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ORIGINAL ARTICLE

Comparison of outcomes of continuation/discontinuation of 5-aminosalicylic acid after initiation of anti-tumor necrosis factor-alpha therapy in patients with inflammatory bowel disease

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Abstract

Background Few maintenance therapeutic options are available for inflammatory bowel disease (IBD). Data on the effects of continuing 5-aminosalicylic acid (5-ASA) treatment in patients who commence on biologics as maintenance treatment remain scarce. We evaluated IBD patient outcomes after continuation/discontinuation of 5-ASA when biologics were administered as maintenance treatment.

Methods We retrospectively reviewed the clinical, laboratory, and imaging data of patients diagnosed with IBD (ulcerative colitis (UC), 763; Crohn's disease (CD), 537) in the Gil Medical Center (GMC) from February 2005 to June 2018. We divided patients administered with biologics as maintenance treatment into those who did and did not continue on 5-ASA and compared the efficacies of the two treatment options using the log-rank test and Cox proportional hazards models.

Results Of 1300 total IBD patients, 128 (UC, 63; CD, 65) were prescribed biologics as induction and maintenance treatments. The median follow-up period was 109.5 weeks. All cases were divided into those who did or did not combine 5-ASA with biologics as maintenance treatments. Kaplan–Meier analysis showed that the event-free survival (exacerbation of disease activity) of UC patients treated with biologics and 5-ASA ($n = 42$) was not significantly lower than that of those taking biologics alone ($n = 21$) (log rank test, $P = 0.68$). The same was true of CD patients ($n = 42$, biologics and 5-ASA; $n = 23$, biologics only) (log rank test, $P = 0.87$).

Conclusions Continuation of 5-ASA after initiation of anti-tumor necrosis factor-alpha agents did not improve prognosis in Korean IBD patients compared with that of those who discontinued 5-ASA during maintenance treatment, particularly in patients who experienced more than two disease aggravations.

Keywords Ulcerative colitis · Crohn's disease · 5-aminosalicylic acid · Biologics

Introduction

Inflammatory bowel disease (IBD) (comprising ulcerative colitis (UC) and Crohn's disease (CD)) is a chronic disease of the gastrointestinal tract [1, 2], the incidence and associated lifestyle burdens of which are increasing worldwide, including in Korea [2–5]. As the disease prevalence increased in recent years, the median disease duration also increased, and induction and maintenance of remission pose major challenges [3, 4, 6–8]. To alleviate acute IBD, the key induction therapies include biologics, systemic corticosteroids, and 5-aminosalicylic acid (5-ASA) [9–11]. To maintain remission and prevent poor clinical outcomes, therapeutic options include biologics, 5-ASA, and immunomodulators (azathioprine, 6-mercaptopurine, and methotrexate) [9–14]. Although these treatments are valuable, many issues require attention [13, 15, 16]. 5-ASA is costly, many pills must be ingested daily, and the side effects include gastrointestinal upset, dizziness, headache, and rash. The question arises: Does 5-ASA discontinuation worsen the outcomes of patients who commence on maintenance biologics? [13, 15–22].

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It remains unclear whether biologics alone or biologics in combination with 5-ASA constitute the optimal maintenance therapy for moderate-to-severe IBD. Here, we explored the levels of IBD-related adverse events after discontinuation of 5-ASA after patients commenced on biologics as maintenance treatment (biologics-only group) compared with continuation of 5-ASA together with biologics (biologics with 5-ASA group) in patients with moderate-to-severe IBD, particularly those who had experienced more than two IBD aggravations.

Methods

Ethics

The study protocol was approved by the institutional review board of Gachon Gil Medical Center (IRB approval number GCIRB 201860453).

Study design

We retrospectively reviewed the clinical and medical histories and laboratory data of IBD patients who commenced on biologics as maintenance treatments. We divided IBD patients into those taking biologics with 5-ASA and those taking biologics alone, and compared their outcomes in terms of IBD-related surgery, changes in or termination of biologics, and any de novo need for systemic steroids [14].

Diagnosis of IBD in Korea

We enrolled IBD patients commencing maintenance treatment with biologics. All patients had been followed up for at least 2 months; we thus excluded those with other chronic inflammatory diseases of the digestive tract including intestinal tuberculosis (ITB) [23–26] (which is endemic, and thus common, in Korea) [26, 27]. The national guidelines seek to prevent misdiagnosis of intestinal tuberculosis as IBD, and vice versa. If physicians are not confident that their diagnoses are correct, 2 months of tuberculosis medication with follow-up colonoscopy are recommended [23, 25, 26]. IBD patients who were pregnant or under 18 years of age or over 90 years of age were excluded.

Korean guidelines for the use of anti-tumor necrosis factor-alpha to treat IBD

In Korea, unlike in other countries, commencement of maintenance biologic therapy for IBD patients is delayed until at least two disease aggravations have been recorded [2, 8, 20]. The diagnosis and treatment of IBD patients are strictly controlled by the national health insurance system (NHIS), which covers over 95% of the population; physicians must thus adhere to the guidelines [28–30]. Biologics are permitted only as rescue therapies for those who experience more than two disease aggravations even after administration of systemic steroids or immunosuppressants (including 6-mercaptopurine or azathioprine); with Mayo scores > 6; endoscopic subscores > 2 for UC patients; and Crohn's disease severity index (CDAI) scores > 20 for CD patients [29, 30].

Guidelines for clinical remission after use of anti-TNF-α agents

IBD patients on rescue biologics must be re-evaluated after 3 months of follow-up if biologics are to serve as a maintenance treatment [29, 30]. Only UC patients exhibiting ≥ 30% reductions in their Mayo scores and a fall of at least one point in the rectal bleeding subscore (to a bleeding score of 0 or 1) after the use of rescue biologics may continue on maintenance biologics [29, 30]. CD patients must exhibit CDAI reductions ≥ 70 points or ≥ 25% before biologics may be used as a maintenance treatment [29, 30]. All of our patients met these criteria; all exhibited clinical responses on biologic rescue therapy commenced after two disease aggravations and were on maintenance biologics. We excluded all patients who did not respond clinically to biologics.

Parameters defining disease activity

All of the enrolled study patients underwent colonoscopy, and guided biopsy for histopathological diagnosis. For Crohn's disease patients, to evaluate the presence of the small bowel involvement, we used abdominopelvic computed tomography (APCT), or magnetic resonance imaging (MRI) or small bowel series. Different from other countries, in Korea, the disease of IBD are designated as a rare incurable disease, and patients with IBD pay less than 10% of total medical costs; physicians are relatively free to make diagnostic procedures for patients.

Outcome measures

IBD aggravations were defined as (1) a need to switch or stop biologics, (2) a new event requiring the use of systemic steroids, and (3) a need for an IBD-related operation or procedure [5, 31, 32]. We divided IBD patients into those who continued with or discontinued 5-ASA when commencing maintenance biologics and evaluated IBD-related disease aggravations. We also recorded the use of immunomodulators (azathioprine, 6-mercaptopurine, and methotrexate).

Subgroup analysis to evaluate the long-term effect of 5-ASA

To evaluate the long-term effect of 5-ASA, we divided the patients with IBD into two groups as follows, respectively,

(A) patients who were followed up for more than 5 years and (B) those who were followed up for less than 5 years), and subgroup analysis was done.

For patients with IBD who were followed up for more than 5 years, we compared the risk of events (including a need for de novo systemic steroid, hospitalization, surgery, and switching or discontinuing biologics, and colorectal cancer). After then, we compared the efficacies of maintenance therapies featuring biologics with and without 5-ASA in IBD patients who had experienced more than two disease aggravations.

Statistical analysis

The cumulative incidences of adverse clinical outcomes (a need to switch biologics, de novo systemic steroid use, and IBD-related surgery) during the entire follow-up period were estimated and compared between the groups by drawing Kaplan–Meier curves and applying the log-rank test to derive hazard ratios (HRs) for adverse clinical outcomes. All statistical tests were two-sided and a P value < 0.05 was taken to reflect significance. All analyses were performed with the aid of IBM SPSS Statistics ver. 20 and MedCalc ver. 12.2.1 software.

Results

Of 1300 patients with IBD, 128 (UC patients, 63; CD patients, 65) evidenced clinical responses on biologic induction therapy and used biologics as maintenance treatments; 84 continued on 5-ASA (UC patients, 42; CD patients, 42) and 44 did not (UC patients, 21; CD patients, 23).

Baseline characteristics of the two UC groups

We enrolled 63 UC patients who entered clinical remission on biologics as a maintenance treatment. Of these, 42 (66.7%) and 21 (33.3%) were on maintenance biologics with 5-ASA and on biologics alone, respectively (Table 1). The ages at initiation of biologic therapy (40.1 ± 16.9 vs. 35.6 ± 13.6 years, $P = 0.3$) and at the time of UC diagnosis (35.1 ± 16.4 vs. 32.5 ± 13.4 years, $P = 0.5$) were similar in the two groups (Table 1), as were the median follow-up times after initiation of biologics (Table 1).

Baseline characteristics of the two CD groups

We enrolled 65 CD patients who entered clinical remission on biologics as the maintenance treatment. Of these, 42 (64.6%) and 23 (33.4%) were on maintenance biologics with 5-ASA and on biologics alone, respectively (Table 2). The ages at initiation of biologic therapy and at the time of CD diagnosis, and the median follow-up durations after initiation of biologic therapy were similar in the two groups (Table 2). The groups did not differ by sex, pre-biologic corticosteroid use, or number of hospitalizations (Table 2).

UC-related adverse events in the two groups

UC-related adverse events (including a need for de novo systemic steroid, hospitalization, surgery, and switching or discontinuing biologics) were reported by six (14.3%) and four (19.0%) patients in the biologics with 5-ASA and biologics-only groups, respectively (Table 3). Kaplan–Meier analysis revealed that these proportions did not differ significantly (Fig. 1). After adjustment for factors that might affect the development of UC-related outcomes, 5-ASA continuation/discontinuation did not affect the incidence of adverse events (Table 3).

CD-related adverse events in the two groups

CD-related adverse events (including a need for de novo systemic steroid, hospitalization, surgery, and switching or discontinuing biologics) were reported by seven (10.8%) and five (7.7%) patients in the biologics with 5-ASA and biologics-only groups, respectively (Table 3). Kaplan–Meier analysis revealed that these proportions did not differ significantly (Fig. 2). After adjustment for factors that might affect the development of CD-related outcomes, 5-ASA continuation/discontinuation did not affect the incidence of adverse events (Table 4).

Subgroup analysis to evaluate the long-term effect of 5-ASA

To evaluate the long-term effect of 5-ASA, we divided the patients with IBD into two groups as follows, respectively, (A) patients who were followed up for more than 5 years and (B) those who were followed up for less than 5 years), and subgroup analysis was done.

For UC patients, patients who were followed up for more than 5 years were 11 (17.5%) patients. Of those, 4 patients discontinued 5-ASA after initiating biologics, and 7 patients did not. In both groups, no events (including a need for de novo systemic steroid, hospitalization, surgery, and switching or discontinuing biologics, and colorectal cancer) were observed.

For CD patients, patients who were followed up for more than 5 years were 16 (24.6%) patients. of them, 6 patients discontinued 5-ASA after initiating biologics, and 10 patients did not. During follow-up periods, one event ($n = 1$, 6.3%) and no event ($n = 0$, 0%) were observed in 5-ASA discontinuation group, and 5-ASA continuing group, respectively (log rank test, $P = 0.2$).

Table 1 Demographic characteristics of ulcerative colitis (UC) patients receiving biologics and 5-aminosalicylic acid (5-ASA) or biologics only ($n = 63$)

	Biologics with 5-ASA ($n = 42$)	Biologics only ($n = 21$)	P value
Demographic features and follow-up			
Duration of follow-up (weeks)	156.9 ± 156.7	146.8 ± 118.4	0.5
Males, *n* (%)	26 (61.9%)	12 (57.1%)	0.8
Age (years)	39.0 ± 17.0	35.1 ± 13.7	0.3
Disease features at diagnosis			
Disease duration, median years (IQR)			
Age at diagnosis (years)	35.1 ± 16.4	32.5 ± 13.4	0.5
Age at commencement of biologic therapy (years)	40.1 ± 16.9	35.6 ± 13.6	0.3
Ulcerative colitis severity			0.3
Mild	0 (0%)	0 (0%)	
Moderate	16 (38.1%)	11 (52.4%)	
Severe	26 (61.9%)	10 (47.6%)	
Ulcerative colitis phenotype			
Location (Montreal criteria), *n* (%)			05
E1: proctitis	6 (14.3%)	1 (4.8%)	
E2: left-sided	13 (31.0%)	7 (33.3%)	
E3: extensive	23 (54.8%)	13 (61.9%)	
Laboratory data (at commencement of biologics)			
Hemoglobin (g/dL)	12.0 ± 2.2	11.0 ± 1.8	0.08
Hematocrit (%)	36.6 ± 5.7	34.5 ± 5.0	0.2
White blood cell count (per mm^3)	9464.5 ± 3377.8	9221.7 ± 6259.3	0.9
Serum albumin (g/dL)	3.6 ± 0.6	3.6 ± 0.5	0.6
CRP level	2.0 ± 2.8	2.6 ± 3.5	0.6
Immunomodulator use ± 30 days from initiation of biologics, *n* (%)	11 (26.2%)	6 (28.6%)	
Concomitant aminosalicylate dose (g), *n* (%)			
≥ 2.4 g/day	42 (100%)	–	
Aminosalicylate formulation, *n* (%)			
Mezavant tab	2	–	–
Mesalamine (Asacol) tab	11	–	–
Mesalamine (Pentasa) suppository*	12	–	–
Mesalamine (Pentasa) tab	15	–	–
Balsalazide (Cloazal) capsule	14	–	–

IQR, interquartile range; *GI*, gastrointestinal tract; *CRP*, C-reactive protein

Post-biologics IBD-related outcomes included IBD-related hospitalization, surgery, prior biologic use, and systemic steroid use

*All patients' cases took mesalamine suppository as pro re nata (PRN) medication

In both UC and CD patients who follow up for more than 5 years after initiating biologics, there was no patient who developed colorectal cancer during follow-up periods in this study.

Discussion

We compared the efficacies of maintenance therapies featuring biologics with and without 5-ASA in IBD patients who had experienced more than two disease aggravations. Patient outcomes (including a need for de novo systemic steroid, hospitalization, surgery, and switching or discontinuing biologics) did not differ after adjustment for potential confounding factors. To our knowledge, this is the first study to compare the efficacies of biologics with and without 5-ASA as maintenance therapies not only in UC but also in CD patients with more than two times aggravation events [32]; our findings will therefore aid clinicians in treating such patients.

Few studies have compared biologics with and without 5-ASA as maintenance therapies for IBD patients in IBD related events including need for de novo systemic steroid,

Table 2 Demographic characteristics of Crohn's disease (CD) patients treated with biologics and 5-ASA or biologics alone ($n = 65$)

	Biologics with 5-ASA ($n = 42$)	Biologics alone ($n = 23$)	P value
Demographic features and follow-up			
Duration of follow-up (weeks)	144.2 ± 165.4	172.8 ± 114.6	0.5
Males, *n* (%)	33 (78.6%)	18 (78.3%)	0.9
Age (years)	30.7 ± 12.5	28.8 ± 9.2	0.6
Disease features at diagnosis			
Disease duration, median years (IQR)			
Age at diagnosis (years)	26.9 ± 12.9	26.1 ± 9.9	0.8
Age at commencement of biologic therapy, years	31.3 ± 12.4	29.3 ± 9.3	0.5
Crohn's disease phenotype			
Disease location (Montreal criteria), *n* (%)			0.3
L1: terminal ileum	11 (26.2%)	10 (43.5%)	
L2: colon	18 (42.9%)	7 (30.4%)	
L3: ileocolon	13 (31.0%)	6 (26.1%)	
L4: upper GI tract	0 (0%)	0 (0%)	
Crohn's disease behavior (Montreal criteria), *n* (%)			0.8
B1: inflammatory	20 (47.6%)	10 (43.5%)	
B2: stricturing	15 (35.7%)	9 (39.1%)	
B3: penetrating	7 (16.7%)	4 (17.4%)	
Laboratory data (obtained at commencement of biologic therapy)			
Hemoglobin (g/dL)	11.4 ± 1.4	12.1 ± 2.1	0.2
Hematocrit (%)	35.0 ± 3.9	36.6 ± 5.6	0.3
White blood cells (per mm^3)	7934.6 ± 3061.7	8433.9 ± 5177.6	0.7
Serum albumin (g/dL)	3.5 ± 0.7	3.8 ± 0.5	0.1
CRP	2.3 ± 3.2	6.5 ± 7.8	0.1
Immunomodulator use ±30 days from initiation of biologic agent, *n* (%)	19 (45.2%)	7 (30.4%)	0.06
Concomitant aminosalicylate dose (g), *n* (%)			
≥ 2.4 g/day	42 (100%)	–	
Aminosalicylate formulation, *n* (%)			
Mezavant tab	15	–	–
Mesalamine (Asacol) tab	11	–	–
Mesalamine (Pentasa) tab	7	–	–
Balsalazide (Cloazal) capsule	9	–	–

IQR, interquartile range; *GI*, gastrointestinal tract; *CRP*, C-reactive protein

hospitalization, surgery, and switching or discontinuing biologics. Pubmed search yielded two previous studies which examined UC patients who discontinued 5-ASA after commencing biologics [33]. Ungaro et al. found that 3589 UC patients (2890 from the USA and 699 from Denmark, enrolled in two nationwide population-based studies) who discontinued 5-ASA when commencing biologics were not at an increased risk of adverse clinical outcomes [33]. In the US cohort, the HR for the group that discontinued 5-ASA (compared with that of the group that did not) was 1.04 (95% CI 0.9–1.2, $P = 0.57$); the Danish figure was 1.09 [33]. The differences between this study and our study may be attributable to differences in the study populations. Our IBD patients had experienced more than two disease aggravations, whereas the patients studied by Ungaro et al. had not [33]. The ethical frameworks also differed. The other study was conducted in Canada by Christopher et al. [34] They reported that concomitant 5-ASA with vedolizumab in UC patients was not associated with significant differences in clinical outcomes as compared with vedolizumab alone [34]. In our study, the only available biologics were infliximab and adalimumab. On subgroup analysis, patients receiving either adalimumab or infliximab did not show differences for clinical outcomes (data now shown). For further clarification, larger multicenter studies are needed.

Table 3 Risk of UC-related outcomes in patients taking biologics with 5-ASA or biologics alone after initiation of biologic therapy

	Biologics only, adjusted HR	Biologics with 5-ASA (95% CI)	*P* value
UC-associated outcomes	6 (14.3%)	4 (19.0%)	
Age and sex odds ratio	1.4 (0.4–5.3)	1 (reference)	0.8
Model 1[¶]	1.6 (0.4–6.5)	1 (reference)	0.5
Model 2[§]	1.7 (0.4–6.7)	1 (reference)	0.4

[¶] Model 1: adjusted for age, sex, UC severity, and UC location

[§] Model 2: adjusted for age, sex, UC severity, UC location, and use of immunomodulatory agents

No previous reports have compared the long-term, CD-related adverse outcomes of CD patients who continued/discontinued 5-ASA after initiating biologics. Concerns have been raised that 5-ASA discontinuation may be associated with CD-related adverse events, including a need for de novo systemic steroids, hospitalization, surgery, and switching or discontinuing biologics [13, 14, 16, 18]. However, we found that this was not the case [3, 13, 17].

Except for the effects of 5- ASA on the IBD-related events including de novo systemic steroid, hospitalization, surgery, and switching or discontinuing biologics in IBD patients as discussed above, several studies have investigated the chemo-preventive effect of 5-ASA use [35]. Since 5-ASA is one of anti-inflammatory drugs that can prevent intestinal inflammation and induce mucosal healing, several suggestions that the 5-ASA might be effective for chronic colitis–associated colon cancer models. Recent meta-analysis showed protective association between 5-ASA use and colorectal neoplasia including colorectal cancer (RR = 0.57, 95% CI 0.45–0.71), even though concern is raised between studies, heterogeneity is moderate and small number of studies might influenced the results in this meta-analysis [35]. The other meta-analysis also showed the reduced the risk of colorectal neoplasia in patients with UC except for the extensive type [36]. However, it varies among clinical studies on the chemo-preventive effects of 5-ASA on the development of CRC and dysplasia in patients with IBD ranging from very protective to even harmful [35–38]. The conflicting findings might be a result of varying study designs and settings.

In our study, there was no patient who developed colorectal cancer during follow-up periods regardless of discontinuation or continuation of 5-ASA. The reasons for the relatively lower rate of colorectal cancer for both groups in this study are as follows. First, relatively short-term follow-up periods might influence the results. Second, the differences in the health screening environments for each country might affect the results. In Korea, colonoscopy is a readily accessible procedure for population than other countries because of its cost. In recent report, colonoscopy cost in Korea is less than 3% than that in the USA [39]. Moreover, when the patients are registered as the rare and intractable disease

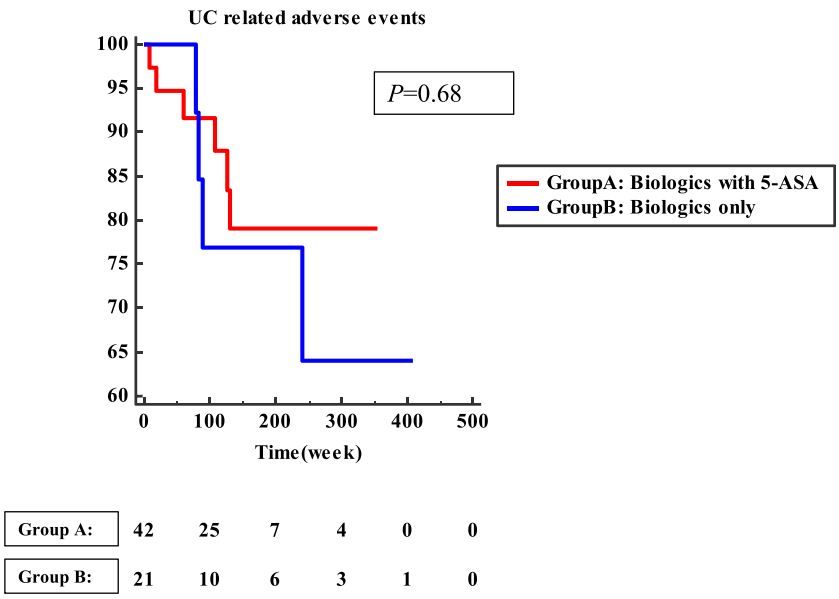

Fig. 1 Kaplan–Meier curve of inflammatory bowel disease (IBD)-related outcomes in ulcerative colitis (UC) patients who received biologics and 5-ASA or biologics only. The proportion of patients with UC-related adverse outcomes compared with the proportions of patients who continued or discontinued 5-ASA

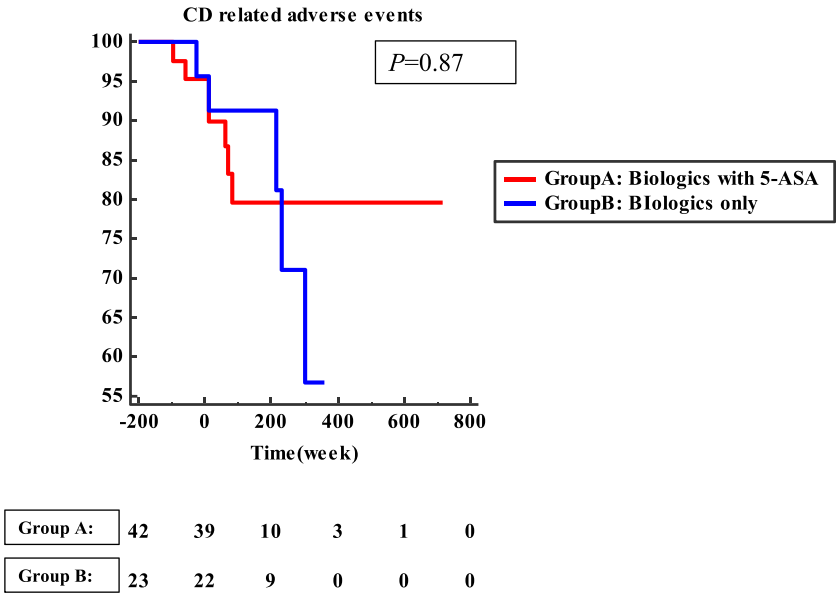

Figure 2 Kaplan–Meier curve of IBD-related outcomes in Crohn's disease (CD) patients who received biologics and 5-ASA or biologics only. The proportion of patients with CD-related adverse outcomes compared with the proportions of patients who continued or discontinued 5-ASA

patients, including inflammatory bowel disease, the patients pay only 10% of total medical costs. One-or two-year intervals, the upper endoscopy is free to all population over 40 years. Moreover, the occult blood positive patients are free for colonoscopy as well. In this circumstance, the early detection and diagnosis for colonic dysplasia and colorectal cancer is possible in Korea. Further large and well-controlled studies are needed.

Our study had certain limitations. First, we work in a tertiary center, associated with a risk of referral bias. Second, our study is retrospectively conducted. Because of the inherent nature of the retrospective study, selection bias or information bias might be issue. Third, we studied Koreans only; our conclusions may therefore not be generalizable to patients of other ethnicities. Applying the results of this paper to other races is limited. Fourth, since the median follow-up period of this study was 109.5 weeks, to draw conclusion whether long-term effect of 5- ASA discontinuation or continuation after initiation of biologics, further large population-based long-term follow-up study is needed. Fifth, our result data should be interpreted with caution since subgroup population (subgroup analysis for effects of subtype of 5-ASA, 5-ASA dose, and subtype of biologics on the results) is not large enough. Further large population-based well-controlled design is needed.

Even with these limitations, our study has strength as below. To date, few studies have compared biologics with and without 5-ASA as maintenance therapies for IBD patients as for IBD-related events including a need for de novo systemic steroid, hospitalization, surgery, and switching or discontinuing biologics**.** In this regard, our study's results might be the base for further prospective, well-controlled nature of the study. These results might provide insights on treatment in Asian IBD patients, where regulations concerning treatment administration do differ and little data is available.

In conclusion, continuation of 5-ASA after initiation of biologics did not improve prognosis in Korean IBD patients compared with that of those who discontinued 5-ASA during maintenance treatment, particularly in patients who experienced more than two disease aggravations. Physicians might carefully consider either options

Table 4 Risk of CD-associated outcomes in patients taking biologics with 5-ASA or biologics alone after initiation of biologic therapy

	Biologics only, adjusted HR	Biologics with 5-ASA (95% CI)	*P* value
CD-related outcomes	7 (10.8%)	5 (7.7%)	
Age and sex odds ratio	1.2 (0.3–4.5)	1 (reference)	0.7
Model 1[¶]	0.7 (0.2–2.9)	1 (reference)	0.7
Model 2[§]	0.5 (0.1–2.6)	1 (reference)	0.5

[¶] Model 1: adjusted for age, sex, Crohn's disease location, and Crohn's disease behavior

[§] Model 2: adjusted for age, sex, Crohn's disease location, Crohn's disease behavior, and use of immunomodulatory agents

of continuing or discontinuing 5-ASA after escalation of biologic treatments. Further large multicenter studies are required to confirm our results.

Author contributions Tae Jun kim, Youn I Choi, Dong Kyun Park, and Yoon Jae Kim contributed to study concept and design, acquisition analysis and interpretation of data, drafting of the manuscript, and obtained funding. Youn I Choi, Jun-won Chung, and Kyung Oh Kim contributed to study analysis and interpretation of data and critically revised the manuscript. Jun-Won Chung, Kyoung Oh Kim, and Kwang An Kwon contributed to study design and critically revised the manuscript. All the authors read and approved the final manuscript.

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Compliance with ethical standards

The study protocol was approved by the institutional review board of Gachon Gil Medical Center (IRB approval number GCIRB 201860453).

Conflict of interest The authors declare that they have no conflict of interest.

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