Comparison of Long-Term Outcomes of Infliximab vs. Adalimumab as Treatment for Ulcerative Colitis in Biologic-naïve Patients

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Directed by Professor Jae Hee Cheon

The Master's Thesis submitted to the Department of Medicine the Graduate School of Yonsei University in partial fulfillment of the requirements for the degree of Doctor of philosophy

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This certifies that the Master's Thesis of
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ABSTRACT

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Background/Aim: Tumor necrosis factor (TNF)-α inhibitors infliximab and adalimumab are standard treatments for moderate to severe ulcerative colitis (UC). However, there has been no head-to-head comparison of the treatment efficacy and outcomes between the two agents. The aim of this study was to compare the efficacy and long-term outcomes of infliximab vs. adalimumab in biologic-naïve patients with UC.

Methods: We retrospectively analyzed the records of 113 biologic-naïve patients with UC who received between September 2012 and December 2017. We compared remission and response rates between groups at 8 and 52 weeks. We used Kaplan-Meier curves to compare long term outcomes and logistic regression analysis and Cox-proportional hazard regression models to assess factors affecting outcomes.

Results: The median follow-up duration was 25.8 months. Baseline clinical characteristics were similar between groups. There were no significant differences between the two groups in the rates of clinical remission and clinical response at 8 and 52 weeks. Multivariate analyses showed long term outcomes, including all-cause hospitalization, UC-related hospitalization, corticosteroid prescription, discontinuation of TNF-α inhibitor therapy, and switching to a secondary TNF-α inhibitor were not significantly different between groups. Elevated C-reactive protein level (more than 5 mg/L) was a significant predictive factor for poor outcomes. During the follow-up period, the rates of adverse event

were not statistically different between the two groups. There were no cases of discontinuation of treatment because of adverse event.

Conclusion: Infliximab and adalimumab have similar treatment efficacy and long-term outcomes in biologic-naïve patients with moderate to severe UC.

Key words: comparative study; infliximab; adalimumab; tumor necrosis factor-alpha; colitis, ulcerative

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INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease characterized by mucosal inflammation which progresses gradually from the rectum to the proximal segments of the colon. UC is characterized by a disease course of exacerbation, relapse, and remission.[1] The main goal of treatment is to induce and maintain steroid-free clinical remission.

Biologic therapy with tumor necrosis factor (TNF)-α inhibitors, such as infliximab and adalimumab, is one of the most effective modes of treatment for moderate to severe UC.[2-5] Several pivotal randomized controlled trials (RCTs) have demonstrated the efficacy of infliximab and adalimumab in UC patients. In 2005, the Active Ulcerative Colitis Trials (ACT-1 and ACT-2) reported that infliximab was effective for clinical remission and clinical response in moderate to severe UC patients at 8 and 52 weeks.[3] In 2011 and 2012, the Ulcerative Colitis Long Term

Remission and Maintenance with Adalimumab (ULTRA-1 and 2) trials reported higher efficacy of adalimumab than a placebo for clinical remission and response rates at 8 and 52 weeks in moderate to severe UC patients.[2,4]

Although RCTs provide the highest level of evidence, the patients included in such trials are not representative of the "real-world" population.[6] A study showed that only 26% of moderate-severe UC patients who presented to a tertiary care unit met the Food and Drug Administration approved selection criteria for RCTs.[7] Therefore, direct application of the results of RCTs in clinical practice is limited.

Furthermore, there have been no head-to-head trials which directly compare the long-term outcomes of infliximab and adalimumab in moderate to severe UC patients. Most studies comparing the agents are indirect comparative meta-analyses.[8-11] There are also several studies based on health claims data and retrospective studies to compare the efficacy of both infliximab and adalimumab in UC patients.[12-16] However, interpretation of the results is limited because the studies did not correlate the selection criteria and comparison methods.

Therefore, the aim of this study was to compare clinical remission and response rates of infliximab and adalimumab using an objective

Disease Activity Score based on recent guidelines, and to compare long-term outcomes between both agents in moderate to severe UC patients.

Patients and Methods

1. Patient identification

This is a retrospective single-center cohort study that analyzed the medical records of patients who were diagnosed with UC and had infliximab or adalimumab therapy between August 2012 and December 2017, at high-volume tertiary referral center in Korea. In Korea, the Korea Food and Drug Administration approved the use of infliximab and adalimumab in UC patients in May 2007 and August 2012, respectively.

Eligible patients had at least 3months follow-up from the initiation of TNF-α inhibitor therapy, and follow-up medical records. Exclusion criteria were as follows: (1) Patients who were not TNF-α inhibitor naïve; (2) TNF-α inhibitor therapy for diseases other than UC (i.e. those who received treatment for ankylosing spondylitis, rheumatoid arthritis); (3) diagnosis of Crohn's disease or indeterminate type of inflammatory bowel disease; or (4) previous colectomy. Figure 1 shows the flow of study cohort enrollment and identification of UC in TNF-α inhibitor

naïve patients. This study was performed in accordance with the ethical guidelines of the Declaration of Helsinki. It was also approved by the Institutional Review Board of Severance Hospital (4-2019-0843).

2. Patient characteristics

Patients were grouped according to the type of TNF-α inhibitor therapy they received (infliximab or adalimumab). Patients treated with infliximab received intravenous induction therapy (5 mg/kg) at 0, 2, and 6 weeks, and received subsequent maintenance therapy (5 mg/kg) at eight-week intervals. Patients treated with adalimumab received subcutaneous induction therapy (160 mg) at week 0, and 80 mg at week 2, and received subsequent maintenance therapy (40 mg) at two-week intervals. Baseline characteristics, including age, sex, smoking history, and body mass index were collected at initiation TNF-α inhibitor treatment. Concomitant medications were as follows: aminosalicylates (mesalazine, sulfasalazine, 5-aminosalicylic acids, balsalazide), corticosteroids (prednisolone, methylprednisolone, hydrocortisone), and immunomodulators (azathioprine, 6-mercaptopurine, methotrexate). Concomitant medications included only those taken within 1 week prior to administration of TNF-α inhibitor. To compare objective disease

severity between the two groups, we investigated the following baseline biochemical parameters: C-reactive protein (CRP), hemoglobin levels, albumin levels, and erythrocyte sedimentation rate (ESR), which reflects the disease activity of UC. Disease extent was determined based on endoscopic and radiologic image results.[17] In some cases we were unable to include complete endoscopic data because of (1) the poor physical condition of the patient disallowed endoscopy; or (2) varying follow-up endoscopic schedules. Endoscopic severity data was not obtained for 33 patients. Therefore, endoscopic UC severity score was excluded from comparisons of baseline characteristics. To compare the baseline disease activity of the two groups, we assessed and compared the partial Mayo score.[18-20] The partial Mayo score includes stool frequency subscore, rectal bleeding subscore, and physician's global assessment subscore. Extra-intestinal manifestations at joint, skin, or mouth were also analyzed.

3. Outcome measures

Primary endpoints were clinical remission and clinical response at 8 and 52 weeks. Clinical remission was defined as a partial Mayo score ≤1 point. Clinical response was defined as a decrease from baseline in the

partial Mayo score by at least two points, which is based on STRIDE guideline.[21] Total Mayo score is primarily used to evaluate treatment response.[19] However, due to incomplete endoscopic subscore data in clinical practice, the total Mayo score often cannot be used to identify treatment response. In which case, the partial Mayo score can be used to assess clinical response and remission, and correlates highly with the total Mayo score.[18-20] Therefore, we compared clinical remission and clinical response rates using the partial Mayo score. Patients who achieved clinical remission or clinical response at 8 and 52 weeks, both were considered to be in sustained clinical remission or sustained clinical response. Patients who underwent colectomy during the follow-up period, discontinued TNF-α inhibitor treatment, or switched to another TNF-α inhibitor were considered to have failed to achieve remission or response and were censored. If an adverse event occurred after at least one TNF-α inhibitor administration, it was considered to be a TNF-α inhibitor-induced side effect.

Secondary endpoints were (1) all-cause hospitalization; (2) UC-related hospitalization (with UC either as the primary diagnosis, or as a secondary diagnosis if the primary diagnosis was related to a gastrointestinal symptom such as abdominal pain, diarrhea, nausea,

vomiting, constipation, gastrointestinal bleeding); (3) corticosteroid use at least 60 days after the initiation of TNF-α inhibitor therapy (to minimize confounding and misclassification by disease severity); (4) discontinuation of TNF-α inhibitor therapy (who were not prescribed more than 12 weeks); (5) switching to a secondary TNF-α inhibitor; and (6) poor outcomes. Hospitalization did not include hospitalization at the initiation of treatment. We also evaluated factors that could predict clinical outcomes.

4. Statistical analyses

We compared the clinical and biochemical parameters of the infliximab and adalimumab groups. Baseline characteristics and demographic features were compared using the $\chi 2$ test or Fisher's exact test for categorical variables. Continuous variables were analyzed using Student's t-test or Mann Whitney test. Adverse events were compared between the treatment groups using Fisher's exact test. Outcome analyses were performed using the intention-to-treat method. The $\chi 2$ test was performed to compared clinical remission and response rate. Kaplan-Meier curves were used to determine poor outcomes including the cumulative rates of all-cause hospitalization, UC-related

hospitalization, corticosteroid prescription, discontinuation of TNF-α inhibitor and switching to secondary TNF-α inhibitor. The difference between curves was assessed using the log rank test. Cox proportional hazard models were used to compare time-to-event outcomes. Multivariate analyses were adjusted for likely confounders such as age, gender, CRP or disease extent. The results of logistic regression and Cox regression analyses were presented as hazard ratios (HRs) with 95% confidence intervals (CIs) and *p* values for the statistical tests of significance. Statistical significance was defined as having a p value of ≤0.05. Statistical analyses were performed using SPSS program (version 25.0; SPSS IBM Corp. in Armonk, NY).

Results

1. Baseline patient characteristics

We identified 113 Biologic-naïve patients who were treated with TNF-α inhibitors infliximab or adalimumab for UC. After the exclusion of 25 patients who were not naïve to TNF-α inhibitors, the remaining patients were grouped into the infliximab group (n=83) or the adalimumab group (n=30) (Figure 1). Baseline clinical characteristics at initiation TNF-α inhibitor therapy are shown in Table 1. Mean age (±

Standard deviation [SD]) was 38.4 ± 17.2 years and 62.8% of the patients were male. Smoking history and body mass index were similar between groups. The concomitant use of immunomodulators, aminosalicylates, and corticosteroids was 52.2%, 90.3%, and 36.3%, respectively, with no statistically significant difference between groups (table 1)

Mean disease duration from UC diagnosis to initiation of treatment was 66.1 months in the infliximab group and 66 months in the adalimumab group. Extra-intestinal manifestations were seen in 23 patients with similar distribution across groups. Mean partial Mayo scores (±SD) at baseline were 6.6 (±1.5) in the infliximab group and 6.0 (±1.8) in the adalimumab group, with no significant difference between groups (p = 0.095). Only the physician's global assessment subscore showed a significant difference between groups (infliximab; 2.2 vs adalimumab; 1.8, p value= 0.028). Stool frequency subscores and rectal bleeding subscores were similar between groups. Furthermore, baseline biochemical parameters, including CRP; hemoglobin levels; albumin levels; and ESR, showed no significant differences between groups. Follow-up duration from initiation of TNF-α inhibitor therapy to occurrence of event (such as colectomy, discontinuation of TNF-α inhibitor, or switching to secondary agents) was similar between groups

(infliximab, 26.3 months vs adalimumab, 24.5 months).

Table 1. Baseline patient characteristics at initiation of TNF-α inhibitor therapy

	Total (n=113), n (%)	Infliximab (n=83), n (%)	Adalimumab (n=30), n (%)	*p* value
Demographic features				
Ages, years (mean, SD)	38.4 ± 17.2	38.2 ± 18.2	39.0 ± 14.1	0.819
Sex				0.165
Male	71 (62.8)	49 (59.0)	22 (73.3)	
Female	42 (37.2)	34 (41.0)	8 (26.7)	
Smoking				0.287
Non-smoker	85 (75.2)	62 (74.7)	23 (76.7)	
Ex-smoker	22 (19.5)	15 (18.1)	7 (23.3)	
Current smoker	6 (5.3)	6 (7.2)	0 (0.0)	
BMI, kg/cm^2, (mean, SD)	21.2 ± 3.2	21.1 ± 2.7	21.5 ± 4.3	0.684
Disease extent				0.820
Extensive	53 (46.9)	37 (44.6)	16 (53.3)	
Left-side	56 (49.6)	43 (51.8)	13 (43.3)	
Proctitis	4 (3.5)	3 (3.6)	1 (3.3)	
Concomitant medications				
Aminosalicylates[a]	102 (90.3)	73 (88.0)	29 (96.7)	0.283
Corticosteroids	41 (36.3)	27 (32.5)	14 (46.7)	0.168
Immunomodulators[b]	59 (52.2)	41 (49.4)	18 (60.0)	0.319

Disease duration, months[c] (mean, SD)	66.1 ± 62.7	66.1 ± 61.4	66.0 ± 67.1	0.992
Extra-intestinal manifestations				
Joint	14 (12.4)	11 (13.3)	3 (10.0)	0.757
Skin	6 (5.3)	4 (4.8)	2 (6.7)	0.655
Oral	3 (2.7)	1 (1.2)	2 (6.7)	0.172
Partial Mayo score	6.4 ± 1.6	6.6 ± 1.5	6.0 ± 1.8	0.095
Stool frequency subscore	2.5 ± 0.7	2.5 ± 0.7	2.3 ± 0.8	0.250
Rectal bleeding subscore	1.9 ± 0.8	1.9 ± 0.8	1.9 ± 0.7	0.838
PGA subscore	2.1 ± 0.9	2.2 ± 0.9	1.8 ± 1.0	0.028
Biochemical parameters at initiation				
CRP, mg/L (mean, SD)	23.4 ± 38.6	25.4 ± 41.3	17.9 ± 29.6	0.403
Hemoglobin, g/dL (mean, SD)	12.1 ± 2.3	11.9 ± 2.3	12.7 ± 2.2	0.121
Albumin, g/dL (mean, SD)	3.7 ± 0.6	3.7 ± 0.6	3.8 ± 0.6	0.201
ESR, mm/hr (mean, SD)	44.6 ± 32.6	45.2 ± 33.0	43.1 ± 32.0	0.696
Follow-up length (mean, SD)	25.8 ± 18.4	26.3 ± 19.6	24.5 ± 14.5	0.964

SD, standard deviation

BMI, Body mass index; CRP, C-reactive protein; PGA, Physician's Global Assessment; ESR, Erythrocyte sedimentation rate

[a]Includes mesalazine, sulfasalazine, aminosalicylic acid, and balsalazide

[b]Includes azathioprine, 6-mercaptopurine, and methotrexate

[c]Duration from the first diagnosis of UC to TNF-α inhibitor administration

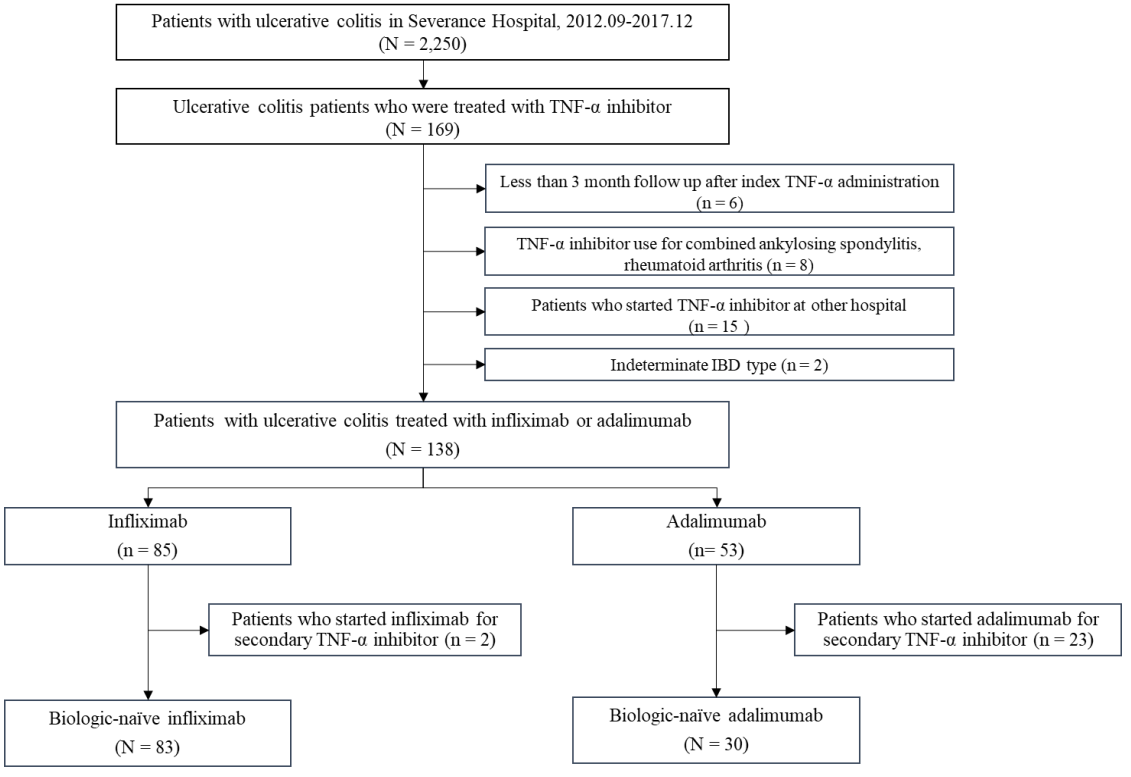


Figure 1. Flow chart of study cohort enrollment and identification of ulcerative colitis (UC) in biologic-naïve patients treated with Tumor Necrosis Factor-α (TNF-α) inhibitors infliximab or adalimumab

TNF-α inhibitor, Tumor Necrosis Factor-α inhibitor

2. Clinical remission and response (Primary endpoints)

Summary of clinical remission and response rates of each TNF-α inhibitor at weeks 8 and 52 are shown in Table 2. The rates of clinical remission and response at 8 and 52 weeks were not significantly different between groups (infliximab, 47%, 39% vs adalimumab, 56.7%, 56%; at 8 and 52 weeks, respectively; p = 0.364; p = 0.331, respectively). Sustained clinical remission and response rates were similar between groups (infliximab, 36.1%, 55.4% vs adalimumab, 36.7%, 50.0%; p = 0.959; p = 0.610, respectively). There were no significant differences in partial Mayo scores at 8 and 52 weeks post initiation of TNF-α inhibitor therapy (infliximab, 2.3, 2.2 vs adalimumab 1.8, 1.4; p = 0.289; p = 0.060, respectively). Numerical change of partial Mayo score from baseline at 8 and 52 weeks after TNF-α inhibitor treatment initiation were also similar (p = 0.775; p = 0.786, respectively). Side effects occurred in 13 patients (11.3%; Table 3) with no significant difference in the two groups. There were no severe adverse events that led to the discontinuation of TNF-α inhibitor treatment. [22]

Table 2. Clinical remission and response at 8 and 52 weeks post initiation of TNF-α inhibitor

	Week 8			Week 52		
	Infliximab (n=83), n (%)	Adalimumab (n=30), n (%)	*p* value	Infliximab (n=83), n (%)	Adalimumab (n=30), n (%)	*p* value
Clinical remission[a]	39 (47.0)	17 (56.7)	0.364	33 (39.8)	15 (50.0)	0.331
Clinical response[b]	72 (86.7)	23 (76.7)	0.196	60 (72.3)	23 (76.7)	0.642
Sustained clinical remission at weeks 8 and 52[c]	N/A	N/A		30 (36.1)	11 (36.7)	0.959
Sustained clinical response at weeks 8 and 52[d]	N/A	N/A		46 (55.4)	15 (50.0)	0.610
Partial Mayo score (mean, SD)	2.3 ± 2.2	1.8 ± 2.0	0.289	2.2 ± 2.4	1.4 ± 1.7	0.060
Stool frequency sub-score	1.1 ± 1.1	0.9 ± 0.9	0.371	1.1 ± 1.2	0.6 ± 0.9	0.304
Rectal bleeding sub-score	0.9 ± 0.7	0.4 ± 0.7	0.115	0.5 ± 0.8	0.3 ± 0.7	0.298
PGA sub-score	0.5 ± 0.7	0.5 ± 0.8	0.809	0.5 ± 0.9	0.4 ± 0.5	0.084
Change of Partial Mayo score from baseline (mean, SD)	4.3 ± 2.5	4.1 ± 2.7	0.775	4.6 ± 2.7	4.7 ± 2.3	0.786

[a]Partial Mayo score ≤1 points

[b]Decrease from baseline by at least 2 points in the partial Mayo score

[c]Patients who were in clinical remission at week 8 and week 52 were considered to be in sustained clinical remission

[d]Patients who had a clinical response at week 8 and week 52 were considered to have a sustained clinical response

SD, standard deviation

PGA, Physician's Global Assessment

Table 3. Summary of TNF-α inhibitor-induced adverse events

	Infliximab (n=83), n (%)	Adalimumab (n=30), n (%)	*p* value
Any AE	12 (14.5)	2 (6.7)	0.441
Acute infusion reaction	7 (7.5)	1 (3.3)	
Headache	1 (1.2)	0 (0.0)	
Dizziness	1 (1.2)	0 (0.0)	
Urticaria	3 (3.6)	1 (3.3)	

AE, Adverse event

3. Long-term outcomes of TNF-α inhibitors (Secondary endpoints)

There were no statistically significant differences between groups in Kaplan-Meier analyses with respect to the following long-term outcomes: poor outcomes, all-cause hospitalization, UC-related hospitalization, corticosteroid prescription after 3 weeks of TNF-α inhibitor administration, discontinuation, or switching to secondary TNF-α inhibitor (Figure 2). Serious infections occurred in eight patients (7.1%) The serious infections occurred in the infliximab group only, but there was no statistically significant difference between the two groups (p = 0.107). Infliximab was replaced with secondary biologics in four patients (3.4%) because serious infections occurred after infliximab administration. During the total follow-up period, 26 patients started secondary biologics including adalimumab in 15 patients, vedolizumab in 9 patients and tofacitinib in 2 patients. During the entire follow-up period, two infliximab-treated patients received colectomy at weeks 2 and 41, respectively. No death was reported during the follow-up period.

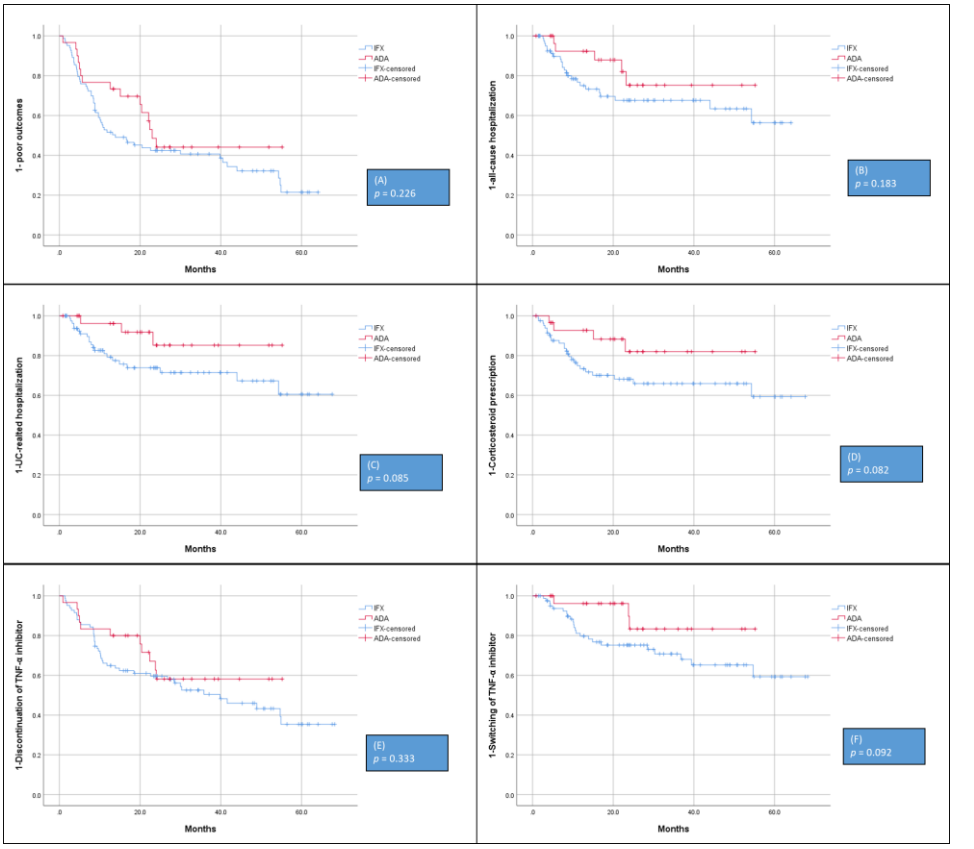


Figure 2. Kaplan Meier curves for cumulative outcomes in TNF-α treated patients with ulcerative colitis. (1- rates of each event) (A) Poor outcomes[a] (B) All-cause hospitalization rate (C) UC-related hospitalization rate (D) Corticosteroid prescription rate (E) Discontinuation rate of TNF-α inhibitor (F) Switching rate to a secondary TNF-α inhibitor

[a]The poor outcomes mean the sum of events incluing all-cause hospitalization, UC-related hospitalization, corticosteroid prescription, discontinuation of TNF-α inhibitor, switching to secondary TNF-α inhibitor

4. Predictive factors for poor clinical outcomes

Adjusted HRs of TNF-α inhibitors for various clinical outcomes are presented in Table 4. After multivariate analysis, type of TNF-α inhibitor used was not a significant factor in any clinical outcomes. During the long-term follow up period, elevated baseline CRP level (>5 mg/L) at initiation of TNF-α inhibitor administration was the only factor that predicted poor outcomes in moderate to severe UC patients (adjusted HR, 2.25; 95% CI, 1.37-3.70; p = 0.001) (Table 5, Figure 3). Subgroup analysis showed that elevated CRP level was significantly associated with poor outcomes in the infliximab-treated group (adjusted HR, 2.41; 95% CI, 1.36 - 4.26; p = 0.002), but not in the adalimumab-treated group (adjusted HR, 3.39; 95% CI, 0.90 – 12.77; p = 0.071) (Table 6, Figure 4-1, 4-2).

Table 4. Adjusted hazard ratio of clinical outcomes according to TNF-α inhibitor

Type of outcomes	Adjusted HR[a] (Inflixmab vs adalimumab)	95% Confidence Interval	*p* value
8 weeks after initiation of drug			
Clinical remission	0.68	(0.29-1.57)	0.365
Clinical response	1.99	(0.69-5.74)	0.201
52 weeks after initiation of drug			
Clinical remission	0.66	(0.29-1.53)	0.332
Clinical response	0.77	(0.28-2.14)	0.613
Long term outcomes			
Poor outcomes[b]	1.45	(0.81-2.56)	0.208
All-cause hospitalization	2.2	(0.83-5.84)	0.113
UC-related hospitalization	3.38	(0.99-11.47)	0.051
Corticosteroid prescription	2.44	(0.85-7.01)	0.099
Discontinuation of TNF-α inhibitor	1.39	(0.72-2.71)	0.331
Switching to secondary TNF-α inhibitor	2.89	(0.87-9.64)	0.085

[a]A hazard ratio of >1 indicates a benefit of infliximab compared with adalimumab.

[b]Poor outcomes is the sum of any of following events; all-cause hospitalization, UC-related hospitalization, corticosteroid prescription, discontinuation of TNF-α inhibitor or switching to secondary TNF-α inhibitor.

Table 5. Risk factors associated with poor outcomes[a] after TNF-α inhibitor treatment in patients with ulcerative colitis (n = 113)

Variables	Univariate analysis	Multivariate analysis	
	p value	*p* value	Adjusted HR[b] (95% CI)
Age (>40/≤40), years	0.639		
Sex (Male/Female)	0.401		
CRP(>5/≤5), mg/L	0.001	0.001	2.25 (1.37-3.70)
Disease extent (Extensive/Left-sided)	0.850		
TNF-α inhibitor (Infliximab/Adalimumab)	0.229	0.208	1.45 (0.81-2.56)

[a]Poor outcomes is the sum of any of following events; all-cause hospitalization, UC-related hospitalization, corticosteroid prescription, discontinuation of TNF-α inhibitor or switching to secondary TNF-α inhibitor.

[b]A hazard ratio of >1 indicates a benefit of infliximab compared with adalimumab.

Table 6. Factors affecting poor outcomes[a] according to type of TNF-α inhibitor treatment in patients with ulcerative colitis

Variables	Univariate analysis	Multivariate analysis	
	p value	*p* value	Adjusted HR[b] (95% CI)
Infliximab subgroup (n = 83)			
Age (>40/≤40), years	0.952		
Sex (Male/Female)	0.144		
CRP(>5/≤5), mg/L	0.004	0.002	2.41 (1.36 - 4.26)
Disease extent (Extensive/Left-sided)	0.789		
Adalimumab subgroup (n = 30)			
Age (>40/≤40), years	0.504		
Sex (Male/Female)	0.309		
CRP(>5/≤5), mg/L	0.167	0.071	3.39 (0.90 - 12.77)
Disease extent (Extensive/Left-sided)	0.323		

[a]Poor outcomes is the sum of any of following events; all-cause hospitalization, UC-related hospitalization, corticosteroid prescription, discontinuation of TNF-α inhibitor or switching to secondary TNF-α inhibitor.

[b]A hazard ratio of >1 indicates a benefit of infliximab compared with adalimumab.

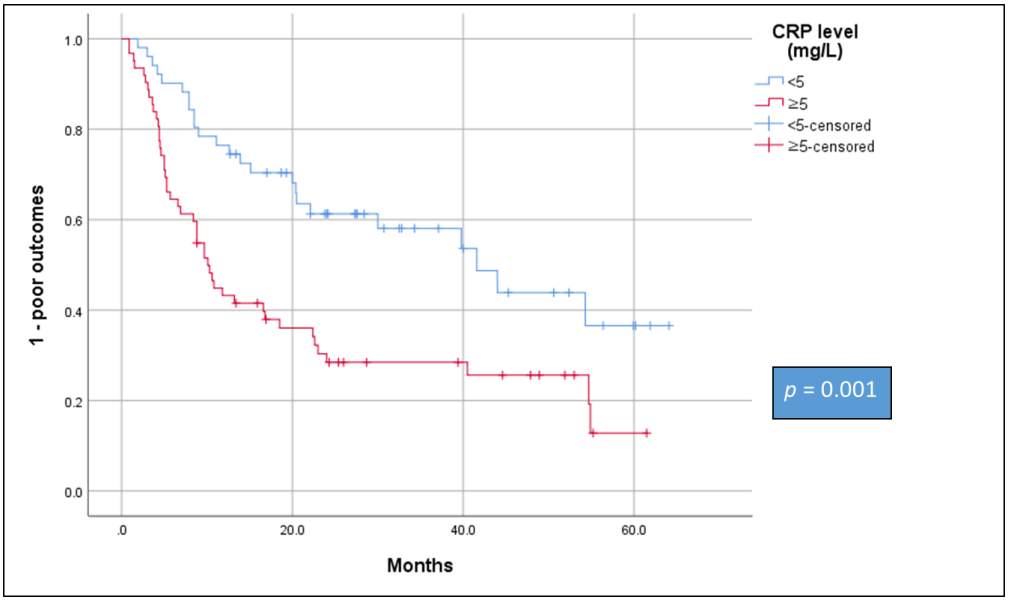
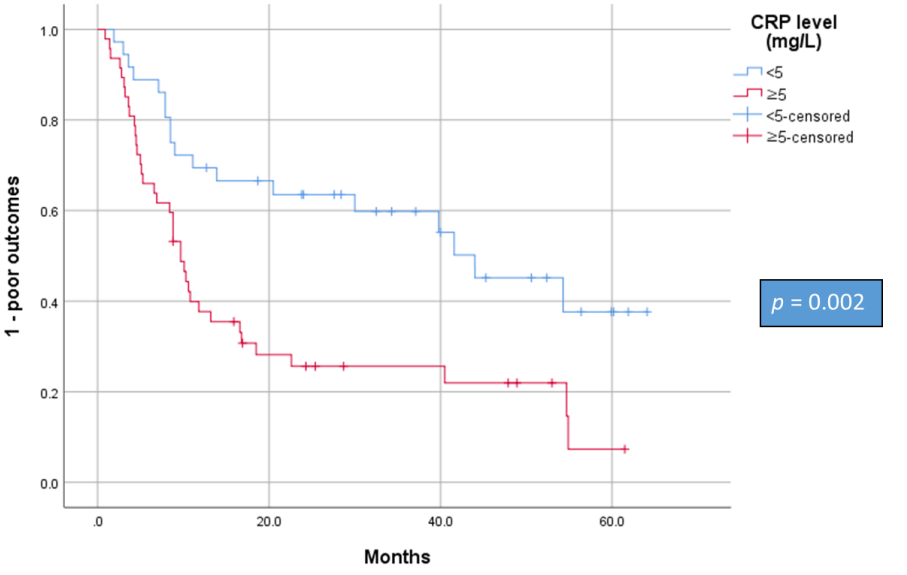


Figure 3. Kaplan Meier curves of cumulative outcomes based on baseline CRP level in TNF-α inhibitor treated patients with ulcerative colitis. (1- rates of poor outcome event)

CRP, C-reactive protein

TNF-α inhibitor, Tumor Necrosis Factor-α inhibitor



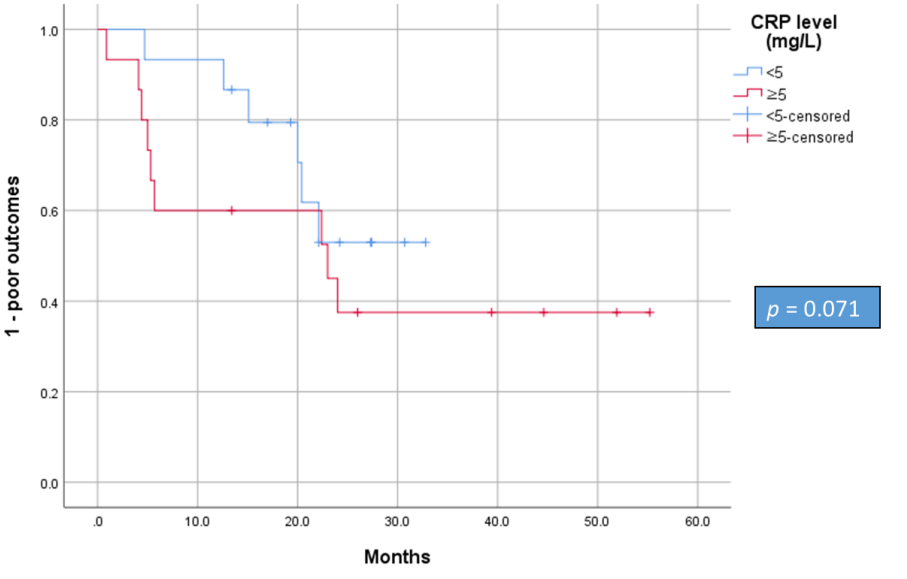


Figure 4-1. Kaplan Meier curves of cumulative outcomes based on baseline CRP level in infliximab treated patients with ulcerative colitis. (1- rates of poor outcome events)

CRP, C-reactive protein

Figure 4-2. Kaplan Meier curves of cumulative outcomes based on baseline CRP level in adalimumab treated patients with ulcerative colitis. (1- rates of poor outcome events)
CRP, C-reactive protein

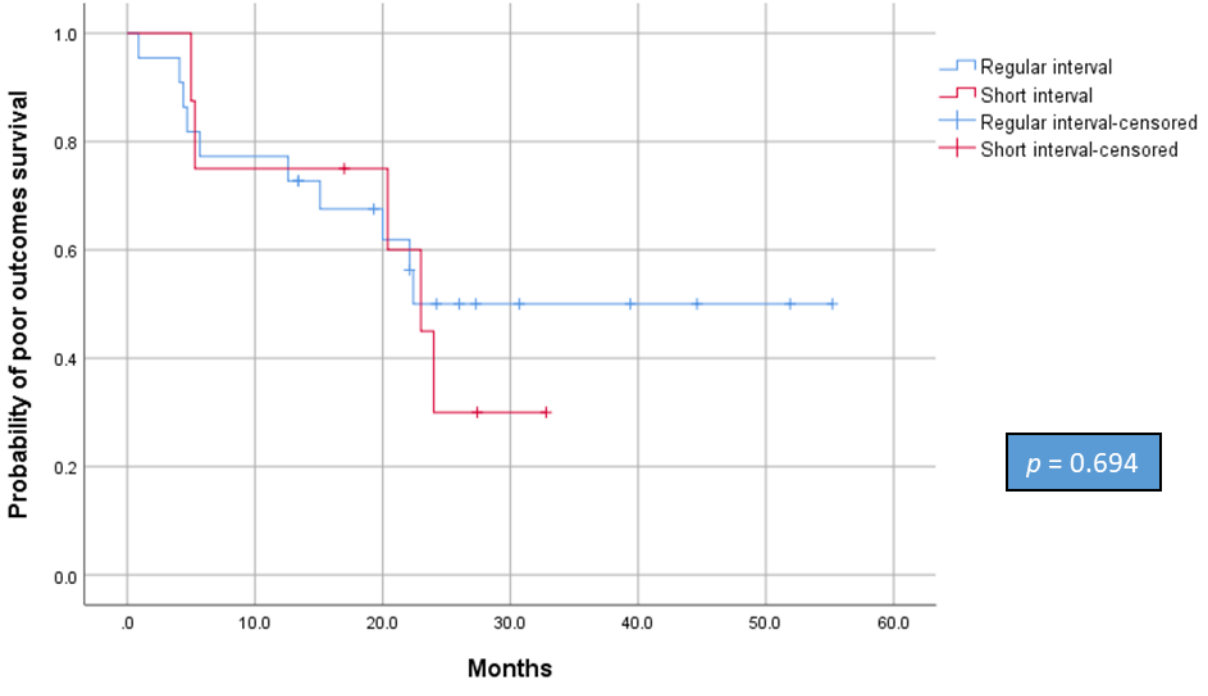
Supplementary Table 1. Baseline characteristics at initiation of adalimumab treatment according to administration interval

	Regular interval (n=22), n (%)	Short interval[a] (n=8), n (%)	*p* value
Demographic features			
Ages, years (mean, SD)	39.6 ± 14.1	37.3 ± 15.0	0.708
Sex			0.999
Male	16 (72.7)	6 (75.0)	
Female	6 (27.3)	2 (25.0)	
Smoking			0.638
Non-smoker	16 (72.7)	7 (87.5)	
Ex-smoker	6 (27.3)	1 (12.5)	
BMI, kg/cm^2, (mean, SD)	21.6 ± 4.6	21.0 ± 3.4	0.728
Disease extent			0.733
Extensive	11 (50.0)	5 (62.5)	
Left-side	10 (45.5)	3 (37.5)	
Proctitis	1 (4.5)	0 (0.0)	
Partial Mayo score	5.8 ± 1.7	6.4 ± 2.1	0.456
Stool frequency sub-score	2.2 ± 0.9	2.6 ± 0.7	0.205
Rectal bleeding sub-score	1.9 ± 0.7	1.9 ± 0.8	0.910
PGA sub-score	1.7 ± 1.0	1.9 ± 1.0	0.719
Biochemical parameters at initiation			
CRP, mg/L (mean, SD)	21.0 ± 33.7	9.1 ± 10.9	0.340
Hemoglobin, g/dL (mean, SD)	12.7 ± 2.2	12.7 ± 2.4	0.969
Albumin, g/dL (mean, SD)	3.8 ± 0.5	3.9 ± 0.8	0.723
ESR, mm/hr (mean, SD)	45.3 ± 35.0	36.8 ± 22.5	0.523
Follow-up length (mean, SD)	26.3 ± 15.7	19.5 ± 10.0	0.262

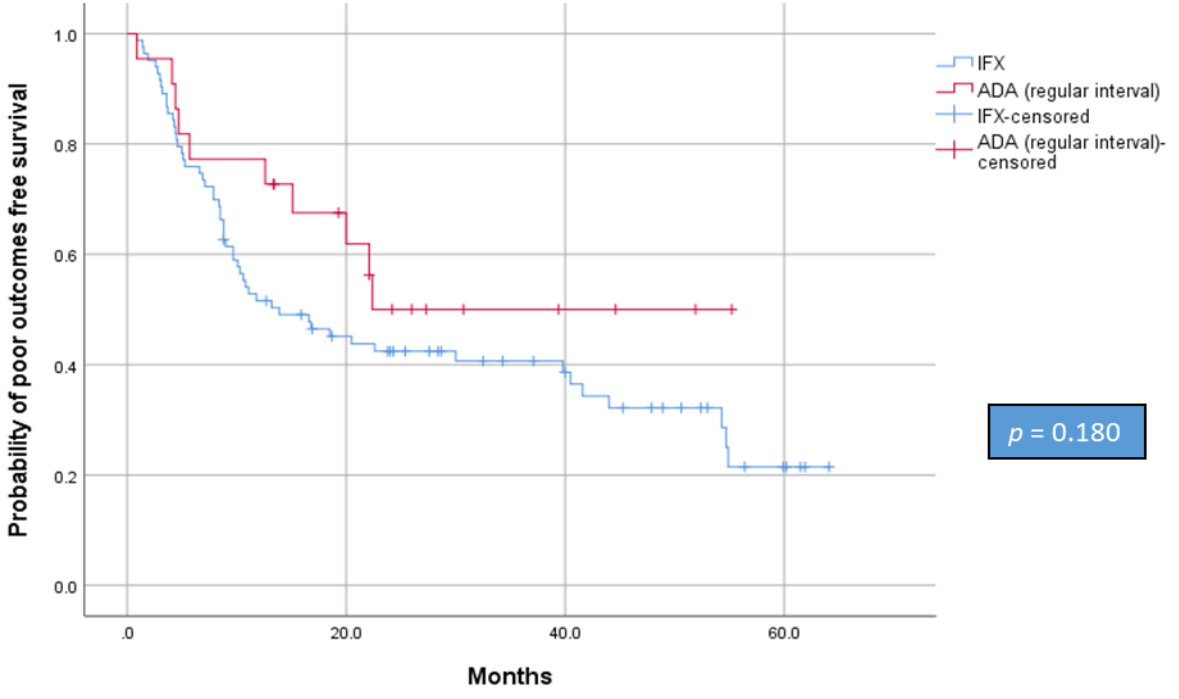
SD, standard deviation

CRP, C-reactive protein; PGA, Physician's Global Assessment; ESR, erythrocyte sedimentation rate

Supplementary Figure 1. Comparision of poor outcome[a] free survival probability between short and regular interval adalimumab group



Supplementary Figure 2. Comparison of poor outcome[a] free survival probability between infliximab and regular interval adalimumab group



[a]Poor outcome is the sum of any of following events; all-cause hospitalization, UC-related hospitalization, corticosteroid prescription, discontinuation of TNF-α inhibitor or switching to secondary TNF-α inhibitor.

Discussion

This study compared clinical remission and response of TNF-α inhibitors infliximab versus adalimumab at 8 and 52 weeks post treatment initiation. Tumor necrosis factor-α inhibitors are the established treatment of choice for patients with moderate to severe UC who are refractory to conventional pharmacotherapy.[23-25] Poor outcomes, including hospitalization, discontinuation of drug, corticosteroid prescription, and switching to another drug, are parameters used to assess the efficacy of UC treatment in clinical practice.[12-16,26] Therefore, we also analyzed the same poor outcomes during long-term follow-up of patients with UC treated with infliximab versus adalimumab. We founded similar rates of clinical remission and clinical response between the two agents at 8 and 52 weeks post treatment initiation, as well as similar rates of poor outcomes during the long-term follow-up period. To the best of our knowledge, this is the first study to directly compare long term clinical remission and response rates as well as various poor outcomes following infliximab or adalimumab treatment in moderate to severe biologic-naïve UC patients in the clinical context.

Although several guidelines recommend infliximab and adalimumab as the gold standard treatments for moderate to severe UC,[23-25] there have

been no comparative head-to-head trials. Comparison of the therapeutic effects of infliximab and adalimumab in patients with UC have been performed by several indirect meta-analyses.[9,11,27,28] However, these network meta-analysis report differing results depending on the types of statistical analysis used, or the types of trials included in the meta-analysis. Thorlund et al. reported that although there was no significant difference at week 52, clinical remission and response rates at week 8 were significantly higher in infliximab group than adalimumab group in patients with moderate to severe UC (odd ratio [OR], 0.42; 95% CI, 0.17 - 0.97).[9] Danese et al. reported that the clinical remission rates were similar, but clinical response rates were significantly higher in the infliximab group (OR, 2.36; CI: 1.22-4.63) than adalimumab group during the induction period.[27] Bonovas et al. performed an indirect network meta-analysis comparing infliximab, adalimumab, golimumab, vedolizumab, and tofacitinib in UC patients with 15 RCTs and reported that infliximab was more effective than adalimumab in both clinical remission (OR 1.87, 95% CI, 1.26-2.79) and clinical response. (OR, 2.01; 95% CI, 1.36-2.98)[11]. On the other hands, Stidham et al. concluded that both infliximab and adalimumab are effective for induction and maintenance treatment of UC inducing both remission and response, and

that no single agent is clinically superior.[28] The indirect network meta-analyses were limited due to a lack of monitoring for various long-term poor outcomes such as hospitalization, discontinuation of study agent, corticosteroid prescription—these are useful indicators of therapeutic effect in clinical practice. It is worth noting that the results of indirect meta-analyses can vary depending on the type of trial, inclusion/exclusion criteria, and methodology (i.e. whether informative or non-informative prior distribution is used).

There were several more studies which indirectly compared the outcomes of infliximab and adalimumab using medical databases. Singh et al. reported two studies comparing outcomes of infliximab and adalimumab using a nationwide administrative claims database.[12,13] In a study using the UC administrative claims database (Optum Labs Data Warehouse), there were no significant differences in rates of UC-related hospitalization, corticosteroid use, and serious infection after propensity score-matching between the two groups. Sing et al. also conducted another nationwide propensity score-matched cohort study using the Danish Civil Registration System.[12] Of the 275 biologic-naïve UC patients (infliximab 171, adalimumab 104) included in the study, adalimumab-treated patients showed a higher risk of hospitalization and

serious infection than infliximab-treated patients. These nationwide administrative-based studies have some disadvantages. First, there was no comparative data of baseline disease severity (such as Mayo score and laboratory biochemical findings). Second, covariates and outcomes using administrative claims codes can be subject to error and some of these covariates and outcomes were defined according to unproven investigator judgements. Third, the median follow-up duration was relatively short in the adalimumab group compared to the infliximab group (median, 1.3 years vs 2.3 years) because they also included infliximab patients prior to FDA approval of adalimumab. However, the mean follow-up duration in this study was similar to that of 26.3 months versus 24.5 months in both groups. A difference in duration can lead to selection bias that may affect results. In the current study, we measured biochemical parameters and partial Mayo score as an objective measure of baseline disease activity. Clinical remission and response rates at weeks 8 and 52 were compared using the partial Mayo score. Comparison of the disease activity parameters eliminates confounders to the direct comparison of the two agents. Direct comparison of the two effective agents through well-designed randomized controlled studies is needed in the future.

A total of 170 physicians participated in a retrospective online

physician chart review study in the US to compare the long-term outcomes of infliximab and adalimumab in biologic-naïve UC patients.[16] The results of this study are meaningful because of its large scale analysis of real-world data in biologic-naive patients, although there was variability of interpretation and verification of medical record quality. It should be noted that, compared to RCTs, results from "real-world" data show higher efficacy of both adalimumab and infliximab.[2-4,16] The US study showed that remission rates after 6 months were 76.8% in the infliximab group and 71.7% in the adalimumab group, respectively. In the ACT 1/2 trials, remission and response rates in the infliximab group at 8 week were 33.9-38.8% and 64.5-69.4%, and at 54 week were 34.7% and 45.5%, respectively [3] In the ULTRA 1/2 trials, remission and response rates for adalimumab at 8 weeks were only 16.5-18.5% and 50.4-54.6%, respectively; and at 52 weeks were 17.3% and 30.2%, respectively.[2,4] The current study also showed remission and response rates in both agents at 8 weeks were 49.6%, 84.1% and at 52 weeks were 42.5% and 73.5%, respectively. The results of the current study appear to be more effective than that of RCTs. There are several possible reasons for the difference of results between the current study and RCTs: First, the inclusion of patients with previous exposure to TNF-α inhibitor in the

RCTs may have influenced the results. The US clinical trials included TNF-α inhibitor-experienced patients but our study only included biologic-naïve patients.[2-4] Given that TNF-α inhibitors have a greater efficacy in biologic-naive UC patients, the higher remission and response rates of this study can be explained.[29,30] Second, the difference in disease duration at the initiation of TNF-α inhibitor treatment may have also influenced results. The ULTRA and ACT RCTs had a mean duration of 6.1-8.4 years, and those of the current study were 5.5 years.[9] A previous study in patients with Crohn's disease demonstrated that early treatment with TNF-α inhibitors results in more effectively controlled Crohn's disease.[31] Third, difference in clinical remission and response evaluating criteria may have influenced results. In the current study, we used the partial Mayo score (which did not include an endoscopic subscore) as a criterion for clinical remission and response in this study but the previous studies used the full Mayo score (which include an endoscopic subscore).

In Korea, it is difficult to adjust dose escalation or interval of infliximab due to insurance limitations imposed by the Health Insurance Review and Assessment Service. However, during the maintenance period of adalimumab administration, it is permissible to reduce 2-week regular maintenance intervals to 1-week "short" intervals, according to

the patient's treatment response and the physician's judgment. In this study, eight of the 30 adalimumab-naive UC patients experienced 1-week short interval administration during the follow-up period. In order to reduce selection bias, subgroup analysis was conducted between the regular interval group and the short interval group and there was no significant difference in baseline characteristics and time to poor outcome events between groups (Supplementary table 1, Supplementary figure 1). Also, there was no difference in the probability of poor outcomes between the infliximab group and 2-week regular interval adalimumab group during the follow-up period. (Supplementary figure 2). In light of these results, it was found that adalimumab-only interval regulation did not affect similar poor outcomes results in both groups. Therefore, the choice of TNF-α inhibitor should be determined by considering various factors such as the patient's condition, ability to pay, and preference for treatment, given similar treatment effects.

Active UC is frequently marked by an elevation in CRP[32] which an important prognostic factor to predict colectomy risk and response to medical therapy in UC patients.[33-35] Moreover, it is well correlated with the endoscopic Mayo score.[36] However, CRP elevation is a nonspecific marker because it may be increased in response to other systemic

inflammatory conditions. One recent study suggested that elevated CRP level is a predictive factor for treatment response in infliximab-treated IBD patients.[37] This is well correlated with our findings and supports the recommendations of the American College of Gastroenterology Ulcerative Colitis Activity Index who call for more accurate measurement of UC disease activity, including the CRP as a biologic marker of disease activity.[23]

The current study complements the information gaps of previous RCTs and meta-analysis studies by including baseline disease activity and comparing various long-term outcomes in real-world biologic-naive patients with UC only. We used the partial Mayo score, which is easy to use in clinical practice, to measure of disease activity in accordance with current guidelines.[19-21]

This study has several limitations. First, it is a retrospective study. There could be a selection bias. Endoscopy data was not available in many cases, so the full Mayo score could not be measured. Instead, we used the partial Mayo scoring system which correlates well with the full Mayo scoring system and enabled us to apply our results to the real-world population.[18,20,21] Second, we did not compare drugs such as golimumab, vedolizumab and tofacitinib which have been proven to be

effective in the treatment of moderate-to-severe UC.[5] As these drugs have been released relatively recently, it is difficult to get a long-term follow-up data about their long-term outcomes. Third, this study has a relatively small sample size. However, various long-term outcome comparisons were consistent between groups, and poor outcomes (the sum of multiple outcomes) of UC are presented for the first time in our study.

This real-world-based retrospective study demonstrates that infliximab and adalimumab are similar in terms of treatment efficacy and long-term outcomes in biologic-naïve moderate-to-severe UC patients. C-reactive protein elevation is an important prognostic factor in UC patients treated with TNF-α inhibitors, especially in infliximab. Further randomized controlled studies comparing treatment efficacy and long-term outcomes between TNF-α inhibitors for UC treatment are needed.

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ABSTRACT(IN KOREAN)

생물학적 제제 사용력이 없는 실제 임상 궤양성 대장염 환자군을 대상으로 한 인플릭시맵과 아달리무맙의 장기 비교 연구

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이 용 일

배경 및 목적: 인플릭시맵과 아달리무맙은 중등도 및 중증 궤양성 대장염 환자에서 표준 치료로 자리매김 해왔다. 하지만, 두 약제의 치료 효과와 장기 예후를 직접 비교하는 임상연구는 없는 실정이다. 본 연구의 목적은 생물학적 제제 사용력이 없는 궤양성 대장염 환자를 대상으로 두 약제의 효과와 장기 예후를 비교하고자 하였다.

방법: 한국에 있는 3차 단일 의료기관 연구로 진행되었으며, 2012년 9월부터 2017년 12월까지 본원에서 113명의 생물학적 제제 사용력이 없는 궤양성 대장염 환자 중 종양 괴사 인자-α를 처음 시작한 환자를 대상으로 하였다. 인플릭시맵군 (83명)과 아달리무맙 군(30명)을 8주, 52주째 임상 관해율와 임상 반응률을 비교 분석하였다. 로지스틱 회귀분석과 Cox 비례 위험 회귀 모델을 사용하였다.

결과: 113명의 평균 추적 관찰 기간은 25.8개월이었다. 양 그룹의 기본 특성은 차이가 없었다. 8주와 52주째 임상 관해율와 임상 반응률에 유의미한 차이는 없었다. 장기 추적 관찰시, 전체 입원률, 궤양성 대장염 관련 입원률, 스테로이드 처방률, 중단 및 2차 약제로의 전환률 등을 포함한 불량한 예후 또한 유의미한 차이가 없었다. 다변량 분석에서, 종양 괴사 인자-α는

어떠한 예후에도 영향을 미치는 인지가 아니었고, 증가된 C-반응 단백질은 불량한 영향을 미치는 인자였다. 추적관찰 기간동안 치료를 중단할만한 부작용은 발생하지 않았으며 부작용의 비율 또한 양 군에서 차이가 나지 않았다.

결론: 인플릭시맵과 아달리무맙은 중등도 및 중증 궤양성 대장염 환자의 치료 효과와 장기 예후에 비슷한 결과를 나타낸다. C-반응 단백질 수치는 장기 예후의 예측 인자였다.

핵심되는 말 : 비교 연구; 인플릭시맵; 아달리무맙; 종양 괴사 인자-α; 궤양성 대장염