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Patients with ulcerative colitis who have normalized histology are clinically stable after de-escalation of therapy

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We have previously demonstrated that histological normalization in ulcerative colitis (UC) is associated with superior maintenance of remission outcomes. This single-center, retrospective case-control study assessed outcomes after the therapeutic de-escalation in UC patients who have achieved histologic normalization. A total of 111 patients were included, of which 24 underwent de-escalation, and 87 patients without therapeutic changes. The most commonly withdrawn therapy was aminosalicylates (50%), followed by immunomodulators (37.5%), and biologics (12.5%). Fourteen patients remained on therapies after de-escalation, including aminosalicylate (9/14), immunomodulators (3/14), and biologics (3/14), while 10 patients were not on any therapy immediately after withdrawal. Median follow-up was 43 months in the de-escalation group and 47 months in the control. The rates of clinical, endoscopic, and histologic recurrence were not significantly different between the two groups, nor was the proportion of patients who subsequently required additional therapies after withdrawal ($P = 0.133$). Clinical and endo-histologic recurrence rates were the lowest in patients who withdrew immunomodulators (0% and 14.3%, respectively). We demonstrate the clinical stability of therapeutic withdrawal in UC patients with histologic normalization.

Guidelines and consensus statements for the management of inflammatory bowel disease (IBD) emphasize the benefit and preferred outcome of achieving deep remission, defined as clinical remission in combination with objectively confirmed endoscopic, radiologic, and laboratory control of disease[1–3] While previous clinical trials of biological therapies for ulcerative colitis (UC) generally defined mucosal healing (MH) as endoscopic healing (Mayo endoscopic subscore ≤ 1)[4–8], more recent studies have demonstrated the importance of achieving both endoscopic and histologic remission to improve clinical outcomes and include both endoscopic and histologic measures in the definition of MH[9].

Reference to histopathological findings of intestinal specimens is important in the diagnosis and in ongoing assessment of disease activity of UC, and traditional descriptions characterize the disease as demonstrating chronic changes of crypt architectural distortion even in the absence of histologically active inflammation (histological quiescence). Multiple histopathological scoring/grading systems are available and have been incorporated into clinical trials and less so, into clinical practice[10–12]. However, these scoring systems do not include "normal" histology as a distinct category, but rather include quiescent and normal findings in the same category. We have previously established a standardized scale of histologic inflammation which discriminated between normal and quiescent disease[10]. In our scale, a score of 0 was given to normal tissue completely uninvolved by disease with no architectural distortion or inflammatory infiltrates[10]. We subsequently demonstrated that histologic normalization was possible and independently associated with an increased odds of relapse-free survival compared with histologic quiescence or histologic activity[9].

Decision-making regarding therapeutic de-escalation for patients with IBD is still based on expert opinion and lacks objective criteria[11]. A recent meta-analysis assessed the relapse rate in patients with deep remission (defined, at least, by a combination of clinical remission and endoscopic remission) who subsequently underwent therapeutic de-escalation and described relapse rates in patients with UC within 1 year and 2 years as 25.4% and 37.4%, respectively[12]. This study suggested that therapeutic de-escalation was significantly associated with the increased risk of relapse

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regardless of deep remission and that the risk is greater in those who were de-escalated from anti-tumor necrosis factor (TNF)α inhibitors. However, the studies in this systematic review and meta-analysis did not include patients who had achieved histologic normalization[12].

This study aimed to assess outcomes after withdrawing therapies in patients with UC who have achieved histologic normalization.

Results

Patient background

We identified 111 patients with UC who achieved histologic normalization (Table 1).

Of the 111 patients, the de-escalation group included 24 patients, and the control group included 87 patients with UC (Table 2). The median follow-up was 43 months (IQR 21–63 months) in the de-escalation group and 47 months (IQR 16–86 months) in the control group.

The study flow was shown in Fig. 1. Of the 24 patients in the de-escalation group, the most commonly withdrawn therapies were aminosalicylates (12/24), followed by immunomodulators (9/24), and biologics (3/24). Among the 24 patients in the de-escalation group, 14 patients (58.3%) remained on other IBD therapies immediately after therapeutic withdrawal, including aminosalicylate (9/14), immunomodulators (3/14), and biologics (3/14), and 2 patients (8.3%) stepped down from thiopurines (1/2) or biologics (1/2) to aminosalicylates. Ten patients (41.7%) were on no therapies immediately after withdrawal. With regard to the timeline of therapy withdrawal, the median duration from histologic normalization to withdrawal of therapy was 7.8 months (IQR 0.2-15.8 months). Nineteen patients (79.2%) abruptly stopped medications, 8 (42.1%) of whom discontinued their therapy based on their preferences. Three patients (12.5%) tapered off their medications and 2 patients (8.3%) had no detailed information regarding the withdrawal strategy.

Outcomes between the de-escalation group and the control group

Comparison between the de-escalation group and the control group showed no significant difference with respect to age at diagnosis, sex, disease duration, disease extent, smoking status, and PSC. As for baseline treatments, patients in the de-escalation group had higher rates of prior exposure to immunomodulators compared with patients in the control group ($P = 0.016$) (Table 2). There was no significant difference in the proportion of patients who subsequently required additional IBD therapies after withdrawal of therapy ($P = 0.133$) (Table 2). Aminosalicylate use after withdrawing therapies in the de-escalation group was significantly lower than that in the control group ($P = 0.033$), whereas immunomodulators or biologic use after withdrawal of therapy was not significantly different between the two groups (Table 2).

In the analysis for clinical recurrence, the de-escalation group and the control group included 23 and 82 patients, respectively. The overall rate of clinical recurrence was not significantly different between the two groups ($P = 0.407$) (Table 2). Consistent with these data, 2-year EFS for clinical recurrence was 89.5% (95% CI 64.1%–97.3%) in the de-escalation group and 95.6% (95% CI 86.8%-98.6%) in the control group ($P = 0.129$) (Fig. 2A). 29 patients were missing a baseline SCCAI in the overall cohort; therefore, a separate complete case analysis including 18 patients in the de-escalation group and 59 patients in the control group and results were similar to the full data analysis: the overall rate of clinical recurrence in the de-escalation group (16.7%) was not significantly different from that in the control group (8.5%) ($P = 0.381$). Two-year EFS for clinical recurrence was 85.7% (95% CI 53.9%-96.2%) in the de-escalation group and 93.6% (95% CI 81.3%–97.9%) in the control group ($P = 0.136$) (Fig. S1)

For the assessments of endoscopic or histologic recurrences, the de-escalation group included 18 patients whereas the control group included 51 patients for endoscopic recurrence and 50 patients for histologic recurrence, as one patient in the control group did not have a histologic assessment. The overall rates of endoscopic and histologic recurrences were not significantly different between the two groups ($P = 0.279$ and $P = 0.168$, respectively) (Table 2). Two-year EFS for endoscopic and histologic recurrences were 82.2% (95% CI 54.3%–93.9%) and 75.4% (95% CI 46.6%–90.0%), respectively, in the de-escalation group, whereas 89.9% (95% CI 77.5%–95.7%) and 89.7% (95% CI 76.9%–95.6%), respectively, in the control group ($P = 0.84$ and $P = 0.73$, respectively) (Fig. 2B, C). There were no significant differences in the risk of hospitalization or colectomy between the two groups (Table 2), as no patients in the study required colectomy, and only one patient in the control group required hospitalization.

We also compared outcomes between the 10 patients (41.7%) who were on no therapies and the 14 patients (58.3%) who remained on IBD therapy immediately after therapeutic withdrawal. No significant differences were found in the requirement of additional IBD therapies as well as clinical, endoscopic, or histologic recurrences between the two groups (Table S1).

Subgroup analysis of outcomes according to withdrawn therapy

Aminosalicylates. Twelve patients in the de-escalation group who were on aminosalicylates at the time of histological normalization had this therapy withdrawn. Oral, topical aminosalicylates, and both were used in 8 patients (67%), 3 patients (25%), and 1 patient (8.3%), respectively. Eight patients (66.7%) were on no therapies immediately after withdrawing aminosalicylates. Among the 4 patients (33.3%) who remained on other IBD therapies, 3 patients (75%) and 1 patient (25%) continued immunomodulators and infliximab, respectively. After withdrawal, 7 patients (58.3%), including 4 patients without therapies, eventually required additional IBD therapies, including aminosalicylates (5/7), immunomodulators (2/7), biologics (3/7), and steroids (2/7). Among them, 3 patients also required dose-escalation of therapies including aminosalicylates (1/3), immunomodulators (1/3), and biologics (2/3). Three patients did not have subsequent endoscopic or histologic assessments after therapeutic withdrawal. Clinical and endoscopic/histologic recurrence rates were 16.7% (2/12) and 44.4% (4/9), respectively (Table 3).

Immunomodulators. Nine patients in the de-escalation group were on immumomodulators at the time of histological normalization. Of those, only one patient (11.1%) was on no therapies immediately after withdrawal of immunomodulators. Among 8 patients (88.9%) who were maintained on other IBD therapies immediately after withdrawal of immunomodulators, 6 patients (75%) stayed on aminosalicylates and 2 patients (25%) who were treated with the combination therapy of immunomodulators and biologics remained on biologics, including infliximab with aminosalicylates (1/2) and vedolizumab (1/2). After withdrawal, 2 patients (25%) subsequently needed additional IBD therapies, including aminosalicylates (1/2) and vedolizumab (1/2). In the analysis of outcomes, 2 patients did not have subsequent endoscopic or histologic assessments and one patient did not have subsequent clinical assessment as well. Clinical and endoscopic/histologic recurrence rates were 0% (0/8) and 14.3% (1/7), respectively (Table 3).

Biologics/Advanced therapies. Three patients in the de-escalation group were on infliximab, and all of them discontinued infliximab. Two patients remained on aminosalicylates (66.7%) and one patient (33.3%) was not on any therapies immediately after withdrawal of infliximab. After withdrawal, one patients subsequently required topical aminosalicylates, cortisone, and adalimumab and another patient restarted infliximab with prednisone. One patient did not have subsequent endoscopic or histologic assessments. Clinical and endoscopic/histologic recurrence rates were 33.3% (1/3) and 50% (1/2), respectively (Table 3).

There were no patients in this analysis who were receiving other biological therapies, upadacitinib, or ozanimod.

Discussion

In this study, we assessed outcomes of patients with UC who withdrew therapies after achieving histologic normalization and demonstrated that

Table 1 | Demographic Characteristics of Patients with Ulcerative Colitis Who Have Achieved Histologic Normalizaiton (*N* = 111)

Age at diagnosis, median (IQR)	**29.7 (22.4–41.2)**
Sex, *n* (%)	
Female	58 (52.3)
Male	53 (47.7)
Disease duration, median (IQR)	23.9 (17.5-30.3)
Disease extent E3, *n* (%)	
Yes	70 (63.1)
No	41 (36.9)
Smoking status, *n* (%)	
No	68 (61.3)
Past	36 (32.4)
Current	7 (6.3)
PSC, *n* (%)	
Yes	3 (2.7)
No	108 (97.3)
Baseline Medications[a]	
5-ASA, *n* (%)	
Yes	109 (98.2)
No	2 (1.8)
IM, *n* (%)	
Yes	40 (36.0)
No	71 (64.0)
Biologics/JAK inhibitors, *n* (%)	
Yes	23 (20.7)[b]
No	88 (79.3)

ASA Aminosalicylates, *IM* Immunomodulators, *JAK* Janus kinase, *PSC* Primary sclerosing cholangitis.
[a]Medications ever before histologic normalization or therapeutic withdrawal.
[b]Only one patient with UC was treated with tofacitinib for polyarthritis as an extraintestinal manifestation.

Table 2 | Comparative analysis between the de-escalation and control groups

	De-escalation *N* = 24	**Control *N* = 87**	***P*-value**
Age at diagnosis, median (IQR)	29.2 (20.7-42.7)	30.0 (23.4-40.1)	0.505
Sex, *n* (%)			1
Female	13 (54.2)	45 (51.7)	
Male	11 (45.8)	42 (48.3)	
Disease duration, median (IQR)	22.8 (16.1-26.0)	24.4 (17.9-36.1)	0.122
Disease extent E3, *n* (%)			
Yes	17 (70.8)	53 (60.9%)	0.476
No	7 (29.2)	34 (39.1%)	
Smoking status, *n* (%)			
No	14 (58.3)	54 (62.1)	0.867
Past	9 (37.5)	27 (31.0)	
Current	1 (4.2)	6 (6.9)	
PSC, *n* (%)			
Yes	0 (0)	3 (3.4)	1
No	24 (100)	84 (96.6)	
Baseline medications[a]			
5-ASA *n* (%)			
Yes	23 (95.8)	86 (98.9)	0.387
No	1 (4.2)	1 (1.1)	
IM, *n* (%)			
Yes	14 (58.3)	26 (29.9)	0.016*
No	10 (41.7)	61 (70.1)	
Biologics/JAK inhibitors, *n* (%)			
Yes	8 (33.3)	15 (17.2)	0.095
No	16 (66.7)	72 (82.8)	
After withdrawal[b]			
5-ASA, *n* (%)			
Yes	14 (58.3)	70 (80.5)	0.033*
No	10 (41.7)	17 (19.5)	
IM, *n* (%)			
Yes	6 (25.0)	17 (19.5)	0.576
No	18 (75.0)	70 (80.5)	
Biologics/JAK inhibitors, *n* (%)			
Yes	9 (37.5)	20 (23.0)	0.19
No	15 (62.5)	67 (77.0)	
Start additional therapies or dose-escalation of therapies, *n* (%)[c]			
Yes	11 (47.8)	24 (29.3)	0.133
No	12 (52.2)	58 (70.7)	
Clinical recurrence, *n* (%)			
Yes	3 (13.0)	6 (7.3)	0.407
No	20 (87.0)	76 (92.7)	
Endoscopic recurrence, *n* (%)			
Yes	5 (27.8)	22 (43.1)	0.279
No	13 (72.2)	29 (56.9)	
Histologic recurrence, *n* (%)			
Yes	6 (33.3)	28 (56.0)	0.168
No	12 (66.7)	22 (44.0)	
Hospitalization, *n* (%)			

outcomes were not significantly different between the de-escalation group and the control group.

The most common components of deep remission include clinical remission and endoscopic mucosal healing[2]. The definition of mucosal healing has evolved to include endoscopic remission and histologic remission[13]. A systematic review and meta-analysis of 20 studies including 2265 patients with UC in clinical and endoscopic remission showed patients with histologic remission had a 61% lower risk of clinical relapse (relative risk, 0.39; 95% CI 0.31–0.51) compared with patients with persistent histologic activity, suggesting that combined endoscopic and histologic remission can be a preferred therapeutic target[14]. Given that the definition of histologic remission varies among studies, this meta-analysis standardized the definition of histologic remission as "the absence of neutrophiles in the epithelium"[14], corresponding to Geboes's score < 3.1[15]. To categorize histologic healing in patients with UC, the common perception was that structural histologic changes are permanent. Hence, classical histologic indices have not included histologic normalization as a distinct category[15–17] and feasibility and clinical benefits of histologic normalization in patients with UC have not been well described. Our group has been conducting studies which focus on histologic normalization in patients with UC[9,18] and demonstrated its clinical impacts on outcomes[9] by using our Chicago histologic scale, which distinguishes histologic normalization from histologic quiescence/active disease[10]. In the present study, we performed a case-control analysis to assess clinical

Table 2 (continued) | Comparative analysis between the de-escalation and control groups

	De-escalation $N = 24$	Control $N = 87$	*P*-value
Yes	0 (0.0)	1 (1.2)	1
No	23 (100.0)	81 (98.8)	
Colectomy, *n* (%)			
Yes	0 (0.0)	0 (0.0)	NA
No	23 (100.0)	82 (100.0)	

ASA Aminosalicylates, *IM* Immunomodulators, *JAK* Janus kinase, *PSC* Primary sclerosing cholangitis, *NA* Not available, *$p < 0.05$.

[a]Medications ever before therapeutic withdrawal in the de-escalation group and medications ever before histologic normalization in the control group.

[b]With regard to 5-ASA, IM, and biologics/JAK inhibitors, we included medications ever after therapeutic withdrawal in the de-escalation group and medications ever after histologic normalization in the control group.

[c]Medications included 5-ASA, IM, biologics/JAK inhibitors, and any type of steroids.

outcomes after therapeutic withdrawal following histologic normalization. Our analysis demonstrated that there were no significant differences in the risk factors of disease recurrence (extensive disease[19], younger age[20], and male gender[19,21]) and in the rate of patients who required additional IBD therapies after therapeutic withdrawal between the two groups. On the basis that patient backgrounds were similar between the two groups, we found no significant differences in the risk of clinical, endoscopic, or histologic recurrences. Our analysis also showed that outcomes between patients who were on no therapies and those who remained on some form of IBD therapy immediately after therapeutic withdrawal were not significantly different, suggesting that patients who have normalized histology are clinically stable after therapeutic withdrawal. Further studies are necessary to understand if histologic normalization is superior to "the absence of neutrophils in the epithelium", which is the commonly accepted definition of histologic remission[22], in improving clinical outcomes after therapeutic withdrawal.

Our subgroup analysis suggested that withdrawal of immunomodulators may be associated with a low risk of relapse when aminosalicylates or biologics are concomitantly used, whereas withdrawal of aminosalicylates and infliximab may increase the risk of relapse, regardless of histologic normalization. According to expert consensus regarding therapeutic withdrawal for patients with IBD conducted by the European Crohn's and Colitis Organization (ECCO), the cumulative risk of relapse after withdrawal of immunomodulators in IBD is estimated to be about 30% of patients by 2 years and 50%-75% of patients by 5 years[21]. A multicenter observational study of patients with IBD who withdrew azathioprine following deep remission defined as clinical, endoscopic, and biochemical remission showed that the rate of relapse (a partial Mayo index > 2) was 26% (9/35) in patients with UC during the median follow-up time of 36.7 months[23]. Their data revealed that 32 patients with UC (91%) were exposed to high doses of aminosalicylates after azathioprine withdrawal, though patients who treated with the combination of thiopurine and anti-TNF inhibitors were excluded. Similar to their findings, our subgroup analysis of patients who withdrew immunomodulators revealed that 89% of patients stayed on other IBD medications (88% aminosalicylates and 25% biologics) immediately after the withdrawal of immunomodulators. Our study found that the rate of patients who withdrew immunomodulators and subsequently required additional IBD therapies was the lowest (25%). Further, clinical and endoscopic/histologic recurrence rates after the withdrawal were 0% and 14%, respectively, demonstrating that the risk of relapse in patients who withdrew immunomodulators was the lowest among subgroups as well. Given that the majority of patients stayed on aminosalicylates immediately after withdrawing immunomodulators, it would be reasonable to consider withdrawal of immunomodulators with continuation of aminosalicylates or biologics (in our study this was only infliximab) after achieving histologic normalization because long-term use of immunomodulators are considerably associated with risks of neoplasms such as lymphoproliferative disorders[24], non-melanoma skin cancers[25], and myeloid disorders[26], and combination with anti-TNF therapies may further potentiate risk of neoplasm and infection[21]. Indeed, our analysis of baseline medications showed that the use of immunomodulators was significantly higher in the de-escalation group than in the control group, perhaps indicating patient awareness of potential safety concerns with immunomodulators. It remains important to consider pharmacokinetic changes that withdrawal of an immunomodulator may bring in patients on combination therapy with anti-TNF treatment.

Withdrawal of TNF inhibitors has several clinical benefits to minimize the risk of side effects such as infection and to reduce its expensive costs[21]. The expert consensus conducted by ECCO discusses that withdrawal of anti-TNF inhibitors is associated with a risk of relapse of 30–40% at 1 year and greater than 50% beyond 2 years, and patients who have needed anti-TNF dose escalation in their history seem to be at higher risk. With such potential for risk of disease relapse in mind, anti-TNF withdrawal may be considered only in patients in longstanding and stable deep remission from a clinical, biological, and endoscopic standpoint[21]. Our subgroup analysis found that among the three patients who discontinued infliximab following histologic normalization, 33% had clinical recurrence and 50% had endoscopic/histologic recurrence, which were the highest recurrence rates among subgroups, despite two patients remaining on concomitant aminosalicylates.

The consensus by ECCO[21] recommended that aminosalicylates should not be discontinued even in patients with UC who achieve deep remission because long-term treatment of aminosalicylates is generally safe and reduces the risks of relapse[27] and colorectal cancer[28]. However, not all patients require long-term aminosalicylates in the actual clinical setting. Although few studies have specifically examined the risk of recurrence after withdrawal of aminosalicylates[21], discontinuation of aminosalicylate monotherapy may be considered in some patients with proctitis[29], whereas withdrawal of aminosalicylates when used as monotherapy should be avoided in patients with risk factors for relapse, including extensive colitis and a history of frequent disease relapses[21]. Importantly, previous studies did not include histologic normalization as the marker of potentially "deeper remission" and a recent analysis by our group demonstrated the cost-effectiveness of discontinuing aminosalicylates in patients who are receiving advanced therapies[30]. In the current study, our subgroup analysis of patients who withdrew aminosalicylates after histologic normalization revealed that 67% of patients were on no IBD medications immediately after the withdrawal and the rates of clinical and endoscopic/histologic recurrence were 17% and 44%, respectively, which were close to the high relapse rates in patients who discontinued infliximab. Further, more than half of patients (58%) subsequently required additional IBD medications. Although our subgroup analysis suggested that withdrawal of anti-TNF inhibitors or aminosalicylates following histologic normalization may not be a preferable approach, further studies are necessary to confirm our findings because the number of patients in each subgroup was limited.

There are several strengths and limitations in this study. It is a significant strength that pathological reports of biopsy specimens were provided by our GI pathologists who have expertise in IBD and distinguished between normal histology and quiescent disease in UC based on our standard operating protocol. This is the first case-control study to compare outcomes in patients who withdrew therapies and those who did not after achieving normalized histology, and that clearly demonstrated the clinical stability in patients achieving histologic normalization even after therapeutic withdrawal. However, our study is limited as a retrospective study in a single tertiary center in that the interval of colonoscopies after histologic normalization was determined at the discretion of the provider and available clinical data was limited for some patients. In our study, the number of patients who withdrew therapies after histologic normalization was small. In particular, only 10 patients were off all IBD medications, and the number of

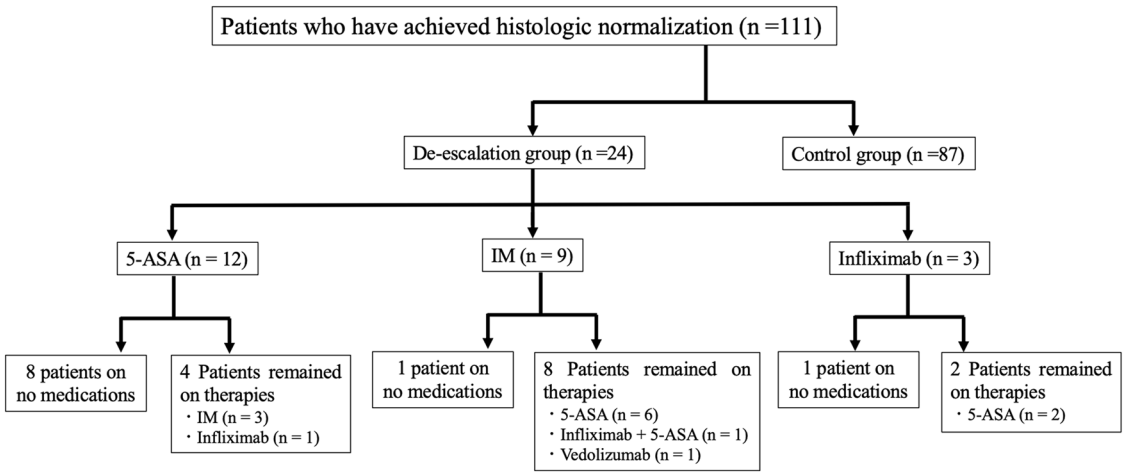

Fig. 1 | Study flow of the case-control study of patients with ulcerative colitis who had achieved histologic normalization. This study compared outcomes in those who de-escalated their medical therapy (the de-escalation group, $n = 24$) to those who continued their therapy (the control group, $n = 87$). ASA Aminosalicylates, IM Immunomodulators.

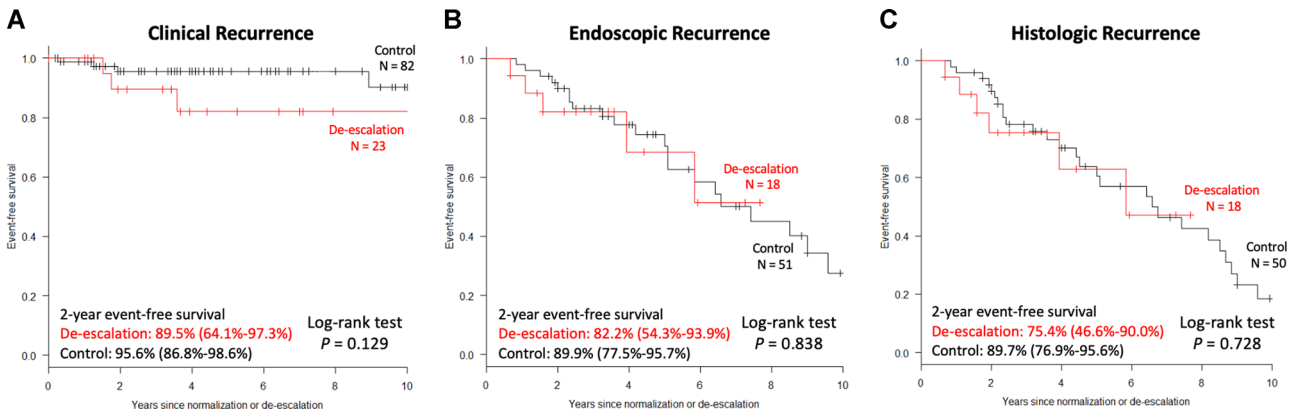

Fig. 2 | Outcomes between the de-escalation group and the control group. Kaplan-Meier curves of event-free survival for (**A**) clinical recurrence, (**B**) endoscopic recurrence, and (**C**) histologic recurrence.

Table 3 | Subgroup analysis of outcomes according to the type of withdrawn therapy

Type of withdrawn therapy	N	No IBD medications immediately after withdrawal	IBD medications immediately after withdrawal	Needed subsequent additional medications	Clinical recurrence rate	Endoscopic recurrence rate	Histologic recurrence rate	Endoscopic histologic recurrence rate
5-ASA	12	66.7% (8/12)	33.3% (4/12)[a]	58.3% (7/12)	16.7% (2/12)	44.4% (4/9)	44.4% (4/9)	44.4% (4/9)
IM	9	11.1% (1/9)	88.9% (8/9)[b]	25.0% (2/8)[d]	0% (0/8)	14.3% (1/7)	14.3% (1/7)	14.3% (1/7)
Biologics (Infliximab)	3	33.3% (1/3)	66.7% (2/3)[c]	66.7% (2/3)	33.3% (1/3)	0% (0/2)	50.0% (1/2)	50.0% (1/2)

ASA aminosalicylates, *IM* immunomodulators.
[a]Four patients remained on other IBD therapies including IM (3/4, 75%) and infliximab (1/4, 25%).
[b]Eight patients remained on other IBD therapies including 5-ASA (6/8, 75%), infliximab + 5-ASA, (1/8, 13%), and vedolizumab (1/8, 13%).
[c]Two patients remained on other IBD therapies including 5-ASA (2/2, 100%).
[d]One patient did not have any clinical follow-up after therapeutic withdrawal.

patients who withdrew infliximab was three. Hence, larger, multi-center studies are necessary to generalize our findings. Furthermore, given that 58% of patients stayed on concomitant IBD therapies immediately after therapeutic withdrawal, our data were limited in assessing outcomes in patients who discontinued monotherapy of each class of drug. It is notable that although this analysis explored the risk of recurrence after withdrawal of therapies, even among those patients who stayed on their therapies, the overall risk of clinical, endoscopic, and histologic relapses demonstrate that histological normalization is not a perfect outcome and that clearly we have more work to do to monitor the disease and to prevent recurrence in our patients with UC.

In conclusion, we demonstrated that patients with UC who have histologic normalization did not have a significant risk of disease recurrence after therapeutic withdrawal. Our findings support the clinical stability of therapeutic withdrawal in patients with UC who have normalized their histology and will inform further work in this important

area. The result of our subgroup analysis suggested that withdrawal of immunomodulators following histologic normalization may be reasonable in patients with UC if they are maintained on concomitant IBD medications. Further prospective studies are under way to confirm the clinical stability of therapeutic withdrawal following histologic normalization in patients with UC, which may support the use of histologic normalization as an achievable and widely accepted target for clinical and practice guidelines.

Methods

We performed a retrospective case-control study that included adult patients with a diagnosis of UC who achieved histologic normalization on colon biopsies, at the University of Chicago between December 1995 and January 2020. Histological normalization was defined below. Patients with histologic quiescence or active histological inflammation in any segment of the rectum or colon were excluded. This study received institutional board review approval (IRB 19-1554). The requirement for informed consent was waived by the Ethics Committee of the University of Chicago because of the retrospective nature of the study. All demographic and clinical data were recorded.

Data collection and clinical assessment

We retrospectively reviewed clinical charts and collected the following data: age at diagnosis of UC, sex, disease duration, disease extent based on Montreal classification (E1, proctitis; E2, left-sided disease; E3, extensive disease)[31], smoking status, primary sclerosing cholangitis (PSC) diagnosis, and IBD medication history, including oral or topical aminosalicylates, immunomodulators such as thiopurines and methotrexate, biologics, and small molecule agents before and after therapeutic withdrawal or histologic normalization (Table 1). We also assessed the proportion of patients who subsequently required the addition or escalation of IBD medications, including aminosalicylates, immunomodulators, biologics, small molecule agents, or steroids after therapeutic withdrawal or histologic normalization.

We use the Simple Clinical Colitis Activity Index (SCCAI)[32] to assess clinical disease activity in our routine clinical notes. Clinical recurrence was defined as SCCAI greater than 5.

Endoscopic assessment

To assess the endoscopic grade of inflammation, we used the Mayo endoscopic subscore criteria[33] in our endoscopic reports. A score of 0 was classified as normal or inactive disease, 1 (erythema, decreased vascular pattern, mild friability) as mild disease, 2 (marked erythema, absent vascular pattern, friability, erosions) as moderate disease, and 3 (spontaneous bleeding, ulceration) as severe disease. Endoscopic recurrence was defined as Mayo endoscopic subscore greater than 0.

Histologic assessment

Per the standard operating protocol at our institution, non-targeted segmental mucosal biopsies are obtained, targeting the lesion with the most significant mucosal disease activity. Our gastrointestinal pathologists report histopathology using the following categories: (1) histologic normalization, (2) histologic quiescence, and (3) histologic activity[9,10]. Histological normalization was defined as the lack of histopathological abnormalities, including crypt architectural distortion or active neutrophilic or plasmocytic infiltrates. Histologic quiescence was defined as features of chronicity including crypt atrophy or branching but no active inflammation, such as erosions, crypt abscesses, or focal neutrophil infiltration. Histologic activity was defined as the presence of any epithelial infiltration by neutrophils, crypt abscesses, erosions or ulceration[9,10]. For a patient to be considered as having a normal histology, all biopsies from all segments collected at the time of the colonoscopy should be categorized as normal. Histologic recurrence was defined as histologic activity in any segment.

Outcomes related to therapeutic withdrawal

Our primary outcome was clinical, endoscopic, or histologic recurrences after therapeutic withdrawal. Secondary outcomes included changes to therapy, including dose escalation or new medication start, rates of hospitalization and colectomy.

We divided patients into a de-escalation group and a control group. The de-escalation group included patients who were withdrawn from IBD therapies, including aminosalicylates, immunomodulators, and biologics, after achieving histologic normalization. The control group included patients who were not withdrawn from IBD therapies and were maintained on their current therapies following histologic normalization. We compared the primary outcomes between the de-escalation group and the control group. We excluded patients who did not have follow-up clinical visits or endoscopic or histologic evaluations after the date of achieving histologic normalization or the date of therapeutic withdrawal. We also excluded patients who had already developed the outcomes before or at the date of therapeutic withdrawal or histologic normalization. In the cases in which baseline SCCAI was missed, we performed a sensitivity analysis excluding them to assess clinical recurrence[34].

Fisher's exact test was used to compare the variables between the two groups. Event-free survival (EFS) was assessed from the date of histologic normalization or therapeutic withdrawal to the date of each outcome. Kaplan-Meier curve and log-rank test were used to compare EFS. P values < 0.05 were considered statistically significant. Data were analyzed by EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan)[35], which is a graphical user interface for R (The R Foundation for Statistical Computing, version 2.13.0, Vienna, Austria).

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Author contributions

SA and DTR contributed significantly to study concept and design. SA, JMS, CT, AS, VR, TGR, AIE, SRS, BC, and DTR contributed significantly to acquisition of data. SA, JSP, and DTR contributed significantly to analysis and interpretation of data. SA, JMS, CT, VR, and DTR contributed significantly to the drafting and critical revision of the manuscript. JSP contributed significantly to the critical revision of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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