

Continuing or stopping 5-aminosalicylates in patients with inflammatory bowel disease on anti-TNF therapy: A nationwide population-based study

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Summary

Background: The impact of continuing or stopping 5-aminosalicylates (5-ASA) after commencing anti-tumour necrosis factor (anti-TNF) therapy in patients with inflammatory bowel disease (IBD) remains unclear.

Aims: To compare the outcomes of patients with IBD who stopped or continued 5-ASA after starting anti-TNF therapy.

Methods: We analysed data from the Korean National Health Insurance claims database between 2007 and 2020. We compared the clinical outcomes of patients who stopped or continued 5-ASA within 90 days of anti-TNF initiation. The primary outcome was any adverse clinical event defined as a composite of new corticosteroid use, IBD-related hospitalisation, or intestinal surgery.

Results: Among 7442 patients included for analysis (4479 [60.2%] with Crohn's disease [CD] and 2963 [39.8%] with ulcerative colitis [UC]), 1037 (13.9%) discontinued 5-ASA within 90 days of starting anti-TNF therapy. During a median 4.3-year follow-up, discontinuation of 5-ASA was not associated with an increased risk of adverse clinical events (adjusted hazard ratio 1.01, 95% confidence interval 0.93–1.10). The cumulative incidence of each adverse clinical event and the composite outcome were not significantly different between groups (all, $p > 0.05$). Additionally, separate analyses in CD and UC cohorts revealed no differences in adverse clinical outcomes between the 5-ASA continuation and discontinuation groups. Subgroup analyses by presumed risk factors for disease relapse showed no significant differences in the risk of adverse events between groups.

Conclusions: In this nationwide population-based study, discontinuing 5-ASA after starting anti-TNF therapy was not associated with an increased risk of adverse events in patients with IBD.

Jeongkuk Seo and Seonok Kim should be considered as joint first authors.

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1 | INTRODUCTION

The escalation to anti-tumour necrosis factor (TNF) therapy is known to be effective for patients with inflammatory bowel disease (IBD) who are refractory to conventional treatments, such as 5-aminosalicylates (5-ASAs) and immunomodulators.¹ Currently, 5-ASA is considered the first-line option for ulcerative colitis (UC) and is still commonly used to treat Crohn's disease (CD).²⁻⁵ However, the clinical impact of continuing or stopping 5-ASA treatment after escalating to treatment with an anti-TNF agent in patients with IBD is unclear. Considering factors such as the long-term costs of 5-ASA therapy, the difficulties associated with the ingestion of multiple pills daily and the potential adverse events, it is necessary to understand this issue that could ultimately help patients and clinicians.⁶⁻⁹

Two recent retrospective studies on patients with UC and CD have addressed the issue of discontinuing 5-ASA when commencing anti-TNF therapy. Both studies used the same cohorts from the United States and Denmark to investigate the risk of adverse clinical events, consisting of new corticosteroid use, hospitalisation, or intestinal surgery when 5-ASA was withdrawn after initiating anti-TNF therapy. The studies found no increase in the risk of adverse clinical events following withdrawal of 5-ASA in either patient group. However, the maximum follow-up time in the cohort in the United States was 3 years, with a median follow-up time of less than 1 year, which was insufficient to detect the long-term impact of 5-ASA discontinuation.^{6,10}

Other studies have addressed the risk factors for relapse after stopping 5-ASA treatment in patients with IBD.¹¹⁻¹⁴ A recent review suggested that among non-anti-TNF-treated patients with IBD, younger age, extensive disease, a history of multiple flares and remission for shorter duration were risk factors for relapse after stopping 5-ASA.¹⁵ However, there is a lack of studies with detailed subgroup analyses that include patients treated with anti-TNF. Therefore, risk factors for relapse after discontinuing 5-ASA in patients who were escalated to biological therapy have not been adequately investigated.

Given the paucity of evidence and the limitations of previous studies, there is a need to validate reported results using a larger, long-term follow-up cohort and to identify risk groups for poor prognosis after stopping 5-ASA in the setting of escalation to anti-TNF therapy. We compared the clinical outcomes of patients with IBD who stopped or continued 5-ASA after starting anti-TNF therapy in a nationwide population-based cohort in Korea.

2 | MATERIALS AND METHODS

2.1 | Data source

We used data from the Health Insurance Review and Assessment Service (HIRA) database, consisting of data on all Korean national health insurance claims. The data of approximately 50 million

patients, accounting for 98% of the nation's population, are included.¹⁶ Data including patient demographic characteristics, diagnoses using the International Classification of Diseases and Related Health Problems, 10th revision (ICD-10), codes for registration of Rare and Intractable Disease (RID) and prescription information were retrieved. The registration of RID codes for IBD, which allow 90% coverage of reimbursable medical expenses by the Korean government, is based on strict diagnostic criteria and requires certification by a doctor; thereby, the operational definition of IBD in the HIRA database is highly reliable.¹⁷

2.2 | Study design and population

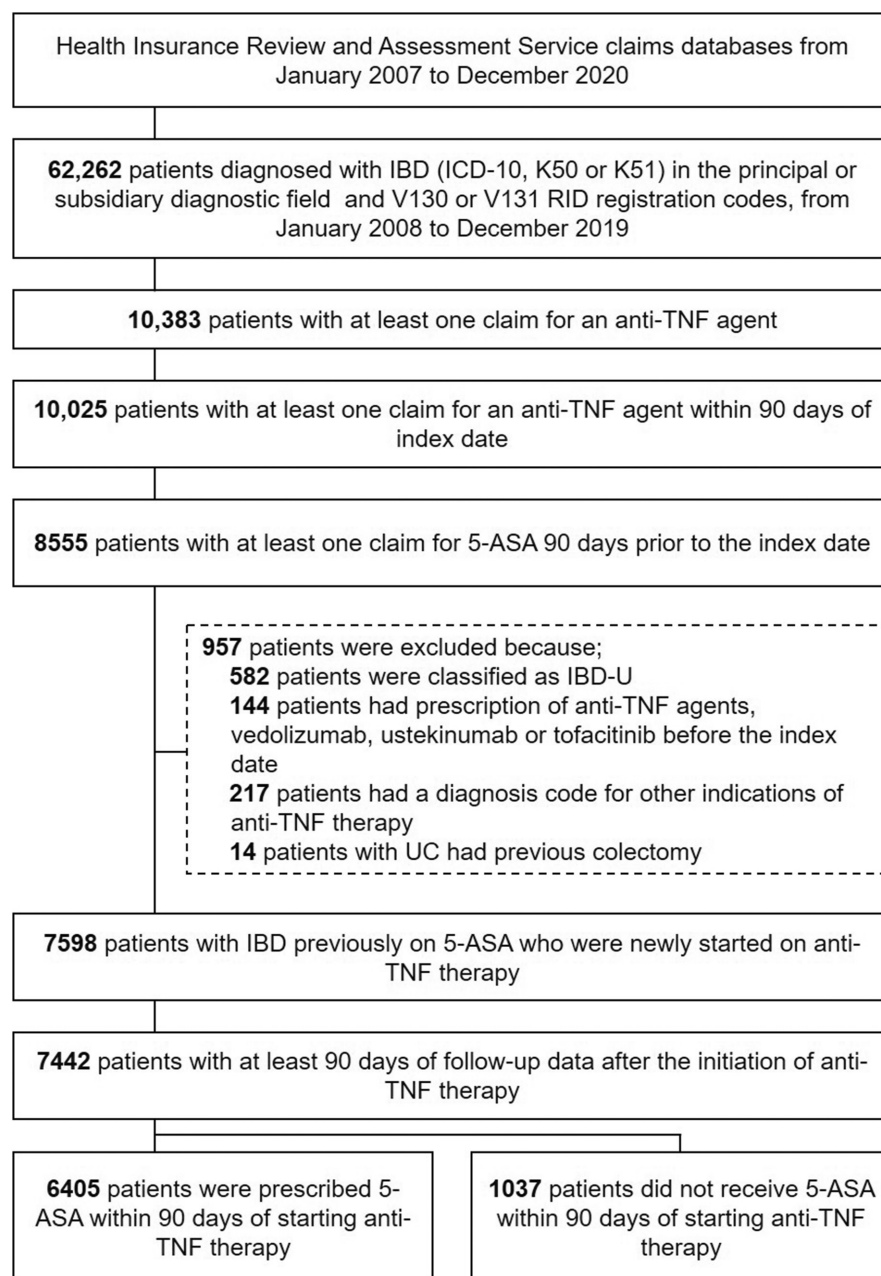
We conducted a nationwide, population-based, retrospective cohort study using HIRA data between 1 January 2007 and 31 December 2020. Based on previous studies, patients with IBD were defined as those satisfying the following criteria: at least one claim involving the K50.x ICD-10 code for CD or K51.x ICD-10 code for UC in the principal or subsidiary diagnostic field and the V130 (for CD) or V131 (for UC) RID registration code for IBD during the study period.¹⁷ Patients with IBD with at least one claim for anti-TNF therapy (i.e., infliximab, adalimumab, or golimumab) were enrolled between 1 January 2008 and 31 December 2019. The index date, which is the follow-up starting date, was defined as the first date when anti-TNF was prescribed within the index period. Patients were included in the analysis if they had at least one prescription of 5-ASA 90 days before the index date and continued anti-TNF therapy for at least 90 days after the index date (Figure 1).

The following exclusion criteria were applied: classification as IBD-unspecified (IBD-U) defined as having both diagnoses of CD and UC during the study period; prescription of anti-TNFs, vedolizumab, ustekinumab or tofacitinib before the index date or a diagnostic code corresponding to other indications for anti-TNF therapy (diagnostic codes listed in Table S1). The study protocol was approved by the Institutional Review Board of Asan Medical Center (IRB number: 2021-1425), which waived the requirement for informed consent from study participants according to the retrospective study design and the anonymisation of data.

2.3 | Outcomes

Eligible patients with follow-up data of at least 90 days after the index date, which is the primary landmark date, were included for analysis. The primary outcome of our study included any adverse clinical events defined as a composite of any new use of corticosteroids, hospitalisation related to IBD, or intestinal surgery. Corticosteroid use was defined as a new prescription of oral or intravenous corticosteroid at least 90 days after the index date. The prescription of intravenous hydrocortisone on the same day as anti-TNF therapy likely used as a premedication before anti-TNF

FIGURE 1 Patient flowchart. 5-ASA, 5-aminosalicylate; IBD, inflammatory bowel disease; IBD-U, IBD-unclassified; ICD-10, International Classification of Disease, 10th revision; RID, Rare and Intractable Disease; TNF, tumour necrosis factor; UC, ulcerative colitis.



therapy, was not counted as an outcome. IBD-related hospitalisation was defined as admission, with IBD as the primary or secondary diagnosis. If the IBD code was used as the secondary diagnosis, a primary diagnosis of IBD-related symptoms such as abdominal pain, diarrhoea, constipation, nausea, vomiting, stenosis, fistula, abscess, intestinal obstruction, ileus, or gastrointestinal bleeding (diagnostic codes listed in Table S2) was required. Hospitalisation was counted as an outcome if it occurred at least 90 days after the index date and lasted for 3 days or more. Intestinal surgery was defined as any intestinal resection or major surgical intestinal procedure undertaken at least 90 days after the index date, identified by the procedural fee codes within the HIRA database (procedural fee codes listed in Table S3).

2.4 | Variables

Continuation of 5-ASA treatment was defined as a prescription of 5-ASA at least once within 90 days after initiating anti-TNF therapy. Discontinuation of 5-ASA treatment was defined as no administration of 5-ASA within the same period. We collected and analysed the following variables in both cohorts: age at first diagnosis of IBD and age at the start of anti-TNF therapy, each classified into three groups according to age (A1: ≤16 years, A2: 17–40 years, A3: ≥41 years), sex, insurance type, medical facility type, subtype of IBD, Charlson comorbidity index (CCI), disease duration before the index date, the timeframe of anti-TNF use, duration of 5-ASA use before the index date, use of

immunomodulator prior to and after the index date, use of corticosteroids prior to the index date, history of intestinal surgery, hospitalisations, emergency care visits before the index date and the type of anti-TNF agent.

2.5 | Statistical analysis

Baseline characteristics of patients were evaluated using descriptive analyses and were presented as numbers with percentages for categorical variables, means with standard deviations (SD), or medians with interquartile range (IQR) for continuous variables. Comparisons between patients who continued or discontinued 5-ASA were performed using Student's *t*-test or the Wilcoxon rank sum test for continuous variables and the chi-squared test for categorical variables. The incidence rate of outcomes was calculated as the number of events divided by the person-time. We used the Kaplan-Meier method and Cox regression models as landmark analyses to calculate the cumulative incidence and adjusted hazard ratios (aHR) with 95% confidence intervals (CIs) for comparing adverse clinical outcomes between patients who continued 5-ASA treatment and those who did not. In the landmark analysis, patients were classified based on their 5-ASA treatment status at a pre-defined time point after starting anti-TNF therapy. This approach allows for the comparison of outcomes between those who continued and those who discontinued 5-ASA from that point onward while adjusting for potential confounders through Cox regression to provide adjusted hazard ratios for adverse outcomes. Clinical outcomes were calculated both individually and as a composite of primary outcomes. The multivariable analysis was adjusted for every variable included in the study.

Follow-up of patients started 90 days after initiation of anti-TNF therapy and continued until emigration, loss, or end of follow-up (December 2020), whichever occurred first. Analysis was performed in an intention-to-treat manner.

To examine the impact of previous clinical history on the outcomes, subgroup analyses of sex, type of IBD, the timeframe of anti-TNF use, duration of 5-ASA use prior to the index date, IBD-related hospitalisations, emergency department visits and use of corticosteroids prior to the index date and type of anti-TNF agent were performed by assessing the interaction between the subgroup and the continuation of 5-ASA.

As the continuation of 5-ASA was a time-dependent covariate, we performed sensitivity analyses using different landmark definitions (discontinuation of 5-ASA decided at 30 or 180 days after the initiation of anti-TNF therapy) to examine its impact on this study. In the sensitivity analysis, the start of follow-up also changed according to the different landmark definitions. We also performed additional sensitivity analyses excluding the use of topical 5-ASA and considering the dosage of 5-ASA. All analyses were performed using SAS Enterprise Guide software (version 7.1; SAS Institute, Inc, Cary, NC, USA) and R software (version 3.5.1; R Foundation for Statistical

Computing, Vienna, Austria) and $p < 0.05$ were considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics

A total of 7442 patients were included for analysis through the patient selection process (Figure 1). Within the cohort, 6405 (86.1%) patients were classified as having continued 5-ASA treatment after initiation of anti-TNF therapy (5-ASA continuation group), while 1037 (13.9%) patients were classified as having discontinued 5-ASA after initiation of anti-TNF therapy (5-ASA discontinuation group; Table 1). The age at IBD diagnosis was higher among patients who continued 5-ASA treatment than those who discontinued treatment (29.4 vs. 25.2 years, $p < 0.001$). Among the included patients, 4479 (60.2%) had CD, while 2963 (39.8%) had UC. Overall, the median follow-up time from initiation of anti-TNF therapy was 4.3 (IQR, 2.6–6.5) years. There were more patients with CD in the 5-ASA discontinuation group compared with the 5-ASA continuation group ($p < 0.001$). Duration of 5-ASA use prior to the index date was significantly longer in the 5-ASA continuation group (423 days vs. 320 days, $p < 0.001$). Previous history of immunomodulator use, as well as immunomodulator use after the administration of an anti-TNF agent, was significantly different between the two groups. Significant differences between the two groups were also observed in the distribution of patients regarding pre-anti-TNF emergency department visits and the type of anti-TNF agents. No significant differences between the two groups were detected regarding the insurance type, medical facility type, sex, CCI, disease duration prior to the index date, corticosteroid use prior to the index date, history of intestinal surgery and hospitalisations prior to the index date.

3.2 | Impact of discontinuing 5-ASA on adverse clinical outcomes

Discontinuation of 5-ASA in patients with IBD starting anti-TNF was not associated with increased risks for the primary outcome, a composite of any new use of corticosteroids, IBD-related hospitalisation and intestinal surgery, in both crude and adjusted analyses (Table 2). Adjusted HRs of the composite outcome, as well as its component outcomes of intestinal surgery, IBD-related hospitalisation, and new corticosteroid use of the 5-ASA discontinuation group over the 5-ASA continuation group, were 1.011 (95% CI, 0.934–1.095), 0.954 (95% CI 0.760–1.198), 0.995 (95% CI 0.894–1.107) and 0.969 (95% CI, 0.890–1.056), respectively. The proportion of patients with adverse clinical outcomes over time was not significantly different between the two groups for each individual outcome component or for the composite primary outcome (all, $p > 0.05$; Figure 2).

TABLE 1 Baseline characteristics of included patients.

Characteristic	Total	5-ASA continuation group	5-ASA discontinuation group	p-value
N (%)	7442	6405 (86.1)	1037 (13.9)	
Age at IBD diagnosis (years)				
Mean years (SD)	28.8 (15.3)	29.4 (15.4)	25.2 (13.6)	<0.001
<16	1693 (22.8)	1370 (21.4)	323 (31.2)	<0.001
17–40	4124 (55.4)	3550 (55.4)	574 (55.4)	
>40	1625 (21.8)	1485 (23.2)	140 (13.5)	
Age at start of anti-TNF therapy (years)				
Mean years (SD)	31.6 (15.7)	32.2 (15.9)	27.9 (14.0)	<0.001
≤16	1092 (14.7)	875 (13.7)	217 (20.9)	<0.001
17–40	4421 (59.4)	3778 (59.0)	643 (62.0)	
≥41	1929 (25.9)	1752 (27.4)	177 (17.1)	
Type of health insurance at index date				
Health insurance	7247 (97.4)	6231 (97.3)	1016 (98.0)	0.196
Medical care	195 (2.6)	174 (2.7)	21 (2.0)	
Type of healthcare institution visited on index date				
Tertiary hospital	5006 (67.3)	4299 (67.1)	707 (68.2)	0.789
General hospital	2088 (28.1)	1806 (28.2)	282 (27.2)	
Hospital and primary clinic	348 (4.7)	300 (4.7)	48 (4.6)	
Sex				
Men	5100 (68.5)	4385 (68.5)	715 (69.0)	0.754
Women	2342 (31.5)	2020 (31.5)	322 (31.0)	
Subtype of IBD				
CD	4479 (60.2)	3700 (57.8)	779 (75.1)	<0.001
UC	2963 (39.8)	2705 (42.2)	258 (24.9)	
CCI				
0	3742 (50.3)	3224 (50.3)	518 (50.0)	0.972
1	2391 (32.1)	2055 (32.1)	336 (32.4)	
2+	1309 (17.6)	1126 (17.6)	183 (17.7)	
Duration of IBD at anti-TNF initiation, median months (IQR)	15.2 (3.9–41.7)	15.44 (3.8–41.7)	13.34 (3.4–42.5)	0.300
Timeframe of anti-TNF use				
2008–2011	652 (8.7)	578 (9.0)	74 (7.1)	0.087
2012–2015	2678 (36.0)	2285 (35.7)	393 (37.9)	
2016–2019	4112 (55.3)	3542 (55.3)	579 (55.0)	
Pre-anti-TNF 5-ASA use duration				
Median days (IQR)	410 (123–981)	423 (129–996)	320 (95–802)	<0.001
0–89 days	1519 (20.4)	1267 (19.8)	252 (24.3)	<0.001
90–179 days	798 (10.7)	679 (10.6)	119 (11.5)	
180–364 days	1181 (15.9)	994 (15.5)	187 (18.0)	
365+ days	3944 (53.0)	3465 (54.1)	479 (46.2)	
Pre-anti-TNF immunomodulator use, n (%)				
No	1860 (25.0)	1635 (25.5)	225 (21.7)	0.008
Yes	5582 (75.0)	4770 (74.5)	812 (78.3)	
Post-anti-TNF immunomodulator use, n (%)				

(Continues)

TABLE 1 (Continued)

Characteristic	Total	5-ASA continuation group	5-ASA discontinuation group	p-value
No	2881 (38.7)	2389 (37.3)	492 (47.4)	<0.001
Yes	4561 (61.3)	4016 (62.7)	545 (52.6)	
Pre-anti-TNF corticosteroid use, n (%)				
No	1626 (21.9)	1387 (21.7)	239 (23.1)	0.314
Yes	5816 (78.2)	5018 (78.4)	798 (77.0)	
Pre-anti-TNF IBD-related hospitalisations, n (%)				
0	2015 (27.1)	1760 (27.5)	255 (24.6)	0.052
1+	5427 (72.9)	4645 (72.5)	782 (75.4)	
Pre-anti-TNF emergency department visits, n (%)				
0	4740 (63.7)	4133 (64.5)	607 (58.5)	0.001
1–2	2104 (28.3)	1773 (27.7)	331 (31.9)	
3+	598 (8.0)	499 (7.8)	99 (9.6)	
Pre-anti-TNF bowel surgery, n (%)				
No	6886 (92.5)	5937 (92.7)	949 (91.5)	0.180
Yes	556 (7.5)	468 (7.3)	88 (8.5)	
Follow-up time from initiation of anti-TNF therapy, median years (IQR)	4.3 (2.6–6.5)	4.3 (2.5–6.5)	4.3 (2.6–6.5)	
Type of anti-TNF agent				
Infliximab	5158 (69.3)	4427 (69.1)	731 (70.5)	0.009
Adalimumab	2018 (27.1)	1732 (27.0)	286 (27.6)	
Golimumab	266 (3.6)	246 (3.8)	20 (1.9)	

Abbreviations: 5-ASA, 5-aminosalicylate; anti-TNF, anti-tumour necrosis factor; CCI, Charlson comorbidity index; CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

TABLE 2 Risk of a composite or separate outcome comparing patients who discontinued 5-ASA with those who continued after initiation of anti-TNF therapy.

Outcomes	5-ASA continuation group			5-ASA discontinuation group			5-ASA discontinuation vs. continuation			
	Events	Person-years	IR per 100 person-years	Events	Person-years	IR per 100 person-years	Crude		Adjusted	
							HR	95% CI	aHR	95% CI
Composite outcome	4442	11,341.1	39.2	737	1832.7	40.2	1.013	0.937–1.095	1.011	0.934–1.095
Separate outcomes										
Intestinal surgery	507	28,530.4	1.8	90	4648.1	1.9	1.086	0.868–1.359	0.954	0.760–1.198
Hospitalisation	2368	21,145.2	11.2	408	3382.1	12.1	1.071	0.964–1.190	0.995	0.894–1.107
New corticosteroid use	4013	13,123.6	30.6	633	2230.2	28.4	0.945	0.869–1.027	0.969	0.890–1.056

Abbreviations: 5-ASA, 5-aminosalicylate; aHR, adjusted hazard ratio; anti-TNF, anti-tumour necrosis factor; CI, confidence interval; HR, hazard ratio; IR, incidence rate.

3.3 | Impact of discontinuing 5-ASA in patients with CD or UC

Separate analyses on the impact of discontinuing 5-ASA in CD and UC cohorts showed no significant differences in either the composite outcome or its components between the groups that continued or discontinued 5-ASA in both cohorts (Table 3). The adjusted HRs of the composite outcome were 0.984 (95% CI, 0.896–1.079)

for patients with CD and 0.996 (95% CI, 0.854–1.161) for patients with UC, respectively. The adjusted HRs for the component outcomes of intestinal surgery, IBD-related hospitalisation and new corticosteroid use were 0.990 (95% CI, 0.782–1.254), 0.989 (95% CI, 0.877–1.116) and 0.924 (95% CI, 0.835–1.022), for patients with CD, respectively, and 0.488 (95% CI, 0.178–1.336), 0.929 (95% CI, 0.735–1.175), 0.984 (95% CI, 0.840–1.153), for patients with UC, respectively.

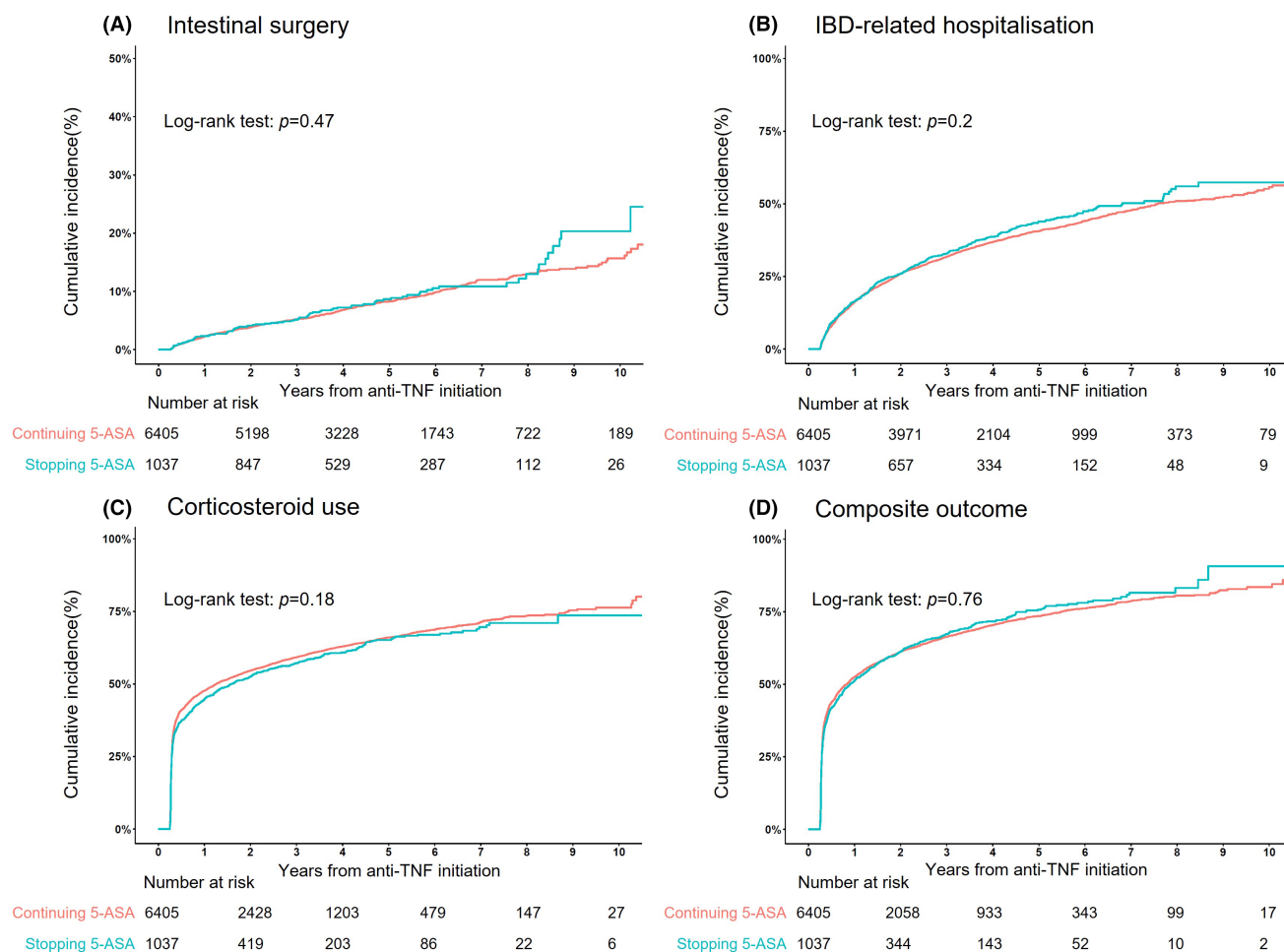


FIGURE 2 Proportion of patients with adverse clinical events comparing those who continued or stopped 5-ASA after initiation of anti-TNF therapy. (A) Kaplan–Meier curve for intestinal surgery. (B) Kaplan–Meier curve for IBD-related hospitalisation. (C) Kaplan–Meier curve for new corticosteroid use. (D) Kaplan–Meier curve for the composite outcome (any event of surgery, hospitalisation, or new corticosteroid use). 5-ASA, 5-aminosalicylate; anti-TNF, anti-tumour necrosis factor; IBD, inflammatory bowel disease.

3.4 | Additional subgroup analyses on individual variables and sensitivity analyses

Subgroup analysis of each variable (sex, IBD type, timeframe of anti-TNF use, pre-anti-TNF 5-ASA use duration, pre-anti-TNF corticosteroid use, pre-anti-TNF hospitalisations, pre-anti-TNF emergency department visits, post-anti-TNF immunomodulator use, and anti-TNF agent types) also showed no significant difference in the risk of adverse clinical events between the two groups (all, $p > 0.05$; Table 4).

Sensitivity analyses using different landmark dates were also performed. When the landmark date was set at 30 days, a total of 7550 patients were included in the analysis. There was no increase in the composite outcome in patients who discontinued 5-ASA in the multivariable analysis (aHR 1.039; 95% CI, 0.975–1.107; Table S4). Outcomes when the landmark was set at 180 days after the index date also showed no significant difference between the 5-ASA continuation and discontinuation groups among a total of 7338 eligible patients (aHR 0.995; 95% CI, 0.910–1.087;

Table S4). Further sub-analyses were performed at the one-year mark after the initiation of anti-TNF therapy ($n = 7187$). Compared with the 5-ASA continuation group, which included patients who continued 5-ASA treatment 1 year after initiating anti-TNF therapy ($n = 5024$; continuation group), no increased risk of adverse clinical events was observed in patients who discontinued 5-ASA after anti-TNF initiation and maintained 5-ASA discontinuation until the one-year mark ($n = 801$; discontinuation group; Table S5). Additional sensitivity analyses, which excluded the use of topical 5-ASA (suppositories or enemas) at both the inclusion and main analysis stages (finally excluding eight patients with CD [$8/4479 = 0.18\%$] and 46 patients with UC [$46/2963 = 1.55\%$]), revealed no significant differences in outcomes between the 5-ASA continuation and discontinuation groups (aHR 1.015; 95% CI, 0.938–1.098; Table S6). Finally, no significant differences were observed in composite or individual outcomes when comparing the 5-ASA discontinuation group with those continuing on either a low dose (<2000 mg/day) or a standard/high dose (≥ 2000 mg/day) of 5-ASA (Table S7).

TABLE 3 Risk of a composite or separate outcome comparing patients with CD or UC who discontinued 5-ASA with those who continued after initiation of anti-TNF therapy.

Outcomes	5-ASA continuation group			5-ASA discontinuation group			5-ASA discontinuation vs. continuation			
	Events	Person-years	IR per 100 person-years	Events	Person-years	IR per 100 person-years	Crude		Adjusted	
							HR	95% CI	aHR	95% CI
Patients with CD (n=4479)										
Composite outcome	2590	6968.9	37.2	553	1416.5	39.0	1.016	0.927–1.114	0.984	0.896–1.079
Separate outcomes										
Intestinal surgery	416	17,314.8	2.4	86	3497.8	2.5	1.020	0.808–1.287	0.990	0.782–1.254
Hospitalisation	1560	12,521.1	12.5	329	2512.5	13.1	1.034	0.918–1.164	0.989	0.877–1.116
New corticosteroid use	2245	8457.4	26.5	460	1772.5	26.0	0.962	0.870–1.064	0.924	0.835–1.022
Patients with UC (n=2963)										
Composite outcome	1852	4372.2	42.4	184	416.2	44.2	1.040	0.893–1.210	0.996	0.854–1.161
Separate outcomes										
Intestinal surgery	91	11,215.6	0.8	4	1150.3	0.3	0.442	0.162–1.203	0.488	0.178–1.336
Hospitalisation	808	8624.1	9.4	79	869.6	9.1	0.998	0.792–1.258	0.929	0.735–1.175
New corticosteroid use	1768	4666.2	37.9	173	457.7	37.8	1.019	0.872–1.192	0.984	0.840–1.153

Abbreviations: 5-ASA, 5-aminosalicylate; aHR, adjusted hazard ratio; anti-TNF, anti-tumour necrosis factor; CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; IR, incidence rate; UC, ulcerative colitis.

4 | DISCUSSION

In this nationwide population-based cohort study of 7442 patients with IBD, we observed that stopping 5-ASA within 90 days after the initiation of anti-TNF therapy did not increase the risk of adverse clinical outcomes, including new corticosteroid use, IBD-related hospitalisation and intestinal surgery. The results were consistent even when adjusted for potential confounders and baseline demographic differences. Our findings were consistent in the survival analyses and across different subgroups and sensitivity analyses. This study provides valuable data on whether patients with IBD who were newly started on anti-TNF therapy can discontinue 5-ASA therapy without concerns on the aggravation of IBD.

Few studies have evaluated the withdrawal of 5-ASA in the setting of escalating to anti-TNF treatment. Two recent retrospective cohort studies from the United States and Denmark have been pivotal in bringing attention to this issue and are cited in guidelines and reviews.^{6,10,18,19} Utilising the same databases from the United States and Denmark, these studies analysed patients according to IBD subtype. The authors compared the composite of adverse clinical events, including new corticosteroid use, IBD-related hospitalisation and intestinal surgery, between the patients who stopped 5-ASA treatment within 90 days after escalating to anti-TNF therapy and those who continued. Overall, stopping 5-ASA was not associated with an increased risk of adverse clinical events in both the UC (n=3589) and CD (n=3178) groups. Although the results were cross-validated in the Danish cohort with a maximum follow-up duration of 9 years, the main cohort using the United States MarketScan database had a 3-year follow-up time, which may have

been insufficient to adequately assess the long-term impact of stopping 5-ASA treatment.

Furthermore, post-hoc analyses from clinical trials have assessed the clinical outcomes of concomitant 5-ASA treatment in patients with UC escalated to anti-TNF therapy/anti-integrin therapy.^{20–22} Although these analyses were not designed to assess the impact of 5-ASA withdrawal, in the post-hoc analysis, maintenance of 5-ASA therapy was not associated with increased odds of clinical remission, clinical response, biochemical response, or mucosal healing in patients with UC who were escalated to infliximab or golimumab therapy.²⁰ However, other important outcomes, such as colectomy or hospitalisation, as well as the risk of colorectal cancer (CRC), were not addressed in the study. In a post-hoc analysis of the GEMINI long-term safety study, no differences were found in the 54-month survival probabilities for patients with UC or CD who continued on vedolizumab, whether they initiated treatment with or without any concomitant medications, including 5-ASA.²¹ Another retrospective cohort study assessed the impact of concomitant 5-ASA therapy in patients initiated with vedolizumab. There were no differences in clinical or endoscopic remission, vedolizumab continuation, or a secondary loss of response between patients who continued or stopped 5-ASA.²² Our results add valuable evidence to the current literature demonstrating outcomes using a nationwide, population-based cohort with a long-term follow-up that the risk of adverse clinical events was not increased in those who stopped 5-ASA after escalating to anti-TNF therapy.

Our subgroup analyses performed with the potential risk factors did not identify any variable associated with the discontinuation of 5-ASA that increased the risk of adverse clinical events. Further

TABLE 4 Hazard ratio by subgroups.

Subgroup categories	5-ASA continuation group				5-ASA discontinuation group				Adjusted Hazard ratio	95% CI	p-value	p for interaction
	N	Events	Person-years	IR per 100 person-years	N	Events	Person-years	IR per 100 person-years				
Sex												
Male	4385	2997	7972.8	37.6	715	490	1329.3	36.9	0.982	0.891–1.081	0.710	0.281
Female	2020	1445	3368.3	42.9	322	247	503.4	49.1	1.076	0.938–1.233	0.295	
Type of IBD												
CD	3700	2590	6968.9	37.2	779	553	1416.5	39.0	1.003	0.914–1.101	0.948	0.737
UC	2705	1852	4372.2	42.4	258	184	416.2	44.2	1.034	0.888–1.205	0.666	
Timeframe of anti-TNF use												
2008–2011	578	518	1100.2	47.1	74	72	108.4	66.4	1.195	0.933–1.530	0.159	0.382
2012–2015	2285	1794	4949.0	36.3	393	315	840.8	37.5	0.989	0.876–1.116	0.856	
2016–2019	3542	2130	5291.9	40.3	570	350	883.5	39.6	0.998	0.890–1.119	0.974	
Pre-anti-TNF 5-ASA use duration												
0–89 days	1267	973	1949.6	49.9	252	188	433.2	43.4	0.889	0.760–1.041	0.144	0.160
90–179 days	679	487	1173.2	41.5	119	91	178.0	51.1	1.179	0.942–1.476	0.149	
180–364 days	994	682	1814.7	37.6	187	134	344.2	38.9	0.979	0.813–1.179	0.825	
365+ days	3465	2300	6403.6	35.9	479	324	877.4	36.9	1.062	0.944–1.194	0.320	
Pre-anti-TNF corticosteroid use												
No	1387	678	3744.2	18.1	239	132	591.1	22.3	1.160	0.962–1.398	0.121	0.116
Yes	5018	3764	7596.9	49.6	798	605	1241.6	48.7	0.984	0.901–1.073	0.712	
Pre-anti-TNF hospitalisations												
No	1760	1121	3195.4	35.1	255	158	467.1	33.8	0.961	0.813–1.137	0.646	0.499
Yes	4645	3321	8145.7	40.8	782	579	1365.6	42.4	1.026	0.938–1.122	0.573	
Pre-anti-TNF emergency department visits												
0	4133	2837	7339.5	38.6	607	430	1071.9	40.1	1.033	0.932–1.145	0.534	0.813
1–2	1773	1252	3154.7	39.7	331	237	592.9	40.0	0.978	0.850–1.125	0.758	
3+	499	353	847.0	41.7	99	70	167.9	41.7	0.990	0.765–1.281	0.941	
Post-anti-TNF immunomodulator use												
No	2389	1714	4149.7	41.3	492	358	848.2	42.2	1.061	0.945–1.192	0.315	0.785
Yes	4016	2728	7191.4	37.9	545	379	984.5	38.5	0.971	0.872–1.082	0.595	
Type of anti-TNF agent												
Infliximab	4427	3446	6588.1	52.3	731	580	1071.4	54.1	1.022	0.935–1.117	0.629	0.197
Adalimumab	1732	866	4322.3	20.0	286	150	717.8	20.9	1.035	0.869–1.233	0.697	
Golimumab	246	130	430.7	30.2	20	7	43.5	16.1	0.508	0.237–1.087	0.081	

Abbreviations: 5-ASA, 5-aminosalicylate; anti-TNF, anti-tumour necrosis factor; CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel disease; IR, incidence rate; UC, ulcerative colitis.

subgroup analysis based on the continuation of 5-ASA 1 year after the initiation of anti-TNF therapy showed results that were consistent with the main analysis. Compared with the long-term continuation group, there was no increased risk of adverse clinical events among patients who maintained discontinuation of 5-ASA after the initiation of anti-TNF therapy.

We also performed sensitivity analyses with landmark dates at 30 and 180 days after the initiation of anti-TNF therapy to check the consistency of the results between different landmark dates. There was no significant difference in the occurrence of composite

outcomes regarding the discontinuation of 5-ASA in both analyses with landmark dates at 30 and 180 days. Further sensitivity analyses performed on the route and dosage of 5-ASA also revealed no significant differences in outcomes between the 5-ASA continuation and discontinuation groups.

The main strengths of this study were the large number of patients with IBD included and the extensive long-term follow-up data. This study has considerable analytic power because it derived data from the HIRA database, which is an unbiased, population-based dataset encompassing approximately 50 million individuals,

accounting for 98% of the national population. With significantly more patients enrolled for analysis, the robustness of the data collected allowed us sufficient power to compare the incidences of adverse clinical events among patients who continued or discontinued 5-ASA therapy and to perform detailed subgroup and sensitivity analyses, including analyses of the subtypes of anti-TNF therapy. This is important considering the negative findings detected in our study. In addition, compared to previous studies, the longer patient follow-up period in this cohort may have enabled a more accurate detection of adverse clinical events.

Nonetheless, our study has some limitations. First, considering the retrospective, observational design of this study, there may be unmeasured confounders across the groups compared to an interventional study. Since our study was based on the HIRA database, detailed clinical data such as endoscopic findings, laboratory values and the location, activity, and severity of disease were not available, which could have enabled more precise clinical phenotyping. For the same reason, the rationale underlying the decision to continue or stop 5-ASA treatment after the initiation of anti-TNF therapy, which may include adverse effects or patient or clinician preferences, could not be identified. However, by designing the study to include 5-ASA users who commenced anti-TNF therapy for the first time, we minimised confounding caused by drug indication. Furthermore, to adjust for disease severity, we utilised variables such as the history of hospitalisations, corticosteroid use and emergency department visits as indirect measures of disease severity to adjust for the multivariable analyses. Furthermore, practice patterns in IBD management vary, and there is a lack of consensus on the discontinuation of 5-ASA, so the likelihood of clinicians adopting a unified algorithm for continuing or discontinuing 5-ASA—which would mean a systemic confounder—is low. Therefore, it is unlikely that any systemic unaccounted confounder would have significantly biased the results. Second, because we utilised data from the national insurance claims database, there could be concerns about discrepancies between actual therapeutic practices and insurance claims. According to a nationwide validation study of a diagnostic algorithm for IBD in the Korean National Health Insurance Service database, an operational definition using a combination of the ICD-10 code, one or more claims for healthcare encounters, and one or more prescription claims for IBD medication achieved excellent performance (sensitivity 93.1%, specificity 98.1%) in diagnosing IBD.²³ Given that our analysis incorporated patients with corresponding ICD-10 codes and patients who were prescribed both anti-TNF agents and 5-ASA, our study provides an accurate representation of the current clinical setting. Moreover, as an assigned RID code grants the endowed a 90% reduction in medical expenses, it is highly unlikely that patients with IBD were prescribed high-priced medications such as anti-TNF agents without an RID code. Third, the operational diagnosis could only employ the prescription and not the actual utilisation of the IBD medication. However, we have adopted the same approach as that used in previously reported studies, so our methodology is consistent with that of the available literature

in the field.^{6,10,17,24} Fourth, we could not include death as an outcome in our study since the HIRA database does not include the mortality of its insurance recipients. Considering the high 7-year survival rates of 95.7% for patients with UC and 96.6% for patients with CD, significant findings would be unlikely.²⁵ Fourth, as the potential benefit of 5-ASA as a preventive agent against dysplasia and CRC is under investigation, we tried to compare the incidences of CRC between patients who stopped 5-ASA and those who continued. However, because of the very low number of CRC cases in both groups, specifically 25 (incidence rate of 0.084 per 100 person-years) in the 5-ASA continuation group and 2 (incidence rate of 0.041 per 100 person-years) in the 5-ASA discontinuation group, a statistically significant analysis was not feasible. Considering the decreasing rate of CRC in patients with IBD in recent decades and the increased rate of immunosuppressant use, further studies are needed to demonstrate the association of each medication with the incidence of CRC.^{26,27}

In conclusion, by analysing a nationwide population-based database, we observed that discontinuing 5-ASA after starting anti-TNF therapy was not associated with an increased risk of adverse clinical events. Considering the robustness of the analyses in this study and the results from recent similar studies, we conclude that discontinuing 5-ASA treatment after initiating anti-TNF therapy in patients with IBD is a safe option.

AUTHOR CONTRIBUTIONS

Jeongkuk Seo: Conceptualization; methodology; investigation; formal analysis; visualization; writing – original draft; writing – review and editing. **Seonok Kim:** Conceptualization; investigation; methodology; formal analysis; visualization; writing – original draft; writing – review and editing. **Seung Wook Hong:** Writing – review and editing. **Sung Wook Hwang:** Writing – review and editing. **Sang Hyoung Park:** Writing – review and editing. **Dong-Hoon Yang:** Writing – review and editing. **Jeong-Sik Byeon:** Writing – review and editing. **Seung-Jae Myung:** Writing – review and editing; funding acquisition. **Suk-Kyun Yang:** Writing – review and editing. **Ye-Jee Kim:** Conceptualization; methodology; supervision; writing – review and editing. **Byong Duk Ye:** Conceptualization; methodology; supervision; writing – review and editing; funding acquisition.

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REFERENCES

- Lawson MM, Thomas AG, Akobeng AK. Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2006;(3):CD005112. <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005112.pub2/information>
- Bressler B, Marshall JK, Bernstein CN, Bitton A, Jones J, Leontiadis GI, et al. Clinical practice guidelines for the medical management of nonhospitalized ulcerative colitis: the Toronto consensus. *Gastroenterology*. 2015;148(5):1035–1058 e1033.
- Burisch J, Kiudelis G, Kupcinskas L, Kievit HAL, Andersen KW, Andersen V, et al. Natural disease course of Crohn's disease during the first 5 years after diagnosis in a European population-based inception cohort: an epi-IBD study. *Gut*. 2019;68(3):423–33.
- Hong SW, Ye BD, Cheon JH, Lee JH, Koo JS, Jang BI, et al. Clinical features and long-term prognosis of Crohn's disease in Korea: results from the prospective CONNECT study. *Gut Liver*. 2022;16(6):907–20.
- Song EM, Na SY, Hong SN, Ng SC, Hisamatsu T, Ye BD. Treatment of inflammatory bowel disease-Asian perspectives: the results of a multinational web-based survey in the 8th Asian Organization for Crohn's and colitis meeting. *Intest Res*. 2023;21(3):339–52.
- Ungaro RC, Limketkai BN, Jensen CB, Allin KH, Agrawal M, Ullman T, et al. Stopping 5-aminosalicylates in patients with ulcerative colitis starting biologic therapy does not increase the risk of adverse clinical outcomes: analysis of two nationwide population-based cohorts. *Gut*. 2019;68(6):977–84.
- Wang J, Nakamura TI, Tuskey AG, Behm BW. Polypharmacy is a risk factor for disease flare in adult patients with ulcerative colitis: a retrospective cohort study. *Intest Res*. 2019;17(4):496–503.
- Park SK, Park SH, Eun CS, Seo GS, Im JP, Kim TO, et al. Adherence to Asacol once daily versus divided regimen for maintenance therapy in ulcerative colitis: a prospective, multicenter, randomized study. *Intest Res*. 2019;17(3):349–56.
- Yagisawa K, Kobayashi T, Ozaki R, Okabayashi S, Toyonaga T, Miura M, et al. Randomized, crossover questionnaire survey of acceptabilities of controlled-release mesalazine tablets and granules in ulcerative colitis patients. *Intest Res*. 2019;17(1):87–93.
- Ungaro RC, Limketkai BN, Jensen CB, Yzet C, Allin KH, Agrawal M, et al. Stopping mesalamine therapy in patients with Crohn's disease starting biologic therapy does not increase risk of adverse outcomes. *Clin Gastroenterol Hepatol*. 2020;18(5):1152–1160 e1151.
- Dissanayake AS, Truelove SC. A controlled therapeutic trial of long-term maintenance treatment of ulcerative colitis with sulphazalazine (Salazopyrin). *Gut*. 1973;14(12):923–6.
- Campbell S, Ghosh S. Effective maintenance of inflammatory bowel disease remission by azathioprine does not require concurrent 5-aminosalicylate therapy. *Eur J Gastroenterol Hepatol*. 2001;13(11):1297–301.
- Mantzaris GJ, Sfakianakis M, Archavlis E, Petraki K, Christidou A, Karagiannidis A, et al. A prospective randomized observer-blind 2-year trial of azathioprine monotherapy versus azathioprine and olsalazine for the maintenance of remission of steroid-dependent ulcerative colitis. *Am J Gastroenterol*. 2004;99(6):1122–8.
- Akobeng AK, Zhang D, Gordon M, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's disease. *Cochrane Database Syst Rev*. 2016;9(9):CD003715.
- Chapman TP, Frias Gomes C, Louis E, Colombel JF, Satsangi J. Review article: withdrawal of 5-aminosalicylates in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2020;52(1):73–84.
- Kim JA, Yoon S, Kim LY, Kim DS. Towards actualizing the value potential of Korea health insurance review and assessment (HIRA) data as a resource for Health Research: strengths, limitations, applications, and strategies for optimal use of HIRA data. *J Korean Med Sci*. 2017;32(5):718–28.
- Ahn HJ, Kim YJ, Lee HS, Park JH, Hwang SW, Yang DH, et al. High risk of fractures within seven years of diagnosis in Asian patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol*. 2022;20(5):e1022–e1039.
- Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. *Gut*. 2019;68(Suppl 3):s1–s106.
- Agrawal M, Spencer EA, Colombel JF, Ungaro RC. Approach to the management of recently diagnosed inflammatory bowel disease patients: a user's guide for adult and pediatric gastroenterologists. *Gastroenterology*. 2021;161(1):47–65.
- Singh S, Proudfoot JA, Dulai PS, Jairath V, Fumery M, Xu R, et al. No benefit of concomitant 5-aminosalicylates in patients with ulcerative colitis escalated to biologic therapy: pooled analysis of individual participant data from clinical trials. *Am J Gastroenterol*. 2018;113(8):1197–205.
- Loftus EV Jr, Peyrin-Biroulet L, Vermeire S, Adsul S, Demuth D, Mokiu S, Patel H, et al. P055 vedolizumab treatment persistence up to 5 years: post hoc analysis in vedolizumab-naïve patients from the GEMINI long-term safety study. *Am J Gastroenterol*. 2019;114:S14–S15.
- Ma C, Kotze PG, Almutairdi A, Jairath V, Panaccione R. Concomitant use of aminosalicylates is not associated with improved outcomes in patients with ulcerative colitis escalated to vedolizumab. *Clin Gastroenterol Hepatol*. 2019;17(11):2374–2376 e2372.
- Lee CK, Ha HJ, Oh SJ, Kim JW, Lee JK, Kim HS, et al. Nationwide validation study of diagnostic algorithms for inflammatory bowel disease in Korean National Health Insurance Service database. *J Gastroenterol Hepatol*. 2020;35(5):760–8.
- Chang K, Lee HS, Kim YJ, Kim SO, Kim SH, Lee SH, et al. Increased risk of herpes zoster infection in patients with inflammatory bowel

diseases in Korea. *Clin Gastroenterol Hepatol*. 2018;16(12):1928–1936 e1922.

25. Kim HJ, Hann HJ, Hong SN, Kim KH, Ahn IM, Song JY, et al. Incidence and natural course of inflammatory bowel disease in Korea, 2006–2012: a nationwide population-based study. *Inflamm Bowel Dis*. 2015;21(3):623–30.
26. Jess T, Simonsen J, Jørgensen KT, Pedersen BV, Nielsen NM, Frisch M. Decreasing risk of colorectal cancer in patients with inflammatory bowel disease over 30 years. *Gastroenterology*. 2012;143(2):375–381 e371.
27. Lutgens MW, van Oijen MG, van der Heijden GJ, Vleggaar FP, Siersema PD, Oldenburg B. Declining risk of colorectal cancer in inflammatory bowel disease: an updated meta-analysis of population-based cohort studies. *Inflamm Bowel Dis*. 2013;19(4):789–99.

SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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