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Original Article

Long-term Prognosis of Ulcerative Colitis and its Temporal Change Between 1977 and 2013: A Hospital-based Cohort Study from Korea

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Abstract

Background and aims: No previous large-scale studies have evaluated the prognosis of ulcerative colitis (UC) over a period of three decades in a non-Caucasian population. The aims of this study were to update the current information on the natural course of UC in a sizable cohort of Korean patients and to evaluate changes in the treatment paradigms and prognosis of UC over time.
Methods: We retrospectively analyzed 2802 Korean UC patients who visited Asan Medical Center. We divided the study subjects into three groups based on the year of diagnosis (cohort 1: 1977–1999; cohort 2: 2000–2006; and cohort 3: 2007–2013).
Results: Five-year cumulative probabilities of prescription of thiopurines (azathioprine or 6-mercaptopurine) and anti-tumor necrosis factor (anti-TNF) agents were 4.1% and 0.0%, respectively, in cohort 1 and 27.9% and 12.7%, respectively, in cohort 3 ($P < 0.001$). A total of 209 patients (7.5%) underwent colectomy, producing cumulative probabilities of colectomy at 10, 20 and 30 years after diagnosis of 7.8%, 14.2% and 21.3%, respectively. The cumulative probability of colectomy was especially low in patients first diagnosed at our center: 3.1% at 10 years and 4.5% at 20 years. Moreover, the cumulative probability of colectomy decreased significantly over the last 30 years ($P = 0.039$).
Conclusion: Thiopurines and anti-TNF agents are used increasingly more frequently and earlier, while the colectomy rate has decreased over the last 30 years in Korean patients with UC. Korean UC patients may have a better clinical course than Western cases, as indicated by a lower colectomy rate.

Keywords: Clinical features; colectomy; Korea; prognosis; ulcerative colitis

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Abbreviations:

anti-TNF,	anti-tumor necrosis factor;
CI,	confidence interval;
HR,	hazard ratio;
IBD,	inflammatory bowel disease;
UC,	ulcerative colitis.

1. Introduction

Ulcerative colitis (UC) is a chronic relapsing disorder with a variable but potentially severe disease course. Although the etiology of UC remains unclear, genetic vulnerability and environmental factors are thought to play important roles in its pathogenesis. Over the past few decades, the incidence of UC in Asia has been rapidly increasing, while the incidence in the West has remained relatively stable.[1–4] The age- and gender-adjusted mean annual incidence rate of UC in Koreans, while still lower than that in Westerners, increased 9-fold from 0.34 per 100 000 in 1986–1990 to 3.08 per 100 000 in 2001–2005.[2] A swift change in the incidence rate within a genetically stable population suggests that environmental factors, such as westernized lifestyles featuring a high-fat diet, antibiotic use, and improved hygiene, may be driving the increasing incidence of UC. Understanding the features of UC may provide insight into its etiology.

Despite the rising incidence and prevalence of UC in Asia, studies on the chronological changes in the course and prognosis of Asian UC are very limited. A few longitudinal studies have reported on the epidemiology and clinical features in the pre-biologic era.[1,2,5–8] However, to the best of our knowledge, no previous longitudinal clinical study has evaluated changes in the treatment and subsequent prognosis of UC over a period of three decades in a non-Caucasian population. The aims of the present study were to update the current information on the natural course of UC based on a large number of Korean patients and to assess different cohorts defined on the basis of the calendar year of diagnosis to evaluate changes in management and the impact on the prognosis of UC in an era of rapid shifts in medical treatment paradigms.

2. Materials and methods

2.1 Study population

Patients with UC who visited the outpatient clinic of Asan Medical Center, a university hospital in Seoul, between June 1989 and December 2013 were enrolled in this study. All patients were diagnosed with UC between 1977 and 2013, based on a composite of clinical, radiological, endoscopic and histopathological criteria.[1,9] Among the 3111 UC patients who visited Asan Medical Center during the inclusion period, 309 were excluded from the present study for the following reasons: a second-opinion referral in 272 patients, a post-colectomy referral in 9 patients, and indeterminate colitis in 28 patients. Of the 2802 patients included in the present study, 529 (18.9%) were first diagnosed with UC at Asan Medical Center (inception cohort) and 2273 (81.1%) were referred to Asan Medical Center after the diagnosis of UC had been made at another clinic or hospital (referred cohort). To provide an update of our previous study, which consisted of an inception cohort of 304 patients,[10] and to mitigate the effects of referral bias, our current inception cohort of 529 patients was analyzed separately. Patients were divided into three consecutive cohorts according to the date of diagnosis (cohort 1, 1977–1999; cohort 2, 2000–2006; and cohort 3, 2007–2013) in order to evaluate changes in treatment paradigms and the prognosis of UC during the study period. The number of study subjects was 704 in cohort 1, 979 in cohort 2, and 1119 in cohort 3.

2.2 Study design

We retrieved detailed demographic and clinical information from the Asan Inflammatory Bowel Disease (IBD) registry, which has been prospectively maintained since 1997 and has been previously described in detail.[11] This study protocol (IRB number: 2014-0384) was approved by the Ethics Committee of Asan Medical Center. The information obtained from the registry included sex, date of birth, date of symptom onset, date of UC diagnosis, family history of IBD, smoking status, disease activity, disease extent at diagnosis and during the course, medication use, and colectomy. Initial disease activity in the inception cohort was evaluated using the Mayo Clinic scoring system, which is based on stool frequency, rectal bleeding, sigmoidoscopic findings, and a physician's global assessment.[10] The extent of disease was determined on the basis of endoscopic findings. Proctitis was defined as disease <15 cm from the anal verge, left-sided colitis as disease up to the splenic flexure, and extensive colitis as disease beyond the splenic flexure.[1] To investigate the subsequent evolution of the disease, we evaluated the rates of proximal disease extension and of colectomy. Proximal disease extension was defined as the extension of macroscopic inflammation beyond the initially involved segment (i.e. from proctitis to left-sided or extensive colitis, or from left-sided colitis to extensive colitis) at any follow-up colonoscopy.[12]

2.3 Treatment policy

Our treatment strategies for UC were detailed previously[10] and are based on a step-up approach that is similar to that of Western countries. Topical and/or oral 5-aminosalicylates are the first-line therapy to induce and maintain remission in mild to moderate UC. Systemic corticosteroid therapy is used in patients with moderately to severely active disease and in those who do not respond to 5-aminosalicylates, and this therapy is tapered and discontinued over 2–3 months. Thiopurines (azathioprine or 6-mercaptopurine) and, in case of its failure, anti-tumor necrosis factor (anti-TNF) agents are used in steroid-dependent or steroid-refractory patients. For hospitalized patients with acute severe UC, the first-line medical therapy is intravenous corticosteroids. A rescue medical therapy with anti-TNF agents or intravenous cyclosporine or colectomy is considered in patients who do not respond to intensive corticosteroids treatment. Anti-TNF agents have been covered by insurance for the treatment of patients with UC since October 2010, although anti-TNF agents were approved for UC treatment in Korea in May 2007. Thus far two anti-TNF agents (infliximab and adalimumab) have been approved for UC by the Korean Food and Drug Administration. Patients need to satisfy strict criteria for reimbursement before they become eligible for anti-TNF agent coverage. An inadequate response to conventional treatment with corticosteroids and/or thiopurines and moderate or severe disease activity are mandatory for government reimbursement coverage for patients. In addition, for the maintenance of anti-TNF agents, Korean government's reimbursement policy requires a positive clinical response based on Mayo scores at Weeks 0 and 8 after induction therapy with anti-TNF agents. Our patients are followed up at the outpatient clinic of our hospital at regular intervals according to their conditions, usually every 1–3 months.

2.4. Statistics

Continuous variables were calculated as medians with ranges. Discrete data were tabulated as numbers and percentages. The chi-squared test was used to compare proportions, and the *t*-test was

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used to compare quantitative variables. Cumulative rates of proximal disease extension and colectomy were calculated according to the Kaplan–Meier method, and group values were compared using the log-rank test. A Cox proportional hazards model with a backward variable elimination procedure was used to identify significant predictors of the cumulative probability of colectomy and to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs). A *P* value of less than 0.05 was considered statistically significant. Statistical evaluation was performed using the statistical software package SPSS 21.0 for Windows (IBM SPSS, Ver. 21.0; IBM Co., Armonk, NY).

3. Results

3.1 Clinical characteristics at diagnosis

Among the 2802 patients in the study cohort, 1507 (53.8%) were men and 1295 (46.2%) were women, yielding a male-to-female ratio of 1.2:1. The median age at diagnosis of UC was 36 years (range, 9–90 years). The demographic and clinical characteristics of the patients are shown in Table 1. The proportion of men ($P < 0.001$), the median age at diagnosis ($P < 0.001$), the proportion of ever smokers at diagnosis ($P < 0.001$), and the proportion of proctitis at diagnosis ($P < 0.001$) increased significantly from cohort 1 to cohort 3, whereas a family history of IBD ($P < 0.001$) decreased significantly from cohort 1 to cohort 3. In the inception cohort, there were no differences between the three temporal cohorts in terms of disease extent at diagnosis or disease activity at diagnosis ($P = 0.201$ and 0.263, respectively; Table 2).

3.2 Medical treatment

Corticosteroids were administered to 56.0% of our patients with UC at diagnosis and/or during follow-up: 65.0% in cohort 1, 57.9% in cohort 2 and 48.9% in cohort 3, respectively. The cumulative probabilities of corticosteroid treatment at 1, 5, 10, 20 and 30 years after diagnosis were 36.3%, 52.9%, 61.0%, 71.2% and 74.7%, respectively. The median interval from diagnosis of UC to the start of corticosteroid therapy was 3.5 months (range, 0.0–279.4 months). Thiopurines (azathioprine or 6-mercaptopurine) was used in 20.0% of our patients at diagnosis and/or during follow-up: 15.2% in cohort 1, 21.7% in cohort 2 and 21.5% in cohort 3. The cumulative probabilities of thiopurines (azathioprine or 6-mercaptopurine) treatment at 1, 5, 10, 20 and 30 years after diagnosis were 4.9%, 15.9%, 22.8%, 32.0% and 37.1%, respectively. The median interval from diagnosis of UC to the start of thiopurines (azathioprine or 6-mercaptopurine) therapy was 31.9 months (range, 0.2–295.5 months). Anti-TNF agents were administered to 174 patients (6.2%) at diagnosis and/or during follow-up (156 patients received infliximab, 13 patients received adalimumab, and 5 patients switched between infliximab and adalimumab)—2.4% in cohort 1, 5.7% in cohort 2 and 9.0% in cohort 3—and the cumulative probabilities of anti-TNF treatment at 1, 5, 10, 20 and 30 years from diagnosis were 0.9%, 4.1%, 7.4%, 11.9% and 12.8%, respectively. The median interval from diagnosis of UC to the start of anti-TNF therapy was 52.3 months (range, 0.9–265.2 months).

Temporal trends in the cumulative probabilities of commencing medications (corticosteroids, thiopurines [azathioprine or 6-mercaptopurine], and anti-TNF agents) in the total cohort and in the inception cohort are presented in Figure 1. The cumulative probability of corticosteroid use did not differ between the three temporal cohorts in the combined inception and referred cohort ($P = 0.292$), although it significantly decreased from cohort 1 to cohort 3 in the inception cohort ($P = 0.013$; Figure 1A). In contrast, there was a statistically significant temporal change toward more frequent and earlier use of thiopurines (azathioprine or 6-mercaptopurine) and anti-TNF agents over the previous three decades, with the 5-year cumulative probability of prescription rising from 4.1% and 0.0%, respectively, in cohort 1 to 27.9% and 12.7%, respectively, in cohort 3 ($P < 0.001$ and $P < 0.001$, respectively; Figure 1B and 1C). The median interval

Table 1. Demographic and clinical characteristics of 2802 Korean patients with ulcerative colitis according to the year of diagnosis.

	Total	Cohort 1 (1977–1999)	Cohort 2 (2000–2006)	Cohort 3 (2007–2013)
Number of patients	2802	704	979	1119
Referred cohort	2273 (81.1%)	547 (77.7%)	815 (83.2%)	911 (81.4%)
Male	1507 (53.8%)	334 (47.4%)	533 (54.4%)	640 (57.2%)
Median age at diagnosis (range), years	36 (9–90)	34 (9–90)	36 (12–77)	38 (12–79)
Median interval from onset to diagnosis (range), months	3 (0–370)	4 (0–300)	3 (0–240)	3 (0–370)
Family history of IBD				
Yes	162 (5.8%)	54 (7.7%)	52 (5.3%)	56 (5.0%)
No	2542 (90.7%)	600 (85.2%)	879 (89.8%)	1063 (95.0%)
Missing	98 (3.5%)	50 (7.1%)	48 (4.9%)	0 (0.0%)
Smoking status at diagnosis				
Never smoker	1634 (58.3%)	445 (63.2%)	543 (55.5%)	646 (57.7%)
Former smoker	577 (20.6%)	85 (12.1%)	200 (20.4%)	292 (26.1%)
Current smoker	468 (16.7%)	100 (14.2%)	188 (19.2%)	180 (16.1%)
Missing	123 (4.4%)	74 (10.5%)	48 (4.9%)	1 (0.1%)
Disease extent at diagnosis				
Proctitis	1158 (41.3%)	223 (31.7%)	393 (40.1%)	542 (48.4%)
Left-sided colitis	763 (27.2%)	208 (29.5%)	283 (28.9%)	272 (24.3%)
Extensive colitis	614 (21.9%)	143 (20.3%)	212 (21.7%)	259 (23.1%)
Missing	267 (9.5%)	130 (18.5%)	91 (9.3%)	46 (4.1%)
Ever use of medications				
Corticosteroids	1564 (56.0%)	451 (65.0%)	566 (57.9%)	547 (48.9%)
Thiopurines	559 (20.0%)	106 (15.2%)	212 (21.7%)	241 (21.5%)
Anti-TNF agents	174 (6.2%)	17 (2.4%)	56 (5.7%)	101 (9.0%)

IBD, inflammatory bowel disease.

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Table 2. Demographic and clinical characteristics of 529 ulcerative colitis patients in the inception cohort according to the year of diagnosis.

	Total	Cohort 1 (1977–1999)	Cohort 2 (2000–2006)	Cohort 3 (2007–2013)
Number of patients	529	157	164	208
Male	278 (52.6%)	76 (48.4%)	82 (50.0%)	120 (57.7%)
Median age at diagnosis (range), years	40 (12–90)	38 (12–90)	40 (17–74)	42 (15–79)
Median interval from onset to diagnosis (range), months	6 (0–172)	8 (0–172)	5 (0–123)	5 (0–121)
Family history of IBD				
Yes	16 (3.0%)	7 (4.5%)	13 (7.9%)	15 (7.2%)
No	478 (90.4%)	138 (87.9%)	147 (89.6%)	193 (92.8%)
Missing	35 (6.6%)	12 (7.6%)	4 (2.4%)	0 (0.0%)
Smoking status at diagnosis				
Never smoker	289 (54.6%)	93 (59.2%)	89 (54.3%)	107 (51.4%)
Former smoker	140 (26.5%)	29 (18.5%)	43 (26.2%)	68 (32.7%)
Current smoker	86 (16.3%)	24 (15.3%)	30 (18.3%)	32 (15.4%)
Missing	14 (2.6%)	11 (7.0%)	2 (1.2%)	1 (0.5%)
Disease extent at diagnosis				
Proctitis	237 (44.8%)	60 (38.2%)	78 (47.6%)	99 (47.6%)
Left-sided colitis	137 (25.9%)	51 (32.5%)	37 (22.6%)	49 (23.6%)
Extensive colitis	155 (29.3%)	46 (29.3%)	49 (29.9%)	60 (28.8%)
Disease activity at diagnosis				
Inactive	10 (1.9%)	1 (0.6%)	2 (1.2%)	7 (3.4%)
Mild	263 (49.7%)	72 (45.9%)	80 (48.8%)	111 (53.4%)
Moderate	205 (38.8%)	69 (43.9%)	64 (39.0%)	72 (34.6%)
Severe	51 (9.6%)	15 (9.6%)	18 (11.0%)	18 (8.7%)

IBD, inflammatory bowel disease.

from diagnosis of UC to the commencement of thiopurines (azathioprine or 6-mercaptopurine) and anti-TNF agents decreased from 111.4 months and 183.4 months, respectively, in cohort 1 to 15.8 months and 27.4 months, respectively, in cohort 3 ($P < 0.001$ and $P < 0.001$, respectively).

3.3 Proximal disease extension

The median duration of follow-up was 89.5 months (range, 0.3–433.1 months). By the end of the current study period, 381 patients (13.6%) were lost to follow-up. Among 1921 patients, composed of 1158 patients with proctitis and 763 patients with left-sided colitis at diagnosis, proximal disease extension was observed in 491 patients (25.6%) during follow-up. The cumulative risk of proximal extension after 10 and 20 years was 29.8% and 44.4%, respectively, for all patients with proctitis or left-sided colitis. When separately analyzed by disease extent at diagnosis, the cumulative risk of proximal extension at 10 and 20 years was 36.8% and 56.1%, respectively, for patients with proctitis at diagnosis, while it was 20.0% and 30.4%, respectively, for patients with left-sided colitis at diagnosis ($P < 0.001$). The probability of proximal disease extension in patients with proctitis or left-sided colitis was lower in the inception cohort than in the referred cohort: 20.8% versus 32.0% at 10 years and 37.6% versus 46.2% at 20 years ($P < 0.001$). Kaplan–Meier estimates of the proportion of patients according to maximal disease extent at 10, 20 and 30 years were 28.9%, 20.2% and 18.0%, respectively, for proctitis; 33.9%, 36.1% and 30.5%, respectively, for left-sided colitis; and 37.2%, 43.7% and 51.5%, respectively, for extensive colitis (Figure 2).

3.4 Colectomy

A total of 209 patients (7.5%) underwent colectomy during the follow-up period. Indications for colectomy included refractory symptoms on maximal medical therapy in 106 patients (50.7%), corticosteroid dependency/intolerance in 51 patients (24.4%), colorectal dysplasia or cancer in 32 patients (15.3%), perforation in 11 patients (5.3%), toxic megacolon in 4 patients (1.9%), massive bleeding in 3 patients (1.4%), and obstruction in 2 patients (1.0%). The cumulative probabilities of colectomy at 1, 5, 10, 20 and 30 years after diagnosis were 2.2%, 5.5%, 7.8%, 14.2% and 21.3%, respectively (Figure 3A). The cumulative probability of colectomy was significantly lower in the inception cohort than in the referred cohort: 3.0% versus 8.9% at 10 years, and 4.4% versus 16.5% at 20 years ($P < 0.001$; Figure 3B). Moreover, the cumulative probability of colectomy decreased significantly in the combined inception and referred cohorts ($P = 0.039$; Figure 3C) as well as in the inception cohort ($P = 0.042$; Figure 3D) over the past 30 years. When we analyzed temporal trends in colectomy rate according to disease extent at diagnosis, we found that the cumulative probability of colectomy decreased significantly over time in patients with extensive colitis at diagnosis, but did not change between the three temporal cohorts in patients with proctitis or left-sided colitis at diagnosis (see Supplemental Figure 1).

Multivariate Cox analysis revealed that the referred cohort, extensive colitis, and ever use of corticosteroids were independent predictors of colectomy (Table 3). When the analysis was confined to 614 patients with extensive colitis at diagnosis, the referred cohort and ever use of corticosteroids were replicated as independent predictors (Table 4). In addition, in a subgroup analysis of patients with extensive colitis at diagnosis, the colectomy rate significantly decreased in cohorts 2 and 3 compared with cohort 1 (Table 4).

4. Discussion

This study compared time trends of medication use and need for colectomy in a well-defined cohort of Korean patients diagnosed with UC between 1977 and 2013. Despite the shorter observation time in the most recent cohort, there was an increase in the use of thiopurines (azathioprine or 6-mercaptopurine) and anti-TNF agents that was paralleled by a decrease in the cumulative probability of colectomy over the three-decade period.

Our cohort comprised more than 2800 UC patients with detailed information and a high rate of follow-up, enabling analysis of

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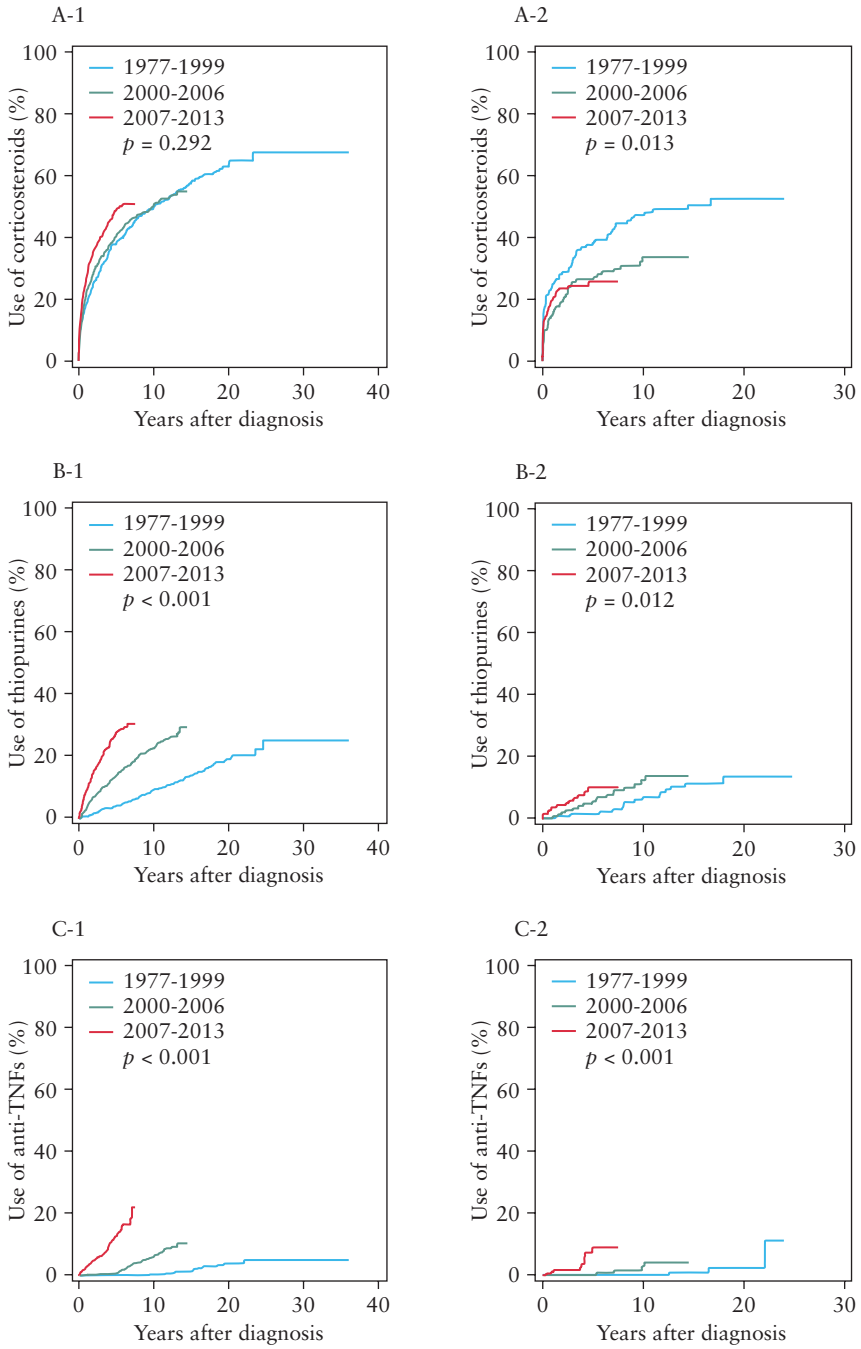

Figure 1. Temporal trends in the cumulative probability of medication use in Korean patients with ulcerative colitis: (A-1) corticosteroids in the total cohort; (A-2) corticosteroids in the inception cohort; (B-1) thiopurines (azathioprine or 6-mercaptopurine) in the total cohort; (B-2) thiopurines (azathioprine or 6-mercaptopurine) in the inception cohort; (C-1) anti-TNF agents in the total cohort; and (C-2) anti-TNF agents in the inception cohort.

temporal trends in the colectomy rate. To the best of our knowledge, our present study is the first to demonstrate a decreasing rate in colectomy over time in non-Caucasian patients with UC, which is in accordance with previous Western studies.[13–16] However, this result must be interpreted cautiously with the following considerations. First, this study was conducted in a referral center that often handles more severe, refractory cases. In our present study, the cumulative probability of colectomy was also significantly higher in the referred cohort than in the inception cohort. Therefore, if there is a decrease in the proportion of referred patients over time, the colectomy rate may decrease spuriously. In the present study cohort, however, the proportion of referred patients was higher in cohort 3 than in cohort 1 (81.4% versus 77.7%; $P = 0.015$). Second, the increasing proportion of patients with proctitis at diagnosis over the study period may explain the decreasing colectomy rate. However, there was no decreasing proportion of patients with extensive colitis at diagnosis that paralleled the increasing proportion of patients with proctitis at diagnosis. The definition of proctitis for this study was a disease <15 cm from the anal verge. Endoscopists may have misclassified proctitis as left-sided colitis or vice versa. Moreover, the increasing proportion of patients with proctitis at diagnosis over the study period could be caused by a simultaneous reduction in

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the proportion of patients with missing data in the recent cohort. In addition, when temporal trends in the colectomy rate were analyzed according to disease extent at diagnosis, no temporal change was noted in the colectomy rate in patients with proctitis or left-sided colitis at diagnosis, but a significant decrease over time was noted in patients with extensive colitis at diagnosis. Taken together, the results suggest that the temporal trend toward a decreasing colectomy rate over the last 30 years was not caused by a change in the proportion or characteristics of referred patients.

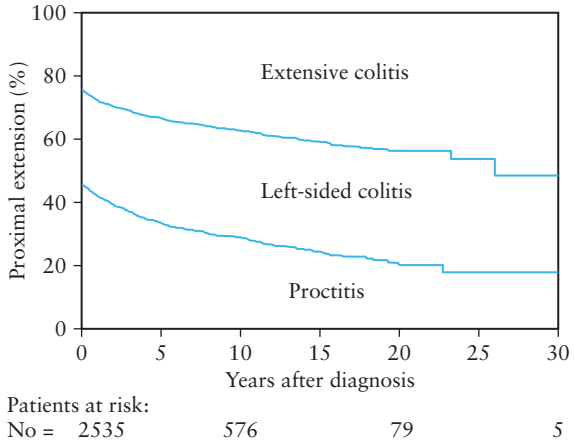

Figure 2. Cumulative probability of proximal extension of disease in Korean patients with ulcerative colitis (upper curve, remaining free of extensive colitis; lower curve, free of extensive and/or left-side colitis).

Our current study showed that thiopurines (azathioprine or 6-mercaptopurine) and anti-TNF agents were used increasingly more frequently and earlier over the last three decades, which is in agreement with previous Western studies.[13,15,17,18] However, it was not possible to assess the impact of this change on the decreasing colectomy rate because these medications are generally used in patients with more severe disease. For the same reason, previous Western studies failed to demonstrate a direct causal relationship between increasing use of thiopurines (azathioprine or 6-mercaptopurine) and/or anti-TNF agents and decreasing colectomy rates.[13,15,19]

Despite overlapping genetic susceptibility loci and clinical features at diagnosis between Koreans and Caucasians,[2,10,20] Korean UC patients may have a less severe disease course than Caucasians, as indicated by the lower colectomy rate. Colectomy rates differ significantly by race/ethnicity and geographic region, although the cause of this variation remains unclear.[21] Lower colectomy rates may be attributed to various factors, including a milder disease course, less extensive disease, better response to medical therapy, improvement in treatment strategy over time, and less acceptance of colectomy by patients and/or physicians.[10,21] Although our study was conducted in a referral center, the colectomy rate appears to be comparable with

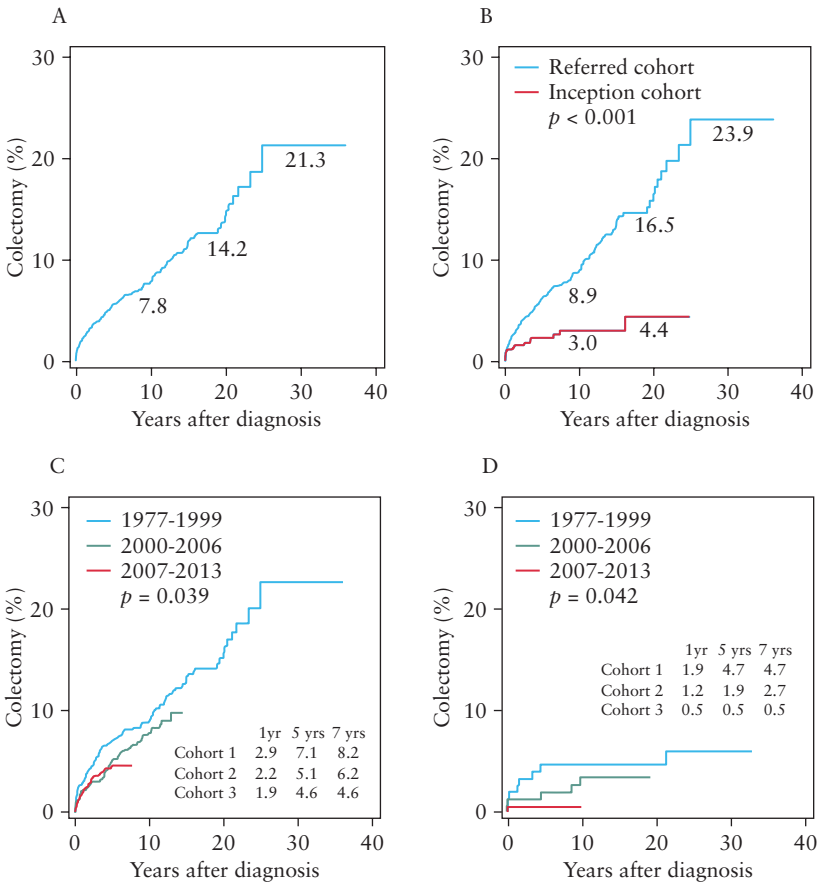

Figure 3. Cumulative probability of colectomy in Korean patients with ulcerative colitis: (A) in the combined inception and referred cohorts; (B) comparison between the inception and referred cohorts; (C) temporal trends in the combined inception and referred cohorts (1977–1999 versus 2000–2006, $P = 0.158$; 1977–1999 versus 2007–2013, $P = 0.018$; 2000–2006 versus 2007–2013, $P = 0.586$); (D) temporal trends in the inception cohort (1977–1999 versus 2000–2006, $P = 0.513$; 1977–1999 versus 2007–2013, $P = 0.018$; 2000–2006 versus 2007–2013, $P = 0.228$).

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Table 3. Univariate and multivariate Cox analysis: risk factors of colectomy in Korean patients with ulcerative colitis.

	Univariate analysis		*p*	Multivariate analysis		*p*
	HR	95% CI		HR	95% CI	
Sex						
Women	Reference			Not included		
Men	1.21	0.92–1.59	0.170			
Age at diagnosis						
<40	Reference			Not included		
≥40	1.18	0.90–1.55	0.235			
Smoking status at diagnosis						
Never smoker	Reference			Not included		
Former smoker	0.95	0.66–1.35	0.757			
Current smoker	0.77	0.51–1.16	0.211			
Source of patients						
Inception cohort	Reference			Reference		
Referred cohort	3.30	1.92–5.68	<0.001	2.40	1.38–4.18	0.002
Disease extent at diagnosis						
Proctitis	Reference			Reference		
Left-sided colitis	2.14	1.31–3.50	0.002	1.42	0.86–2.33	0.171
Extensive colitis	5.99	3.84–9.35	<0.001	3.56	2.25–5.62	<0.001
Diagnosis period						
Cohort 1 (1977–1999)	Reference			Reference		
Cohort 2 (2000–2006)	0.791	0.57–1.10	0.160	0.78	0.52–1.18	0.238
Cohort 3 (2007–2013)	0.666	0.45–0.99	0.048	0.75	0.46–1.20	0.221
Ever use of medications						
Corticosteroids	10.17	5.79–17.83	<0.001	6.81	3.52–13.19	<0.001
Thiopurines	2.15	1.61–2.86	<0.001	1.16	0.81–1.64	0.418
Anti-TNF agents	1.89	1.20–2.97	0.006	1.21	0.70–2.10	0.496

CI, confidence interval; HR, hazard ratio; anti-TNF, anti-tumor necrosis factor.

Table 4. Univariate and multivariate Cox analysis: risk factors of colectomy in Korean patients with extensive ulcerative colitis at diagnosis.

	Univariate analysis		*p*	Multivariate analysis		*p*
	HR	95% CI		HR	95% CI	
Sex						
Women	Reference			Not included		
Men	0.79	0.50–1.23	0.294			
Age at diagnosis						
<40	Reference			Reference		
≥40	1.64	1.04–2.59	0.033	1.78	1.12–2.84	0.015
Smoking status at diagnosis						
Never smoker	Reference			Reference		
Former smoker	0.90	0.48–1.69	0.751	0.83	0.42–1.63	0.580
Current smoker	0.50	0.25–0.98	0.042	0.51	0.26–1.00	0.049
Source of patients						
Inception cohort	Reference			Reference		
Referred cohort	2.76	1.38–5.53	0.004	2.79	1.38–5.65	0.004
Diagnosis period						
Cohort 1 (1977–1999)	Reference			Reference		
Cohort 2 (2000–2006)	0.61	0.36–1.05	0.073	0.56	0.32–0.96	0.035
Cohort 3 (2007–2013)	0.52	0.28–0.96	0.037	0.47	0.25–0.87	0.016
Ever use of medications						
Corticosteroids	6.43	2.03–20.40	0.002	4.84	1.52–15.42	0.008
Thiopurines	1.17	0.73–1.88	0.508	0.82	0.50–1.35	0.436
Anti-TNF agents	0.91	0.40–2.10	0.829	0.87	0.35–2.12	0.752

CI, confidence interval; HR, hazard ratio; anti-TNF, anti-tumor necrosis factor.

that of previous Western population-based studies.[14–16,22,23] The high proportion of proctitis may be responsible for the relatively lower colectomy rate in the present study. However, even considering only patients with left-sided colitis or extensive colitis, the cumulative risk of colectomy remained relatively low: 9.4% after 10 years, 14.6% after 20 years, and 22.4% after 30 years. Furthermore, when we focused on the data from our inception cohort, the cumulative risk of colectomy for 529 patients was only 3.0% after 10 years and

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4.4% after 20 years. Considering these findings, we suggest that Korean UC patients have a less severe disease course compared with Westerners. However, further studies are required to clarify whether differences in patient and physician attitudes toward colectomy have an impact on the lower colectomy rate in our study.

During the follow-up, 18 patients developed colorectal cancers. Although we did not present all the detailed data for colitis-associated cancers in the current article, the risk of colorectal cancer in Korean UC patients may be comparable with that in Western UC patients, based on our previous investigation (standardized incidence ratio: 1.68, 95% CI: 1.00–2.66).[24]

There were several limitations to our current study. First, our findings should be interpreted carefully due to the retrospective and referral center–based design of our investigation. To mitigate the issue of selection bias and subsequent confounding, we analyzed the inception cohort separately. The proportion of patients with proctitis at diagnosis was 44.8% in the inception cohort of our study, which is similar to the 43.7% in a previous population-based study from Korea.[2] This suggests that the clinical characteristics of the inception cohort in our current study may be similar to those of the general Korean UC patient population. However, the need remains for a long-term population-based study to reduce the referral bias. Second, data regarding disease activity at UC diagnosis was not available for the referred cohort, and we could not therefore evaluate the impact of disease activity at UC diagnosis (a well-established risk factor) on the risk of colectomy. Third, the follow-up duration of cohort 3 was relatively short. Nevertheless, when we performed sensitivity analyses in the three temporal cohorts that were censored at 7 years of follow-up, the results showed similar patterns with regard to the use of medication and colectomy (data not shown). Fourth, in consideration of the missing data for family history of IBD, smoking status at diagnosis, and disease extent at diagnosis, careful interpretation of the change in the epidemiologic features during the study period is required. Therefore, further studies are needed with longer follow-ups to determine the changing trends in the clinical features in Korean UC patients.

In conclusion, our present hospital-based cohort study demonstrates that thiopurines (azathioprine or 6-mercaptopurine) and anti-TNF agents have been used increasingly more frequently and earlier, and that the colectomy rate has decreased over the last three decades. In addition, Korean UC patients may have better clinical courses than Westerners, as indicated by the lower colectomy rate.

Supplementary material

Supplementary data to this article can be found online at: XXXXX
Supplementary Figure 1 Cumulative probability of colectomy in Korean patients with extensive ulcerative colitis at diagnosis. (A) Temporal trends in the combined inception and referred cohorts (1977–1999 versus 2000–2006, $P = 0.071$; 1977–1999 versus 2007–2013, $P = 0.022$; 2000–2006 versus 2007–2013, $P = 0.761$); (B) temporal trends in the inception cohort (1977–1999 versus 2000–2006, $P = 0.461$; 1977–1999 versus 2007–2013, $P = 0.012$; 2000–2006 versus 2007–2013, $P = 0.116$).

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Conflict of Interest

Potential conflicts of interest: Suk-Kyun Yang received a research grant from Janssen Korea Ltd, but this grant is not related to the topic of the current study. The remaining authors have no competing interests.

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