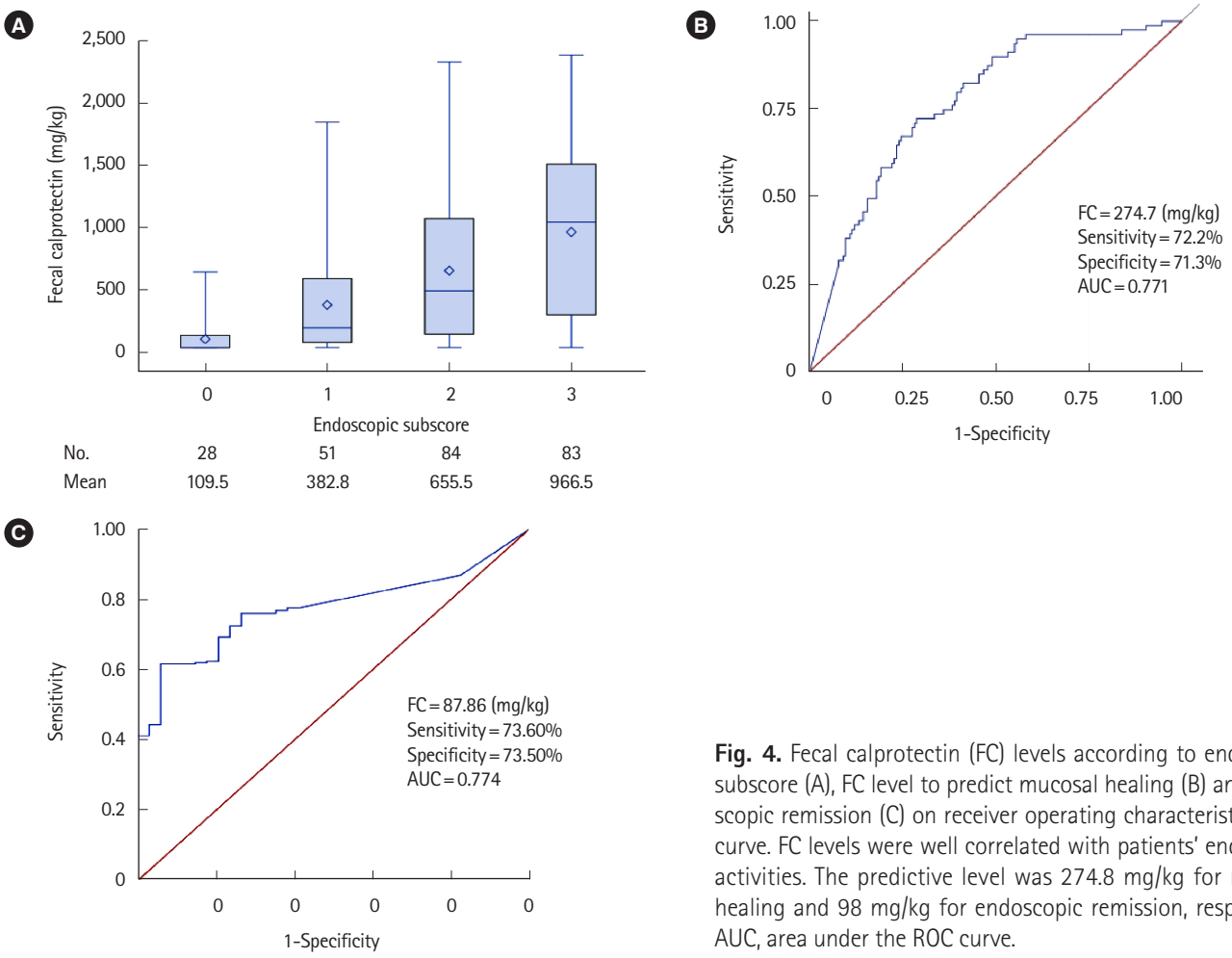

Fig. 4. Fecal calprotectin (FC) levels according to endoscopic subscore (A), FC level to predict mucosal healing (B) and endoscopic remission (C) on receiver operating characteristic (ROC) curve. FC levels were well correlated with patients' endoscopic activities. The predictive level was 274.8 mg/kg for mucosal healing and 98 mg/kg for endoscopic remission, respectively. AUC, area under the ROC curve.

5. Safety

During the study period, 6.2% (9/146) of patients experienced adverse drug reactions. Serious adverse drug reactions that induced hospital admission were identified in 2.8% (4/146) of patients as follows: pneumonia, pulmonary tuberculosis, renal failure, and abdominal pain (Supplementary Table 2).

DISCUSSION

In this prospective multicenter study, we evaluated the real-world clinical effectiveness of ADA treatment and factors associated with the clinical response in Korean patients with moderately to severely active UC. Our study showed similar or slightly higher rates of clinical response and remission than 2 previous pivotal studies conducted in Western countries: ULTRA-1 and ULTRA-2 (response rates, 50.4%–54.6%; remission rates, 16.5%–18.5% at week 8 and 30.2%–17.3% at week 52).[14,16] Several studies investigating the real-world efficacy of ADA have been reported worldwide. Although it is difficult to directly compare these results, because each study defined clinical response and remission differently, they show similar trends in outcomes.[17-19] A Japanese real-world study that applied the same definition for clinical response and remission as this study, reported similar outcomes.[17] The mucosal healing rate in our study tended to be lower than that reported in previous Western studies,[18,19] but similar to that reported in a Japanese study.[17] Collectively, ADA was similarly effective for induction and maintenance treatments in Korean patients with active UC who were unresponsive to corticosteroids and/or azathioprine/6-mercaptopurine.

Previous experience with anti-TNF-α therapy was not found to impact the short- or long-term outcomes in our study. Prior anti-TNF-α therapy has been reported to have controversial effects on clinical outcomes of ADA in patients with UC. The ULTRA-2 and ULTRA-3 studies reported better outcomes in patients not treated with anti-TNF-α.[14,20] A retrospective multicenter study in Spain investigated the influence of previous anti-TNF-α use on the outcomes of ADA maintenance treat-

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ment in patients with UC; patients not previously treated with anti-TNF-α had a numerically higher rate of clinical response at week 56 without statistical significance.[21] They had significantly lower probabilities of avoiding colectomy and dose escalation. However, in a previous Hungarian prospective study, response to ADA and need for dose escalation were not associated with previous infliximab (IFX) therapy.[19] A retrospective study performed in Ireland showed a trend towards better outcomes in patients previously received anti-TNF-α compared with those who were not.[22] It is difficult to explain this inconsistency. Relatively small portion of patients with anti-TNF-α (n = 36, 24.7%), and higher rate of dose escalation in patient with anti-TNF exposure (41.9%) compared with anti-TNF naïve patients (9.0%) (data not shown) in our study may affect the results. Although a note of caution is due, ADA can be suggested as a beneficial option for Korean patients with moderately to severely active UC treated previously with anti-TNF-α therapy. In addition, the combination therapy with azathioprine/6-mercaptopurine did not affect clinical response rate. This finding is consistent with that of previous studies showing no efficacy-related benefits following immunomodulator/ADA combination therapy.[20,23,24]

In this study, baseline BMI, endoscopic findings, and serum albumin level were associated with clinical response at week 8. At week 56, baseline BMI and clinical response, mucosal healing, CRP level, and Mayo score at week 8 were associated with clinical response. In the multivariate analysis, baseline non-severe endoscopic finding and clinical response at week 8 were independent factors for predicting response at weeks 8 and 52, respectively. Although it was a significant factor only in the univariate analysis, BMI was associated with both short- and long-term response. Previous studies have shown that obese patients tended to have higher risk of nonresponse to biologic agents because of their direct effect on inflammation and modification of pharmacokinetics.[14,25,26] However, average BMI of both responder and nonresponder groups were within the normal range in our study. Relatively higher BMI within the normal range might reflect less severe disease status. CRP level has been suggested as a predictor of poor outcome in UC patients[27] and considered a biomarker of response to IFX induction therapy.[28,29] Endoscopic finding is also one of the major factors determining the severity and prognosis of UC. In this study, the baseline CRP levels were lower in responders than in nonresponders, though without statistical significance. The less severe endoscopic activity was associated with better response to induction therapy of ADA. The findings from this study suggest that ADA therapy may be more effective in moderately active UC than in severely active UC.

Parameters associated with early response such as mucosal healing, clinical response, and CRP level were associated with long-term response. Mucosal healing has been reported to be associated with long-term clinical outcomes[18,30] and suggested as a predictive factor of long-term outcome in Korean UC patients treated with IFX.[31] Early clinical response has also been demonstrated as a predictive factor of better long-term clinical outcomes in several real-world studies.[17,32,33] In Korean patients with moderately to severely active UC, early response is also a positive predictor for long-term clinical response.

During the study period, 25 patients (17.1%) required dose escalation, and 40% and 20% of these regained clinical response and remission, respectively, at week 56. Compared to previous Western studies, the proportion of patients who experienced dose escalation in our study was relatively small; however, the clinical outcomes are similar to those of these studies.[21,34,35]

Consistent with previous studies on mucosal healing-associated FC levels,[36-38] in this study, FC levels were well correlated with not only patients' clinical outcomes, but also endoscopic activities. The predictive level was 274.8 mg/kg for mucosal healing and 98 mg/kg for endoscopic remission. These novel findings can be used to predict endoscopic activities in UC patients.

Serum ADA concentrations (trough level) at week 8 were associated significantly with clinical outcomes of induction therapy. The mean ADA concentrations in patients without clinical response, remission, and mucosal healing were relatively higher compared with those in previous studies.[39-41] It can be assumed that different mechanisms other than signaling pathway via TNF may be involved in the development of UC in these patients. In addition, most previous studies included both patients with UC and Crohn's disease, and few studies have been conducted to investigate ADA concentration in patients with UC only. A Belgian study including IFX responders and nonresponders showed similar ADA concentrations as those in this study with respect to short-term mucosal healing.[42] The researchers reported that the average ADA concentration of patients with mucosal healing at week 4 was 10.6 μg/mL, which was significantly higher than the concentration in those without mucosal healing (7.4 μg/mL, $P = 0.014$). More real-world data may be needed to establish optimal level for treatment target, but our finding suggests that the higher the drug concentration at week 8 after ADA induction therapy,

the better was the expected clinical effect.

No new safety signals were observed in the present study, and the incidence rate was similar to that described in other studies.[18,43] Any different tendency in safety from the approved label of ADA was not observed. Patients with severe adverse drug reactions including abdominal pain and pulmonary tuberculosis were treated properly, and no deaths were reported.

This was an observational study in routine clinical practice, having certain inherent limitations such as the lack of randomization, leading to potential bias. Moreover, the proportion of subjects who completed the evaluation without any major protocol deviation among the intent-to-treat set was relatively small. Therefore, with a small sample size, these data must be interpreted with caution. Furthermore, anti-ADA antibodies were not evaluated in this study, although it is used in clinical practice in Western countries. However, this study was the first multicenter prospective study to evaluate the efficacy and safety of ADA in Korean UC patients in the real-life clinical setting and explore clinical predictors of response to ADA, including FC and ADA drug levels.

In conclusion, this study showed that ADA is effective and safe for Korean patients with moderately to severely active UC regardless of prior anti-TNF-α therapy. ADA drug level is associated with the efficacy of induction therapy. A good response to induction therapy suggests positive long-term outcomes in Korean patients with moderately to severely active UC.

ADDITIONAL INFORMATION

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Conflict of Interest

There are no conflicts of interest to disclose, except for Teng D: employees of AbbVie, Inc. and may hold stock or stock options. Kim DH is a former employee of AbbVie, Inc.

Kim JW, Park DI, Kim YS are editorial board members of the journal but were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

Data Availability Statement

Not applicable.

Author Contribution

Designed the study: Choi CH, Park SJ, Im JP, Kim HJ, Jung SA, Kim HK, Kim JW, Lee KM, Lee J, Kang SB, Shin SJ, Kim YS, Kim TO, Kim HS, Park DI, Kim Eun Sun, Kim Eun Soo, Kim YH, Kim DH, Teng D. Data curation: Shin SY, Kim Y, Choi CH. Formal analysis: Shin SY, Kim Y, Kim JH, Kim W. Visualization: Shin SY, Kim Y, Choi CH. Writing – original draft: Shin SY, Park SJ. Writing – review & editing: Choi CH, Im JP, Kim HJ, Jung SA, Kim JW, Lee KM, Lee J, Kang SB, Shin SJ, Kim YS, Kim TO, Kim HS, Park DI, Kim HK, Kim Eun Sun, Kim Eun Soo, Kim YH. Approval of final manuscript: all authors.

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Supplementary Material

Supplementary materials are available at the Intestinal Research website (https://www.irjournal.org).

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See "Clinical outcomes and predictors of response for adalimumab in patients with moderately to severely active ulcerative colitis: a KASID prospective multicenter cohort study" on pages 350-360.

Supplementary Table 1. Patients Who Discontinued Adalimumab and Related Reasons

Related reason	Value (n = 62)
Lack of efficacy	34 (54.8)
Adverse event	11 (17.7)
Follow-up loss	9 (14.5)
Subject's decision	6 (9.7)
Pregnancy	1 (1.6)
Others	1 (1.6)

Values are presented as number (%).

Supplementary Table 2. Adverse Drug Reactions with Adalimumab

Variable	Value (n = 146)
Adverse drug reaction	
Gastrointestinal disorders	3 (2.1)
Hematochezia	2 (1.4)
Abdominal pain	1 (0.7)
Infections and infestations	3 (2.1)
Cytomegalovirus infection	1 (0.7)
Pneumonia	1 (0.7)
Pulmonary tuberculosis	1 (0.7)
General disorders and administration site conditions	1 (0.7)
Injection site reaction	1 (0.7)
Renal and urinary disorders	1 (0.7)
Renal failure	1 (0.7)
Skin and subcutaneous tissue disorders	1 (0.7)
Swelling face	1 (0.7)
Total	9 (6.2)
Severe adverse drug reaction	
Gastrointestinal disorders	1 (0.7)
Abdominal pain	1 (0.7)
Infections and infestations	2 (1.4)
Pneumonia	1 (0.7)
Pulmonary tuberculosis	1 (0.7)
Renal and urinary disorders	1 (0.7)
Renal failure	1 (0.7)
Total	4 (2.8)

Values are presented as number (%).
Adverse drug reaction: adverse events whose casualty with the adalimumab is "Probable," "Possible," "Probably not," "Not assessable."

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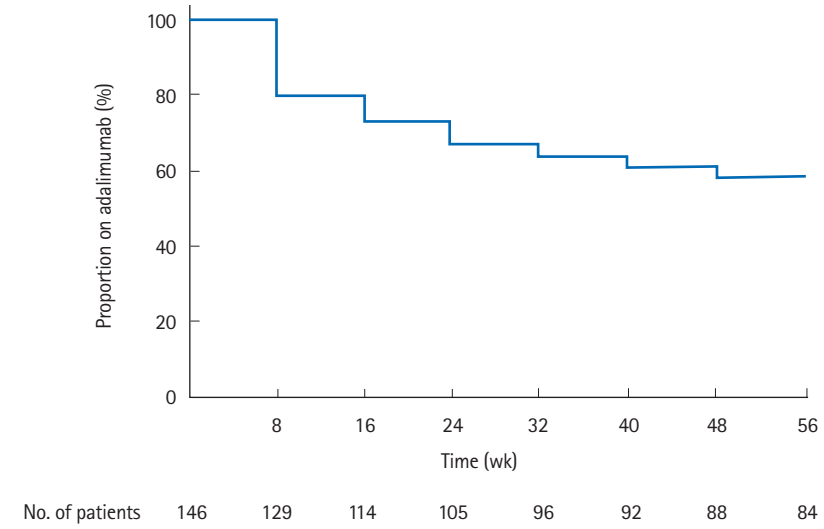
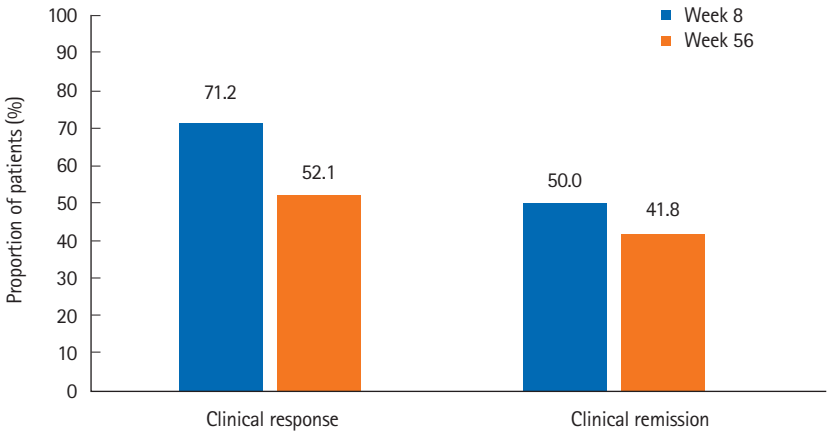


Supplementary Fig. 1. Proportion of patients remaining on adalimumab during the follow-up period.



Supplementary Fig. 2. Proportion of patients with clinical response and remission according to partial Mayo Clinic score.