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Budesonide Foam for Ulcerative Colitis Patients Experiencing Inadequate Response to Biological Therapy

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Background: In recent years, a plethora of therapeutic agents for ulcerative colitis (UC), especially novel biologics (Bio), have become available. Although it is now possible to use biological drugs, there should be no need for frequently changing medications. To avoid first-pass metabolism in the liver, thus reducing systemic bioavailability, budesonide foam has been applied as a topical steroid. We therefore evaluated whether budesonide foam has therapeutic value in UC patients who responded inadequately to Bio or to tacrolimus.

Material/Methods: We enrolled 10 patients who were experiencing an inadequate response to Bio (n=7) or to tacrolimus (n=3) at Juntendo University. We used Lichtiger's index to assess UC activity and clinical response.

Results: Of the study patients, 4 were receiving adalimumab, 3 golimumab, and 3 tacrolimus. The average Lichtiger's index before budesonide administration was 7.1 (range 13–3), which improved to 3.4 (range 7–0) after budesonide therapy (p=0.01). Notably, 4 of the 6 cases with a Lichtiger's index >4 before budesonide administration achieved improvement of ≥3 points or remission.

Conclusions: Although the number of patients was small, budesonide foam had significant efficacy when added to the treatment of patients having an inadequate response to Bio or to tacrolimus. These results suggest that in cases responding poorly to Bio, adding budesonide foam as combination therapy can achieve a clinical remission.

MeSH Keywords: Biological Therapy • Budesonide • Colitis, Ulcerative

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Background

Ulcerative colitis (UC), one of 2 major phenotypes of chronic inflammatory bowel disease (IBD), affects millions worldwide. Its symptoms impair function and quality of life [1,2]. Clinical manifestations of UC are abdominal discomfort, diarrhea, and hematochezia, while histologically UC is characterized by diffuse, continuous, superficial, and ulcerating inflammation confined to the large intestine (colon and rectum). The lesions of UC are continuous from the rectum and have the property of spreading into the proximal colon.

There has been a paradigm shift in the treatment of inflammatory bowel disease through the use of anti-tumor necrosis factor-α (TNF-α) agents that directly inhibit inflammatory cytokines [3]. In recent years, many therapeutic agents for UC have been developed. These include TNF-α agents (e.g., infliximab, adalimumab, and golimumab), an anti-integrin molecule (vedolizumab), and a Janus kinase inhibitor (tofacitinib), as well as tacrolimus, which is a calcineurin inhibitor [4–9]. Although it is now possible to use various medicines such as biologics (Bio), about 40% of patients who initially respond to anti-TNF-α therapy showed a secondary loss of response (LOR), often leading to discontinuing treatment [10]. In therapeutic settings, since treatment options are limited, it is important to persist with a current drug regimen until efficacy can be confirmed or denied to avoid changing to a new drug.

Budesonide is a topical second-generation corticosteroid that is rapidly metabolized in the liver and has low systemic bioavailability [11]. Thus, budesonide is thought to have a safety profile superior to that of conventional corticosteroids [12–15]. Applied rectally, budesonide foam may be efficacious in treating colonic mucosal inflammation in those with UC [16,17]. Because budesonide has a higher receptor affinity than other glucocorticoids, its topical potency is more than 200 times higher than that of hydrocortisone or prednisolone [18]. Therefore, budesonide has a high potential for anti-inflammatory and immunosuppressive therapy, with actions mainly limited to the sites of administration [11,18].

With foam preparations, drug spread is expanded, drug retention is optimized, and drug delivery is standardized compared with enema preparations [16,19]. Budesonide foam was reported to induce remission in mild-to-moderate ulcerative proctitis and ulcerative proctosigmoiditis [11] and healing of rectal lesions, which is a key step in the treatment of UC regardless of the spread of lesions [20]. Clinical remission through mucosal healing of distal lesions in left-sided colitis, pancolitis, or proctitis was also reported [21].

Based on this background, the present retrospective study evaluated the effect of adding budesonide foam to biotherapy for the treatment of patients who responded inadequately to Bio or to tacrolimus.

Material and Methods

Patients

In a retrospective setting, we reviewed an appropriately maintained database on consecutive patients with UC who had been treated with budesonide foam (brand name: RECTABUL 2mg®, 2 mg/25 ml) at Juntendo University between February 2018 and August 2018. Patient information was obtained from the prescription history in the hospital's electronic medical records.

The inclusion criterion was additional treatment with budesonide foam after a poor response to Bio or tacrolimus. Among the 86 patients treated with budesonide foam, 10 met the selection criterion.

Assessment of treatment efficacy

The Lichtiger's index (Tablde 1) [22] and the partial Mayo (p-Mayo) (Table 2) [23] score (Mayo score without endoscopy [24,25]) were used to evaluate the efficacy of budesonide foam in the 10 patients who met the selection criterion. Lichtiger's index ≤4 indicated clinical remission, and a decrease of ≥3 points from baseline in the Lichtiger's index score indicated a clinical response including remission. A p-Mayo score ≤2 and a score of ≤1 in all categories were indicative of clinical remission. Treatment efficacy had been determined at 6 weeks after initiating budesonide administration or when a patient's condition worsened. All patients had been regularly monitored for treatment-related adverse events.

Ethical considerations

Data presented here showed that all patients had been treated according to accepted clinical practice with approved medications. Our protocol for this retrospective investigation was reviewed and approved by the Juntendo University Hospital Ethics Committee (IRB No.18-025). This study adhered to the principles of the Declaration of Helsinki.

Statistical analyses

When appropriate, Lichtiger's index and p-Mayo scores were compared by the Wilcoxon signed-rank test. All statistical tests were done using a 5% significance level.

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Table 1. Lichtiger's index.

Symptom	Score
Diarrhea (No. of daily stools)	
0 to 2	0
3 or 4	1
5 or 6	2
7 to 9	3
10	4
Nocturnal diarrhea	
No	0
Yes	1
Visible blood in stool (% of movements)	
0	0
<50	1
≥50	2
100	3
Fecal incontinence	
No	0
Yes	1
Abdominal pain or cramping	
None	0
Mild	1
Moderate	2
Severe	3
General well-being	
Perfect	0
Very good	1
Good	2
Average	3
Poor	4
Terrible	5
Abdominal tenderness	
None	0
Mild and localized	1
Mild-to-moderate and diffuse	2
Severe or rebound	3
Need for antidiarrheal drugs	
No	0
Yes	1

The Lichtiger's index ranges from 0 to 21, with higher scores indicating more severe disease. Data are from Lichtiger et al. [22].

Results

Patient characteristics

Table 3 provides information on the 10 patients (6 males and 4 females; age range 35–62 years, mean age 47.2 years) who satisfied our inclusion criterion. Mean disease duration was 8.7 years. Clinical manifestations of UC in these 10 patients were pancolitis in 4 and left-sided colitis in 6. These 10 patients had previously received oral 5-aminosalicylate (5-ASA). Additionally, 4, 3, and 3 cases, respectively, were not responding well to adalimumab (AbbVie GK, Tokyo, Japan), golimumab (Mitsubishi Tanabe Pharma Corporation, Osaka, Japan), and tacrolimus (Astellas Pharma, Inc., Tokyo, Japan). The median duration of administration of these drugs was 9.1 months [range 1.6–64.1 months]. None of the 10 patients was satisfied with the treatment they were receiving and these 10 patients were selected to receive additional treatment with budesonide foam. Budesonide was administered twice a day in 4 patients and once a day in 6 patients. Before budesonide foam treatment, in 5 cases, the blood inflammatory marker C-reactive protein (CRP) level was low due to pretreatment medications. The mean CRP was 0.46±0.55 before treatment and 0.35±0.59 after treatment, a difference that was not statistically significant. Similarly, the mean hemoglobin value was 12.26±1.35 before treatment and 12.41±1.15 after treatment, with no significant difference. Although budesonide foam had been effective, one of the 10 patients was excluded from the analysis because symptoms could not be confirmed adequately by the Lichtiger's index.

Changes in the Lichtiger's index

Figure 1A shows the Lichtiger's index scores before and after budesonide foam treatment in the remaining 9 study patients. Stool frequency before budesonide treatment was high and the average Lichtiger's index score was 7.1 (range 3–13 points). In 4 of the 9 cases, the pretreatment UC activity level based on Lichtiger's index was mild, with scores of 3–5. Therefore, in these mild cases it was difficult to distinguish differences between before and after budesonide foam therapy. Nonetheless,

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Table 2. Partial Mayo score.

	Score
Stool frequency*	
Normal no. of stools for this patient	0
1–2 stools more than normal	1
3–4 stools more than normal	2
5 or more stools more than normal	3
Rectal bleeding**	
No blood seen	0
Streaks of blood with stool less than half the time	1
Obvious blood with stool less than half the time	2
Blood alone passed	3
Physician's global assessment***	
Normal	0
Mild disease	1
Moderate disease	2
Severe disease	3

The partial Mayo (p-Mayo) score is the Mayo score minus the endoscopy score. The p-Mayo score ranges from 0 to 9, with higher scores indicating more severe disease. Data are modified from Schroeder et al. [23]. * Each patient served as his or her own control to establish the degree of abnormality of stool frequency; **The daily bleeding score represented the most severe bleeding of the day; *** The Physician's Global Assessment acknowledged the 2 other criteria (stool frequency and rectal bleeding), the patient's daily record of abdominal discomfort, general sense of well-being, and other observations, such as physical findings and the patient's performance status.

Table 3. Clinical characteristics of patients.

Age (years)	47.2 (35–62)
Sex Male: Female, n	6: 4
Disease duration (years)	8.7 (1–21)
Location Left-sided colitis, n (%) Pancolitis, n (%)	 6 (60%) 4 (40%)
Pretreatments, % 5-ASA Corticosteroids Thiopurine Anti-TNF-α therapy Adalimumab Golimumab Tacrolimus Extended-release Tacrolimus	 100% 10% 40% 70% 40% 30% 20% 10%
Clinical activity Lichtiger's index (range)	 7.1 (3–13)
Data at start of the treatment Hb (g/dL) CRP (mg/dL)	 12.26±1.35 0.46±0.55

Disease duration is expressed as mean (range). Data are expressed as mean±SD. ASA – aminosalicylic acid; TNF – tumor necrosis factor; Hb – hemoglobin; CRP – C-reactive protein; SD – standard deviation.

overall statistically significant differences were observed before and after budesonide treatment (p=0.012).

In a separate analysis of the subgroup of patients with Lichtiger's index >4 before treatment, the response rate was 66.7% (4/6) (Figure 1B). In 2 patients (Case 3 and Case 5), budesonide foam was ineffective. However, in 2 severe cases,

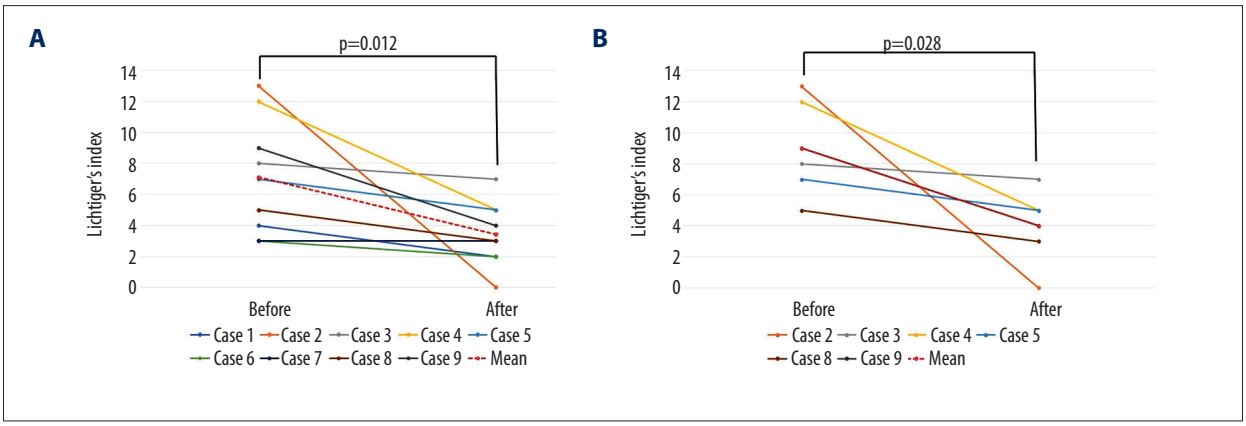

Figure 1. Variations in the Lichtiger's index. (**A**) All patients, (**B**) patients who had Lichtiger's index >4 before treatment. A significance level of 0.05 was employed using the Wilcoxon signed-rank test.

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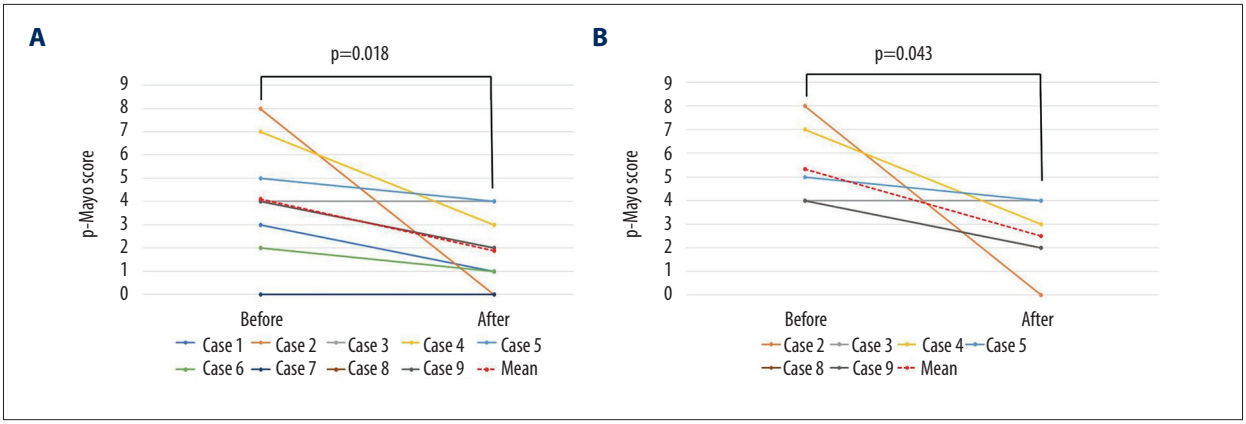

Figure 2. Variations in the partial Mayo score (p-Mayo score). (**A**) All patients, (**B**) patients who had p-Mayo score ≥4 before treatment. Statistical analyses were performed at a significance level of 0.05 by using the Wilcoxon signed-rank test.

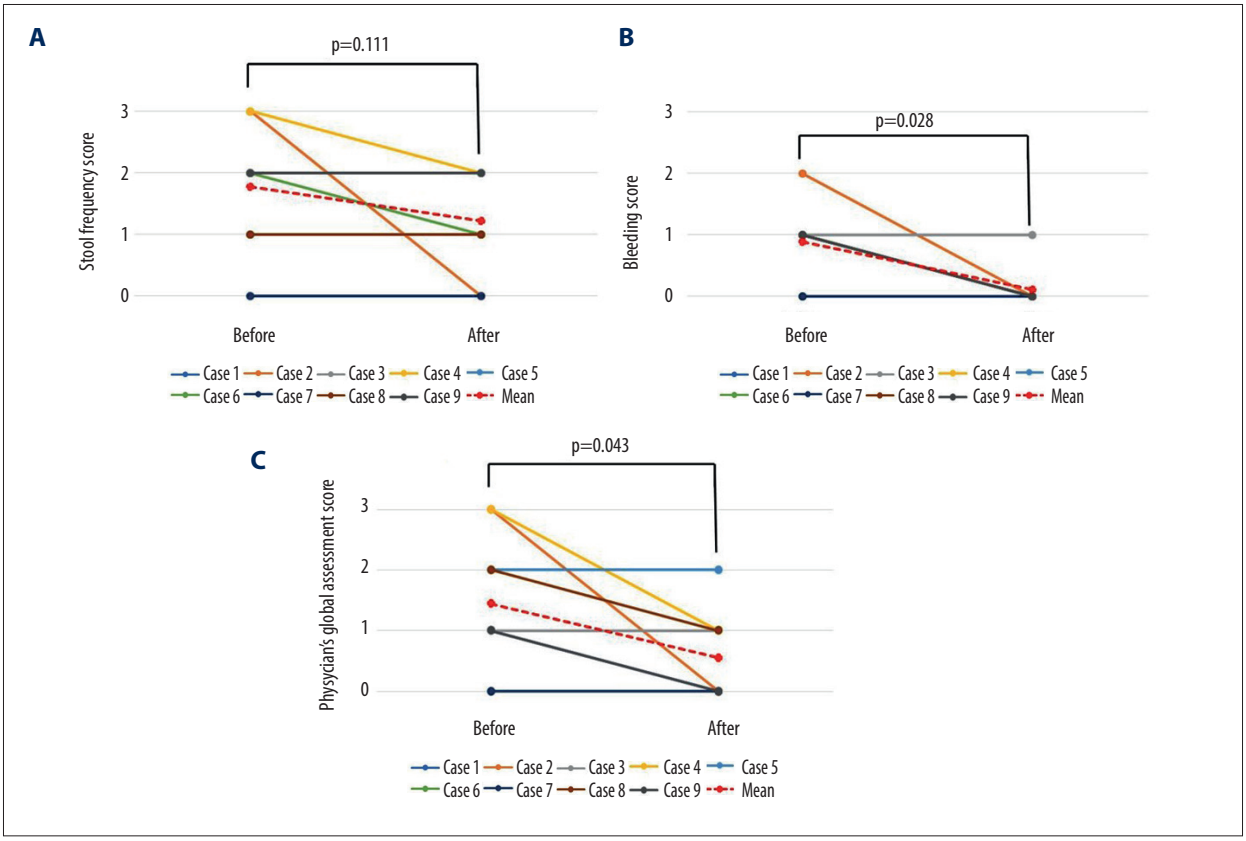

Figure 3. Subscore of p-Mayo score. (**A**) Stool frequency score of p-Mayo score, (**B**) Bleeding score, (**C**) Physician's Global Assessment score. Statistical analyses were performed at a significance level of 0.05 by using the Wilcoxon signed-rank test.

the Lichtiger's index improved from 13 to 0 (Case 2) and from 12 to 5 (Case 4).

Changes in the partial Mayo score (p-Mayo score)

Regarding clinical remission, the average p-Mayo score before budesonide treatment was 4.1 (range 0–8), which improved to 1.9 at week 6 (p=0.018) (Figure 2A). In a subgroup analysis of patients with a p-Mayo score ≥4 before treatment, the clinical remission rate showed 50.0% efficacy (3 of 6 cases). The overall p-Mayo score improved from 5.3 to 2.5 (p=0.043) (Figure 2B).

The bleeding score was improved, with statistical significance, from 0.9 to 0.1 (p=0.028) (Figure 3B), and the Physician's Global Assessment score was improved from 1.4 to 0.6 (p=0.043) (Figure 3C). The stool frequency score was improved from

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1.8 to 1.2 (p=0.111). However, stool frequency did not differ significantly (Figure 3A).

In the subgroup analysis of patients with p-Mayo scores ≥4 before treatment, the bleeding score was improved, with statistical significance, from 1.2 to 0.2 (p=0.043) (Figure 4B). The stool frequency score improved from 2.2 to 1.5 (p=0.183) and the Physician's Global Assessment score improved from 2.0 to 0.8 (p=0.424) (Figure 4A, 4C), but without a statistically significant difference.

Budesonide foam was shown to be safe and well tolerated by all study patients. No serious adverse events occurred, such as an infectious disease that required specific treatment or discontinuation of budesonide foam, nor were there minor adverse events such as moon face or hyperglycemia.

Treatment history and outcomes in 2 typical cases

Case 2. A 39-year-old man was treated at our hospital for UC. His medical history included a diagnosis 19 years previously of relapsing-remitting, left-side colitis-type UC. Additionally, his UC was a steroid-dependent refractory case. Initially, he had achieved clinical remission with adalimumab, but after 4 months he experienced LOR. After receiving budesonide foam therapy twice a day for 1 week and then once a day, his Lichtiger's index improved from 13 to 1 at week 3. His UC remained in remission with the administration of budesonide foam once every few days.

Case 4. A 54-year-old woman received treatment at our hospital for UC. Her medical history included a diagnosis 9 years previously of relapsing-remitting, left-side colitis-type UC. Due to LOR, her treatment had been changed from infliximab to golimumab. However, because of inadequate efficacy, she had used concomitant steroid enemas. This patient used budesonide foam once a day and her Lichtiger's index improved from 12 to 5 after 6 weeks. Clinical remission (Lichtiger's index 3) was achieved at week 9. Although she discontinued the use of budesonide foam, she remained in remission with golimumab during a 30-week follow-up (Figure 5).

Discussion

We assessed the efficacy of budesonide foam in patients with active UC despite treatment with Bio or with the calcineurin inhibitor tacrolimus, which is an approved and widely used medication in Japan. Budesonide foam showed promising efficacy in this clinical setting, although the number of study patients was small. The overall response rate was 67%, and efficacy was sustained in those patients who responded. More interestingly, the UC was affected at sites well beyond the site of application. All respondent patients had reduced stool frequency. The bleeding score most greatly reflected the effect of treatment, improving in 86% of patients (6/7). On the other hand, although the stool frequency score and the Physician's Global Assessment scores improved, statistically significant differences in these parameters could not be determined, primarily because of the small sample size.

Topical formulations were shown to be effective in rectal and left-side colitis in UC patients. Data on clinical remission at week 6 were reported by 4 randomized controlled trials. In these 4 trials, clinical remission rates induced by budesonide foam ranged from 38.3% to 50.9% [11,21,26,27]. Complete mucosal healing with the use of budesonide foam in distal lesions and clinical remission were reported to be 31.8% and 40.9%, respectively, in the proctitis subgroup and 35.5% and 41.9%, respectively, in the left-sided colitis group [21]. Further, according to Naganuma et al., topical preparations were also effective for pancolitis-type UC [21]. Complete mucosal healing of distal lesions and clinical remission occurred in 27.3% and 36.4% of patients, respectively, in the pancolitis subgroup [21]. In fact, 5-ASA suppositories were effective in treating mucosal lesions as well as inducing clinical remissions in patients with pancolitis and left-sided colitis [20]. Thus, complete mucosal healing of distal lesions can be considered to improve systemic clinical symptoms in those with UC [20,21]. Local control helps to improve patient's quality of life. Furthermore, the budesonide foam was well tolerated, and most patients preferred the foam to enemas (83.6% versus 6.2%, respectively) [16]. In cases of 5-ASA treatment failure, a treatment algorithm in which the use of budesonide foam has been recommended was proposed [17]. Although the present cases were refractory with an inadequate response to Bio or tacrolimus, as previously reported, budesonide foam achieved the equivalent therapeutic effect in mild-to-moderate cases who did not use biologics [20,21].

Treatment modalities for UC have changed greatly with the appearance of biologic agents, but many patients who initially respond may experience LOR with time. However, our view is that there should be no need for frequently changing from one biological drug to another. Therefore, since optimization of therapy is highly important, LOR to biologics limits the therapeutic options for IBD patients who fail anti-TNF therapy. In light of this reality, alternative novel agents, including anti-interleukin-23 antibodies and Janus kinase inhibitors, may offer alternative options in the near future. Nonetheless, the optimal use of anti-TNF agents is crucial to improve treatment efficacy, reduce adverse effects, and manage costs [28]. Measurement of anti-drug antibodies and therapeutic drug monitoring are important to optimize serum drug levels, especially in patients with LOR to these agents. According to the European Crohn's and Colitis Organisation statement guidelines, confirmed LOR to an anti-TNF agent should be managed

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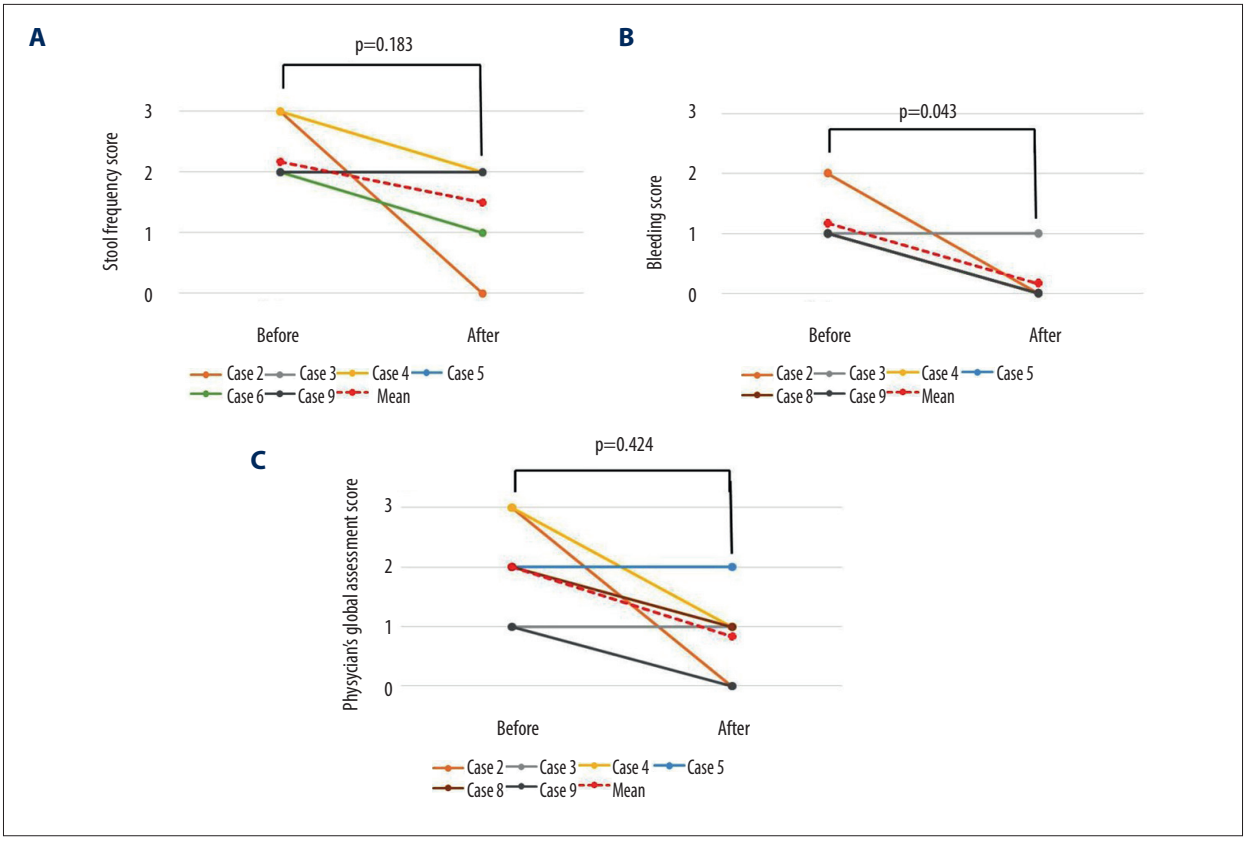

Figure 4. Subscore of p-Mayo score in patients whose p-Mayo score was 4 or more before treatment. (**A**) Stool frequency score, (**B**) Bleeding score, (**C**) Physician's Global Assessment score. Statistical analyses were performed at a significance level of 0.05 by using the Wilcoxon signed-rank test.

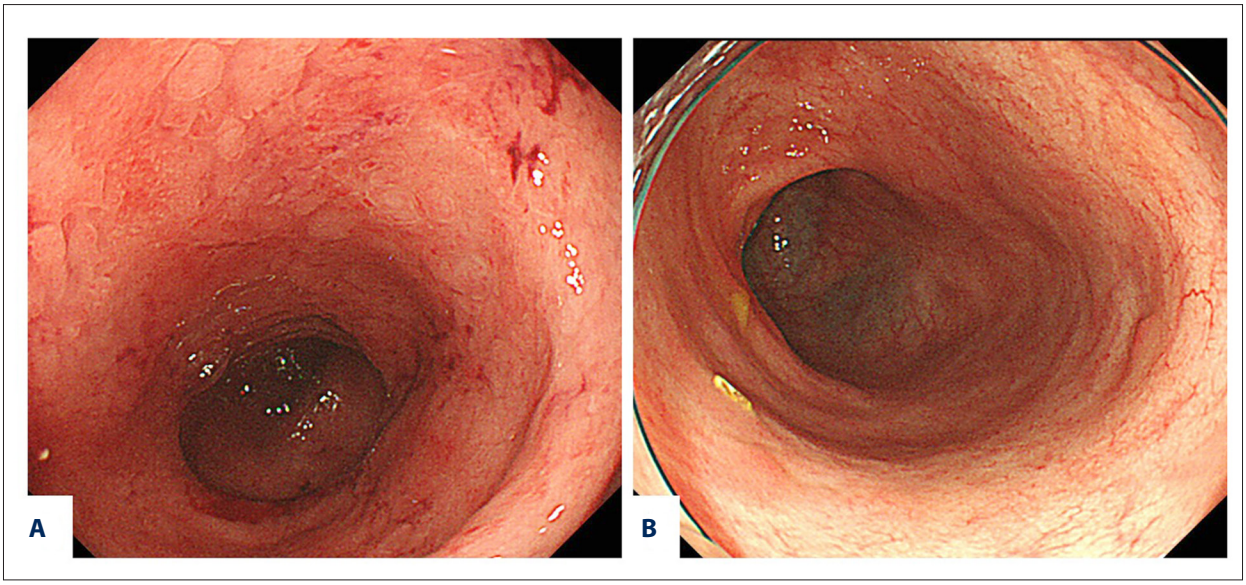

Figure 5. Endoscopic findings (case 4). Endoscopic findings in a 54-year-old woman with left-side colitis-type UC. (**A**) Before budesonide foam treatment, (**B**) after budesonide foam treatment.

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by dose optimization. Dose escalation and interval shortening are equally recommended to optimize treatment and are equivalent strategies. If dose escalation is ineffective, switching to another agent (within or out of class) can be a reasonable treatment option [29]. We believe, however, that inducing remission by combining budesonide foam with a currently ineffective biologic therapy could be an alternative strategy to optimize efficacy. Combining a current therapy, though ineffective, with budesonide foam, would be worth trying if a time delay were needed before switching to another agent. Achieving clinical remission in the early stage of treatment positively affects quality of life and costs, since maintaining and achieving an early remission should minimize the need for additional treatments. Although it is a topical formulation, budesonide is a steroid, and, therefore, its administration should be gradually decreased and, when feasible, discontinued.

This study had some limitations. Firstly, the number of cases was small, and larger samples are needed to further determine if the use of budesonide is efficacious. Secondly, as this was a retrospective study, we could not fully evaluate the contribution of concomitant medications on the efficacy of budesonide foam. Therefore, a prospective study is necessary. Thirdly, endoscopic evaluation before and after treatment was not possible. Endoscopic remission is known as a therapeutic goal for UC. However, in refractory cases, obtaining clinical remission is an important task in practice settings. We believe that data from a large sample in a prospective, randomized, double-blind multicenter study with a focus on patient selection is necessary for better positioning of budesonide foam in the treatment of IBD. We also believe that treatment assessment by endoscopy is necessary.

Conclusions

Our experience in this small cohort of patients in whom UC was not responding well to biologics or to tacrolimus suggests that budesonide foam may be a safe and effective option in this clinical setting. Further studies of a larger cohort of UC patients, preferable in a multicenter setting, are warranted to fully evaluate the efficacy of budesonide foam as a concomitant add-on medication for UC patients.

Conflict of interest

None

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