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Similar Clinical Outcomes of Early and Late Anti-TNF Initiation for Ulcerative Colitis: A Nationwide Population-Based Study

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Purpose: The optimal timing of anti-tumor necrosis factor (anti-TNF) initiation in patients with ulcerative colitis (UC) remains unclear. Very little is known about the clinical outcomes after the early versus late initiation of anti-TNF therapy, especially in Asian UC patients. Here we aimed to assess whether earlier anti-TNF treatment initiation results in favorable clinical outcomes in Korean UC patients.

Materials and Methods: Using the Korean National Health Insurance claims database, we studied patients who were diagnosed with UC and received anti-TNF therapy for more than 6 months between 2010 and 2016. Using a Cox proportional hazard model, clinical outcomes including colectomy, UC-related emergency room (ER) visits, UC-related hospitalizations, and the need for corticosteroids were compared between early (≤2 years of diagnosis) and late (>2 years of diagnosis) initiators of anti-TNF therapy.

Results: Among 17167 UC patients, 698 patients who received anti-TNF therapy for more than 6 months were included (420 infliximab, 242 adalimumab, and 36 golimumab). Of the 698 patients, 299 (42.8%) initiated anti-TNF therapy within 2 years of diagnosis. There were no significant differences in the risk of colectomy [adjusted hazard ratio (aHR), 0.41; 95% confidence interval (CI), 0.04–3.90], ER visits (aHR, 0.98; 95% CI, 0.50–1.92), hospitalization (aHR, 0.76; 95% CI, 0.57–1.01), and corticosteroid use (aHR, 1.04; 95% CI, 0.71–1.50) between early and late initiators of anti-TNF therapy.

Conclusion: Patients receiving early anti-TNF therapy had similar clinical outcomes to those of late initiators, suggesting that early anti-TNF therapy initiation offers little benefit in patients with UC.

Key Words: Ulcerative colitis, anti-TNF, early use, clinical outcome

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INTRODUCTION

Ulcerative colitis (UC) is an inflammatory bowel disease that results in chronic inflammation of the large intestine due to immune dysregulation.[1] UC is an incurable disease with alternating periods of remission and relapse. Due to this chronic clinical course, most patients with UC require life-long medical treatment. The medical treatment of UC has changed dramatically over the past decade, with the introduction of biological agents that target tumor necrosis factor-alpha (TNF-α).[2] Pivotal randomized controlled trials (RCTs) demonstrated the efficacy of anti-TNF agents, including infliximab, adalimumab, and golimumab, for inducing and maintaining remission in patients with moderately to severely active UC.[3-6] Anti-TNF

therapy targeting mucosal healing may also lead to changes in the natural course of UC. Indeed, previous RCTs demonstrated that anti-TNF therapy reduces the risk of colectomy and hospitalization.[7,8]

However, the optimal timing of anti-TNF initiation in UC patients remains a challenging issue. Several studies have proven the benefit of earlier anti-TNF initiation on the clinical outcomes of patients with Crohn's disease (CD),[9-11] while very little is known about the effects of earlier anti-TNF initiation on the natural history of UC. The results of CD patients may not be generalized for UC patients, as the two diseases have different features. To date, only a few studies have examined the effect of earlier anti-TNF initiation on the clinical outcomes of UC.[12-14] However, the number of UC patients included in previous studies was insufficient to draw a clear conclusion. Furthermore, all previous studies on this topic were performed in Western countries,[12-14] and their results may not be generalizable in Asian UC patients. To better understand the association between anti-TNF initiation timing and clinical outcomes of UC, an analysis of population-based Asian data of a large number of patients is warranted.

Therefore, in this nationwide population-based study of data from the South Korean health insurance claims database, we evaluated the impact of early initiation of anti-TNF therapy on the clinical outcomes [abdominal surgery, UC-related emergency room (ER) visits, UC-related hospitalization, and new corticosteroid use] of patients with UC during maintenance therapy in the real-life clinical setting.

MATERIALS AND METHODS

Study design and data source

This study analyzed data from the National Health Insurance (NHI) claims database of South Korea, a mandatory nationwide health insurance program established by the Korean government that covers all forms of health-care utilization, including outpatient care, pharmaceutical services, and hospitalization, for the entire population of South Korea (approximately 51 million people). Medical institutions must electronically submit all information regarding health-care utilization for reimbursement; this information is registered in a comprehensive database operated by the Health Insurance and Review Agency (HIRA). The HIRA database contains information on personal demographics, outpatient and inpatient medical use, prescriptions, diagnostic and surgical procedures, as well as diagnoses identified by the International Classification of Diseases 10th revision (ICD-10) codes.[15-17] The source population for this study was NHI claims data registered between 2008 and 2016.

Patient ascertainment and definitions

To improve the diagnostic accuracy of UC, only patients with data on both appropriate diagnostic codes and UC-related medicine prescriptions were included. The ICD-10 codes K51.0–51.9 indicate UC. UC-related medicine prescriptions were defined as prescriptions of 5-aminosalicylic acids (5-ASA) for ≥1 month, immunomodulators (azathioprine or 6-mercaptopurine) at least once, and/or biologics at least once.[15-17] To rule out the use of drugs for other autoimmune diseases, the included medications were confined to prescriptions received from a gastroenterology clinic. During the study period, the biologics approved for UC treatment in South Korea were infliximab, adalimumab, and golimumab. However, the actual use of golimumab was rare during the study period, as this anti-TNF agent was only approved in May 2015.

The date of UC registration in the HIRA database was considered as the date of diagnosis. Given that previous prevalent cases could confound the incidence rate, we set a washout period of 2 years; as a result, patients who were diagnosed with UC from January 1, 2010 to December 31, 2016 were analyzed.

Patients were stratified by the time to their first dose of induction anti-TNF agent after diagnosis. Based on the previous studies,[13,14,18] early initiation of anti-TNF therapy was defined as starting infliximab, adalimumab, or golimumab within 2 years of diagnosis, whereas late initiation of anti-TNF therapy was defined as starting >2 year after diagnosis.

To properly assess the effectiveness of anti-TNF therapy on long-term clinical outcomes, patients who received anti-TNF therapy for less than 6 months were excluded from the analysis. Since the effects of anti-TNF therapy may differ between patients undergoing colectomy or not, patients with a history of colectomy before starting anti-TNF therapy were also excluded from the analysis.

Clinical outcomes

The primary objective of this study was to determine if the early initiation of anti-TNF therapy within 2 years of UC diagnosis affected the need for colectomy, UC-related ER visits, UC-related hospitalization, or new corticosteroid use during anti-TNF maintenance therapy. These clinical outcomes were determined based on the previous studies.[12-14] Colectomy was identified using the procedural code. ER visits were defined as patient visits to the ER with UC as the primary diagnosis. Hospitalization was defined as admission for ≥3 days in the department of gastroenterology. Finally, new corticosteroid use was defined as moderate to high dose of corticosteroid use (≥30 mg prednisolone, ≥50 mg methylprednisolone, or ≥200 mg hydrocortisone) for more than 2 months after the first anti-TNF agent prescription.

Statistical analysis

Incidence rates for colectomy, ER visits, hospitalization, and corticosteroid use were calculated per 100 person-years with 95% confidence intervals (CIs) using Poisson distribution. The crude risk of outcomes between early and late initiators was

compared using Kaplan-Meier method and log-rank tests. We used Cox proportional hazards models to adjust for potential confounding variables. Baseline covariates including sex, age, first anti-TNF agent, region, and hospital scale were adjusted as time-fixed covariates. The cumulative use period of anti-TNF agents and concomitant medications, including 5-ASA and immunomodulators, were adjusted as time-dependent covariates. The results are presented as hazard ratios (HRs) with corresponding 95% CIs. All analyses were performed using the SAS Enterprise Guide (SAS Institute, Inc., Cary, NC, USA), and *p*-values<0.05 were considered statistically significant.

Ethical considerations

As the information in the HIRA database is encrypted, the database does not contain personal identifiers. The study protocol was approved by the Institutional Review Board of Severance Hospital, Yonsei University College of Medicine (IRB no. 4-2017-0927).

RESULTS

Baseline patient demographics

We identified that 17167 patients were diagnosed with UC in 2010–2016; among them, 1125 patients started their first anti-TNF agents during the study period. Of these 1125 patients, 419 were excluded as they received anti-TNF therapy for less than 6 months, while another 8 were excluded for having undergone colectomy before the start of anti-TNF therapy. Ultimately, 698 patients were included in the study, of whom 399 were early initiators of anti-TNF (≤2 years) and 299 were late initiators of anti-TNF (>2 years) (Fig. 1). The median period from UC diagnosis to the first anti-TNF agent in all 698 pa-

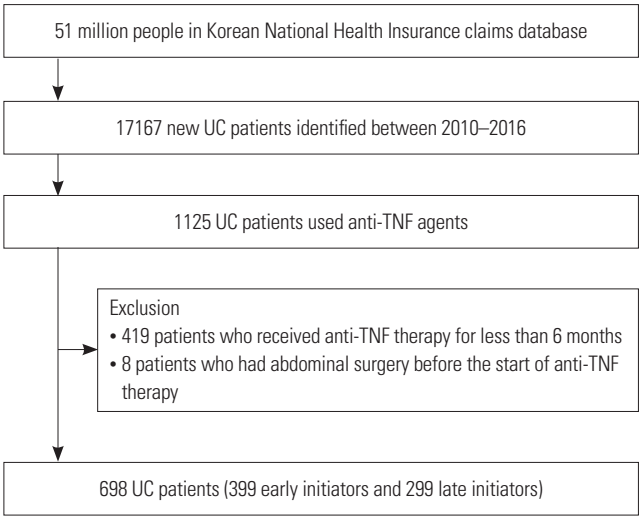

Fig. 1. Patient enrollment flow chart. UC, ulcerative colitis; TNF, tumor necrosis factor.

Table 1. Baseline Characteristics of the Study Population

Characteristics	Early initiators of anti-TNF agents (n=399)	Late initiators of anti-TNF agents (n=299)	*p* value
Sex, male	255 (63.9)	191 (63.9)	1.000
Age at diagnosis of UC (yr)	36.4±16.1	39.7±15.0	0.006
Age at anti-TNF agent initiation (yr)	37.3±16.1	43.1±15.1	<0.001
Period from UC diagnosis to first anti-TNF agent use (yr)	0.9±0.6	3.4±1.1	<0.001
Anti-TNF agent use duration (yr)	2.0±1.4	1.6±1.0	<0.001
First anti-TNF agent			<0.001
Infliximab	264 (66.2)	156 (52.2)	
Adalimumab	118 (29.6)	124 (41.5)	
Golimumab	17 (4.2)	19 (6.3)	
Medication use at anti-TNF agent initiation			
5-ASA	277 (69.4)	191 (63.9)	0.144
Steroid	176 (44.1)	97 (32.4)	0.002
Immunomodulator	175 (43.9)	129 (43.1)	0.911
Concomitant immunomodulators (±30 days)	240 (60.2)	189 (63.2)	0.457
Previous immunomodulator exposure	288 (72.2)	253 (84.6)	<0.001
Region at first anti-TNF agent use			0.016
Seoul	156 (39.1)	145 (48.5)	
Outside Seoul	243 (60.9)	154 (51.5)	
Hospital size at first anti-TNF agent use			0.010
Tertiary	269 (67.4)	229 (76.6)	
General/community/clinic	130 (32.6)	70 (23.4)	

5-ASA, 5-aminosalicylic acid; TNF, tumor necrosis factor; UC, ulcerative colitis.
Data are presented as number (%) or mean±SD.

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tients was 1.7 years (interquartile range, 0.8–2.9 years). Among the 399 early initiators, 264 (66.2%), 118 (29.6%), and 17 (4.2%) patients started with infliximab, adalimumab, and golimumab, respectively; among the 299 late initiators, 156 (52.2%), 124 (41.5%), and 19 (6.3%) patients started with infliximab, adalimumab, and golimumab, respectively (p<0.001). The proportion of patients who started with infliximab was higher in early initiators than in late initiators.

Table 1 shows the baseline characteristics of early and late initiators of anti-TNF. Sex did not differ between the two groups. Age at diagnosis of UC and at the start of anti-TNF was younger, and the mean period of anti-TNF use was longer in early versus late initiators. The rate of steroid use at the start of anti-TNF was higher in early initiators than in late initiators. The rate of concomitant immunomodulator use did not differ between early and late initiators, whereas the rate of previous immunomodulator exposure was lower in early initiators than in late initiators. The proportion of patients who first started anti-TNF in the Seoul region and at tertiary hospitals was lower in early versus late initiators.

Comparison of clinical outcomes between early and late initiators

The rates of colectomy, ER visits, hospitalization, and corticosteroid use (per 100 patient-years) were not significantly different between early and late initiators (Table 2). The median time to colectomy, ER visit, hospitalization, and corticosteroid use after anti-TNF initiation also did not differ significantly between early and late initiators. Only five patients underwent colectomy during the study period (four early, one late initiator).

Fig. 2 compares the clinical outcomes of Kaplan-Meier method and log-rank test. There were no significant differences in the cumulative probabilities of colectomy (p=0.415) (Fig. 2A), UC-related ER visits (p=0.967) (Fig. 2B), or corticosteroid use (p=0.789) (Fig. 2D) between early and late initiators. However, early initiators showed significantly higher cumulative probabilities of hospitalization compared to late initiators of anti-TNF (p=0.041) (Fig. 2C).

Cox proportional hazard regression analysis of factors associated with clinical outcomes

The HRs of univariate and multivariable Cox proportional hazards models are summarized in Table 3. Univariate analysis showed that late initiation of anti-TNF therapy was associated with a reduced risk of hospitalization (HR, 0.75; 95% CI, 0.57–0.99). However, the significant association disappeared after adjusting for confounding variables [adjusted HR (aHR), 0.76; 95% CI, 0.57–1.01]. Additionally, on multivariable Cox regression analysis, there were no significant differences in the risk of colectomy (aHR, 0.41; 95% CI, 0.04–3.90), ER visits (aHR, 0.98; 95% CI, 0.50–1.92), and corticosteroid use (aHR, 1.04; 95% CI, 0.71–1.50) between early and late initiators.

Anti-TNF use period (years) was associated with a reduced risk of hospitalization (aHR, 0.56; 95% CI, 0.43–0.74) and steroid use (aHR, 0.65; 95% CI, 0.48–0.88). The use of 5-ASA at the start of anti-TNF was associated with an increased risk of steroid use (aHR, 2.61; 95% CI, 1.25–5.41).

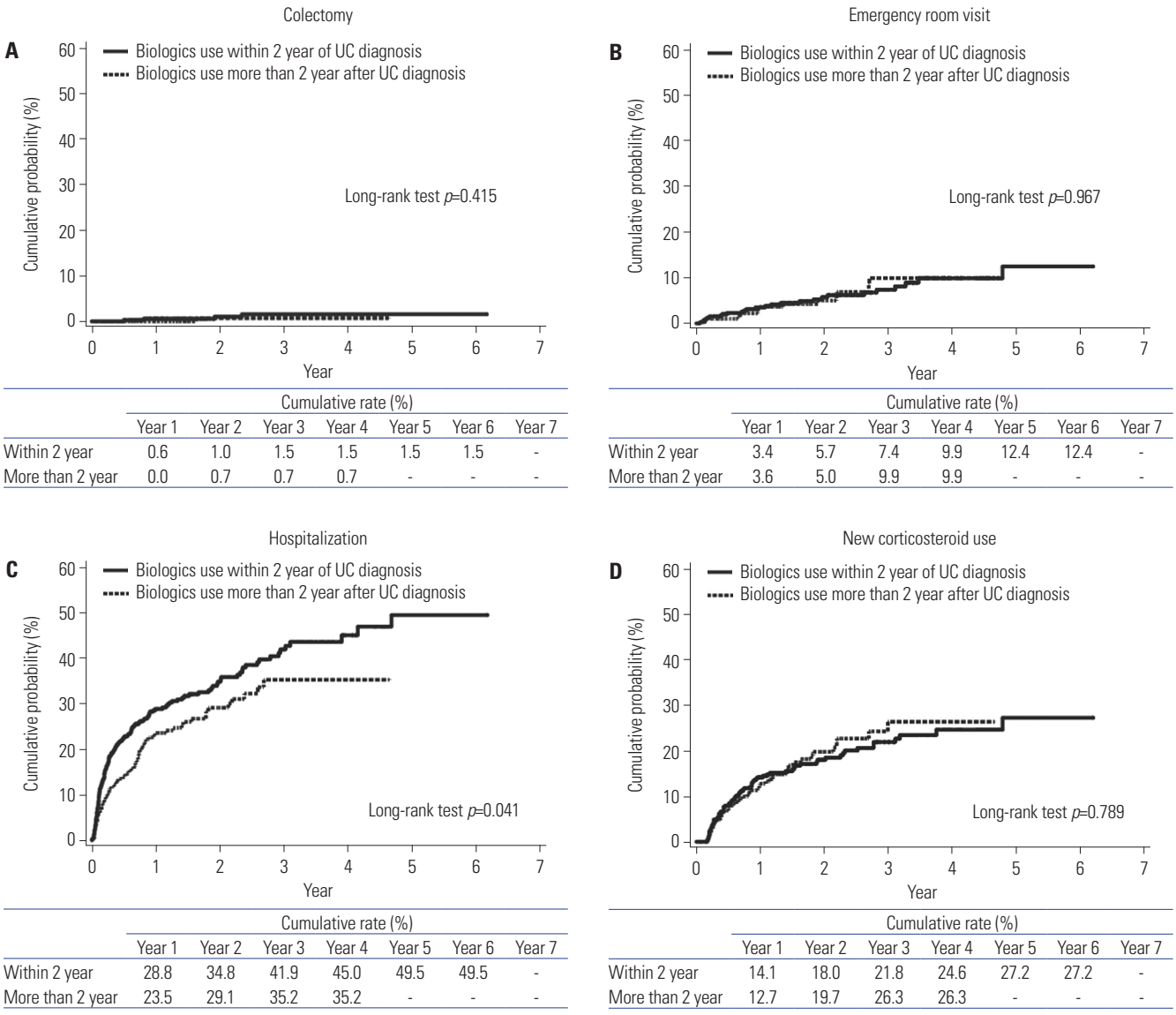
DISCUSSION

This nationwide population-based study was able to confirm that UC patients receiving early anti-TNF therapy had similar clinical outcomes to those of late initiators. More specifically,

Table 2. Outcomes of Early versus Late Initiators of Anti-TNF Agents

Outcome	Early initiators of anti-TNF agents (n=399)	Late initiators of anti-TNF agents (n=299)	*p* value
Colectomy outcomes			
Colectomy (n, %)	4 (1.0)	1 (0.3)	0.399
Surgery rate (per 100 patient-years, 95% CI)	0.42 (0.13–0.98)	0.19 (0.01–0.84)	0.479
Median time to surgery (yr, IQR)	1.37 (0.66–2.13)	1.64 (1.64–1.64)	1.000
ER visit outcomes			
ER visit (n, %)	26 (6.5)	15 (5.0)	0.502
ER visit rate (per 100 patient-years, 95% CI)	2.76 (1.83–3.96)	2.91 (1.67–4.65)	0.870
Median time to ER visit (yr, IQR)	0.99 (0.38–2.04)	0.96 (0.64–2.18)	0.936
Hospitalization outcomes			
Hospitalization (n, %)	143 (35.8)	77 (25.8)	0.006
Hospitalization rate (per 100 patient-years, 95% CI)	21.73 (18.36–25.49)	18.75 (14.87–23.26)	0.298
Median time to hospitalization (yr, IQR)	0.27 (0.11–0.90)	0.40 (0.13–0.79)	0.664
New steroid use (after 2 months) outcomes			
New steroid use (n, %)	74 (18.6)	50 (16.7)	0.600
New steroid use rate (per 100 patient-years, 95% CI)	8.91 (7.03–11.10)	10.97 (8.20–14.29)	0.258
Median time to new steroid use (yr, IQR)	0.60 (0.27–1.14)	0.64 (0.31–1.19)	0.941

CI, confidence interval; ER, emergency room; IQR, interquartile range; TNF, tumor necrosis factor.



	Cumulative rate (%)						
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Within 2 year	0.6	1.0	1.5	1.5	1.5	1.5	-
More than 2 year	0.0	0.7	0.7	0.7	-	-	-

	Cumulative rate (%)						
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Within 2 year	3.4	5.7	7.4	9.9	12.4	12.4	-
More than 2 year	3.6	5.0	9.9	9.9	-	-	-

	Cumulative rate (%)						
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Within 2 year	28.8	34.8	41.9	45.0	49.5	49.5	-
More than 2 year	23.5	29.1	35.2	35.2	-	-	-

	Cumulative rate (%)						
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Within 2 year	14.1	18.0	21.8	24.6	27.2	27.2	-
More than 2 year	12.7	19.7	26.3	26.3	-	-	-

Fig. 2. Kaplan-Meier survival analysis of clinical outcomes from initiating anti-tumor necrosis factor agents. (A) Cumulative probabilities of intestinal surgery. (B) Emergency room visits. (C) Hospitalization. (D) New steroid use. UC, ulcerative colitis.

we found no significant differences in the risk of colectomy, ER visits, hospitalization, or corticosteroid use between early and late initiators of anti-TNF therapy. Only three studies to date have directly evaluated the effect of earlier initiation of anti-TNF therapy on the clinical outcomes of UC. Similar to our results, none of those studies found more favorable outcomes of early versus late initiators.[12-14] A retrospective Hungarian study involving 42 UC patients demonstrated no difference in hospitalization or colectomy rate with time to anti-TNF exposure.[12] Similarly, a Dutch population-based study of 66 CD patients and 16 UC patients observed no beneficial effect of early anti-TNF initiation (<16 months) versus late anti-TNF initiation (>16 months) with respect to surgery, abscess formation, fistula formation, extraintestinal manifestations (EIMs), or mucosal healing.[13] However, in this Dutch study, CD and UC were analyzed together. A retrospective Canadian study of 115 UC patients (78 infliximab, 37 adalimumab) also revealed that early anti-TNF initiation, defined as starting treatment within 3 years of diagnosis, was not associated with colectomy (aHR, 2.02; 95% CI, 0.57–7.20), hospitalization (aHR, 1.66; 95% CI, 0.84–3.30), or secondary loss of response (aHR, 0.86; 95% CI, 0.52–1.42).[14] However, drawing a firm conclusion from the results of these three prior studies is difficult, as the number of included patients was too small. Since our study included a relatively larger sample size (698 patients), it can more reliably support the results of previous studies showing no benefit of earlier anti-TNF initiation in UC patients. Our findings are also in line with those of a recent U.S. study that evaluated the effects of vedolizumab stratified by disease duration.[18] In this study, UC patients treated early with vedolizumab (≤2 years, n=109) did not show different rates of clinical remission, corticosteroid-free remission, or endoscopic remission

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Table 3. Cox Regression Analysis of Clinical Outcomes

Variable	Colectomy		ER visit		Hospitalization		New steroid use	
	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Initiation of anti-TNF								
Early (≤2 yr)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Late (>2 yr)	0.41 (0.05–3.71)	0.41 (0.04–3.90)	1.01 (0.53–1.94)	0.98 (0.50–1.92)	0.75 (0.57–0.99)	0.76 (0.57–1.01)	1.05 (0.73–1.51)	1.04 (0.71–1.50)
Sex								
Female	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Male	-	-	1.04 (0.55–1.96)	1.10 (0.57–2.11)	1.02 (0.78–1.34)	1.05 (0.79–1.39)	1.29 (0.89–1.89)	1.29 (0.88–1.90)
Age at anti-TNF agent initiation (yr)	1.01 (0.95–1.06)	1.00 (0.95–1.06)	0.99 (0.97–1.01)	0.99 (0.97–1.01)	0.99 (0.99–1.01)	0.99 (0.99–1.01)	0.99 (0.99–1.01)	0.99 (0.98–1.01)
Anti-TNF use period* (yr)	0.61 (0.21–1.79)	0.56 (0.19–1.69)	0.87 (0.61–1.24)	0.85 (0.59–1.22)	0.57 (0.43–0.75)	0.56 (0.43–0.74)	0.69 (0.51–0.93)	0.65 (0.48–0.88)
First anti-TNF agent								
Infliximab	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Adalimumab	1.80 (0.30–10.93)	1.73 (0.27–10.94)	1.85 (0.96–3.56)	1.90 (0.98–3.70)	0.96 (0.72–1.28)	0.98 (0.73–1.32)	1.34 (0.92–1.97)	1.36 (0.93–2.01)
Golimumab	-	-	1.28 (0.17–9.71)	1.31 (0.17–10.04)	0.53 (0.22–1.29)	0.55 (0.22–1.35)	1.64 (0.70–3.80)	1.61 (0.69–3.76)
5-ASAs use*								
No	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	-	-	1.31 (0.51–3.38)	1.40 (0.53–3.67)	0.98 (0.66–1.44)	1.08 (0.73–1.61)	2.31 (1.13–4.75)	2.61 (1.25–5.41)
Immunomodulators use*								
No	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	0.23 (0.03–2.11)	0.21 (0.02–1.88)	1.19 (0.63–2.22)	1.21 (0.64–2.27)	1.01 (0.77–1.33)	1.06 (0.81–1.39)	0.88 (0.62–1.26)	0.89 (0.62–1.27)
Region†								
Outside Seoul	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Seoul	1.92 (0.32–11.51)	1.20 (0.19–7.51)	1.00 (0.54–1.86)	1.09 (0.55–2.13)	0.96 (0.74–1.26)	1.04 (0.78–1.40)	0.85 (0.59–1.22)	0.81 (0.55–1.19)
Hospital scale†								
General/community/clinics	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Tertiary	-	-	0.84 (0.43–1.62)	0.85 (0.41–1.74)	0.88 (0.66–1.17)	0.90 (0.66–1.23)	1.08 (0.72–1.60)	1.21 (0.79–1.86)

5-ASA, 5-aminosalicylic acid; CI, confidence interval; ER, emergency room; HR, hazard ratio; TNF, tumor necrosis factor.
*Time-dependent covariate, †Region and hospital scale use was defined as the hospital where a patient's first anti-TNF agent was prescribed.

from those who were treated late with vedolizumab (>2 years, n=328).[18]

These results are in contrast with evidence from studies of CD in which early anti-TNF initiation improved clinical outcomes, such as reducing the risk of bowel stricture development or abdominal surgery.[9-11,19] Although the reason for the difference in the effect of early anti-TNF therapy between UC and CD cannot be clearly elucidated, there are several potential explanations. First, differences in the pathophysiological mechanisms of UC and CD may be a contributing factor. In CD, early control of the inflammatory burden with aggressive medical treatment reduces the development of irreversible mechanical complications, such as fibrostenotic strictures and penetrating disease, that require surgical treatment.[9,19] In contrast, UC is characterized by mucosal rather than transmural inflammation; therefore, fibrostenotic or penetrating disease is very rare.[20] Patients with UC usually require colectomy due to refractoriness to medical treatments or the development of colorectal cancer (CRC) or colorectal dysplasia rather than mechanical complications. One of the reasons for early anti-TNF treatment showing no beneficial clinical outcome in patients with UC may be that patients with UC are much less likely to develop irreversible bowel damage than those with CD. Second, symptom differences between UC and CD may also be a contributing factor. UC flares usually present dramatically with bloody diarrhea, urgency, and tenesmus, which are difficult to overlook. A Japanese study demonstrated that self-reported symptoms by patients are useful to estimate endoscopic activity in UC.[21] In contrast, patients with CD are often asymptomatic, even in uncontrolled CD-related inflammation conditions, reducing the likelihood that they receive medical attention or undergo hospitalization.[22] Given these differences, it may be more difficult to determine the appropriate timing of anti-TNF initiation in CD than in UC; for patients with CD, the timing may depend largely on the physician's decision. Indeed, our preceding studies showed that variation in the prescription rate of anti-TNF agents was greater in CD than that in UC.[17] Since clinical symptoms better reflect the real severity and inflammatory burden of UC than CD, delays in anti-TNF treatment may occur less often in UC than in CD, and early anti-TNF treatment may be less helpful in UC than in CD. Our findings suggest that, for patients with UC, a conventional step-up strategy may be more reasonable than top-down or accelerated step-up strategies. Third, there might be differences in disease severity between early and late initiators of anti-TNF therapy. Patients requiring early anti-TNF therapy are more likely to have more severe disease. Indeed, in the aforementioned Canadian study, patients treated with early anti-TNF therapy had more severe endoscopic disease at anti-TNF therapy induction (mean Mayo endoscopy subscore, 2.46 vs. 1.86; $p<0.001$); when adjusted for endoscopic disease activity, the timing of anti-TNF initiation did not affect the risk of colectomy or hospitalization.[14] Likewise, in our study, early initiators may have had more severe disease than late initiators, although information on disease severity was not captured in the HIRA database. High steroid use and younger age at the start of anti-TNF in early initiators (Table 1) may support our hypothesis. UC patients with severe serologic and endoscopic activities reportedly have poor prognosis, such as an increased risk of colectomy and hospitalization.[23,24] Given that anti-TNF therapy for early initiators with more severe disease who have poorer outcomes may equalize the clinical outcomes of late initiators with less severe disease, early anti-TNF therapy may have been helpful for early initiators. Based on our findings, the necessity of early anti-TNF agent use should not be overlooked, even in UC patients with severe activity who do not respond to corticosteroids or immunomodulators in the early disease stages. There is strong evidence that anti-TNF agents should be used early as a rescue therapy for corticosteroid-refractory patients with severe or fulminant UC.[23] However, our results suggest that, conversely, other therapeutic options, such as 5-ASAs and immunomodulators, should be optimized for patients with mild to moderate disease. It is also important to select patients who are more likely to develop stenosis or CRC, so that anti-TNF use is not delayed in these high-risk patients. Fourth, longer follow-up periods may be needed to observe disease modifications in UC. In this study, we only examined data from 2010 to 2016. Whether early intervention with anti-TNF agents can change the natural course of UC should be explored further in long-term longitudinal studies.

Interestingly, we found that the use of 5-ASA at the start of anti-TNF was associated with an increased risk of steroid use. Although it is difficult to explain the reasons for this result in a clear manner, a possible explanation is that this drug might have been discontinued in patients whose prognosis was expected to be good. In addition, some patients may have discontinued 5-ASA due to side effects, and they might have received an earlier step-up therapy with immunomodulators or anti-TNF agents, although the disease activity is not severe.

To the best of our knowledge, this is the largest study to date to assess the impact of early initiation of anti-TNF on the clinical outcomes of UC patients. Furthermore, this is also the first population-based study on this topic in Asia. Nonetheless, our study had several limitations. First, disease extent and severity (e.g. clinical, serologic, and endoscopic activities), which can affect clinical outcomes, were not considered, as these information could not be captured in the HIRA database. Although anti-TNF agents are approved only for patients with moderate to severe disease activity (Mayo score, 6–12; endoscopy subscore≥2) in South Korea, due to the non-randomized design of this study, early initiators might have had more severe and extensive diseases than late initiators did. Therefore, the effects of early anti-TNF use might have been offset. Second, detailed clinical outcomes, such as mucosal healing, EIMs, compliance with the use of anti-TNF, loss of response requiring anti-TNF agent dose escalation, and reasons for discontinua-

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tion of anti-TNF therapy, were not assessed. Third, we did not evaluate the safety issue and cost effectiveness according to anti-TNF induction timing. Fourth, we did not verify the accuracy of UC diagnosis and UC-related ER visits. Although we defined ER visits as patient visits to the ER with UC as the primary diagnosis, it may be difficult to accurately view them as true UC-related ER visits. However, we consider our definition of UC diagnosis to be quite reliable. When defining UC, we considered the prescription of UC medications as well as the diagnostic code. Moreover, our study included only patients who received anti-TNF therapy from a gastroenterology clinic to rule out the use of anti-TNF agents for other autoimmune diseases. Finally, although our study included the largest number of UC patients, there were limitations in comparing the colectomy rates. Since colectomy is very rarely required in UC, much larger cohorts are needed to increase the statistical power to determine the difference in colectomy rates.

In conclusion, similar clinical outcomes, including colectomy, ER visits, hospitalization, and the need for corticosteroids, were observed for early and late initiators of anti-TNF therapy among South Korean patients with UC. These results suggest that indiscriminate early anti-TNF treatment should be avoided for patients with UC. The timing of anti-TNF initiation must be carefully determined for each patient according to the disease severity and refractoriness to other therapeutic options. Further long-term large-scale studies are warranted to clarify the ability of early use of anti-TNF agents to alter the natural course of and prevent disease progression in UC.

AUTHOR CONTRIBUTIONS

Conceptualization: Yoon Suk Jung and Jae Hee Cheon. Data curation: Minkyung Han. Formal analysis: Minkyung Han. Investigation: all authors. Methodology: all authors. Project administration: Minkyung Han and Yoon Suk Jung. Resources: all authors. Software: Minkyung Han and Yoon Suk Jung. Supervision: all authors. Validation: all authors. Visualization: Minkyung Han and Yoon Suk Jung. Writing—original draft: Yoon Suk Jung. Writing—review & editing: all authors. Approval of final manuscript: all authors.

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