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 $\geq3$ 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

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/918562
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 (Table 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.
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 foam 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,
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, 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,
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 9 to 5 (Case 2) and from 8 to 2 (Case 4).

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.
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.

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...
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.
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

**References:**

1. Irvine Ei: Quality of life of patients with ulcerative colitis: Past, present, and future. Inflamm Bowel Dis, 2008; 14: 554–65
2. Moradkhani A, Beckman LJ, Tabibian JH: Health-related quality of life in inflammatory bowel disease: Psychosocial, clinical, socioeconomic, and demographic predictors. J Crohns Colitis, 2013; 7: 476–73
3. Peyrin-Biroulet L, Deltenre P, de Suray N et al: Efficacy and safety of tumor necrosis factor antagonists in Crohn’s disease: Meta-analysis of placebo-controlled trials. Clin Gastroenterol Hepatol, 2008; 6: 644–53
4. Rutgeert’s P, Sandborn WJ, Feagan BG et al: Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med, 2005; 353: 2462–76
5. Reineis W, Sandborn WJ, Hommes DW et al: Adalimumab for clinical remission in moderately to severely active ulcerative colitis: Results of a randomised controlled trial. Gut, 2011; 60: 780–87
6. Sandborn WJ, Feagan BG, Marano C et al: Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology, 2014; 146: 85–95
7. Feagan BG, Rutgeerts P, Sands BE et al: Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med, 2013; 369: 699–710
8. Sandborn WJ, Su C, Sands BE et al: Tofacitinib as induction and maintenance therapy for ulcerative colitis. N Engl J Med, 2013; 369: 376: 1723–36
9. Ogata H, Kato J, Hirai F et al: Double-blind, placebo-controlled trial of oral tacrolimus (FK506) in the management of hospitalized patients with steroid-refractory ulcerative colitis. Inflamm Bowel Dis, 2012; 18: 803–8
10. Ben-Horin S, Chowery V: Review article: loss of response to anti-TNF treatments in Crohn’s disease. Aliment Pharmacol Ther, 2011; 33: 987–95
11. Sandborn WJ, Bosworth B, Takko S et al: Budesonide foam induces remission in patients with mild to moderate ulcerative proctitis and ulcerative proctosigmoiditis. Gastroenterology, 2015; 148: 740–50
12. Yokoyama K, Kobayashi K, Muke M et al: Clinical study of the relation between mucosal healing and long-term outcomes in ulcerative colitis. Gastroenterol Res Pract, 2013; 2013: 192794
13. Edsbäcker S, Bengtsson B, Larsson P et al: A pharmacocinetic graphic evaluation of oral budesonide given as controlled-release (Entocort) capsules. Aliment Pharmacol Ther, 2003; 15(17): 525–36
14. Edsbäcker S, Larsson P, Wollner P: Gut delivery of budesonide, a locally active corticosteroid, from plain and controlled-release capsules. Eur J Gastroenterol Hepatol, 2002; 14: 1357–62
15. Dignass A, Lindsay IJ, Sturm A et al: Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: Current management. J Crohns Colitis, 2012; 6: 991–1030
16. Gross V, Bar-Meir S, Lavy A et al: Budesonide foam versus budesonide enema in active ulcerative proctitis and proctosigmoiditis. Aliment Pharmacol Ther, 2006; 23: 303–12
17. Pokrotek’s I, Sitkin S: A proposed treatment algorithm for mild to moderate ulcerative colitis with an emphasis on budesonide foam and mucosal healing. J Gastroenterol, 2018; 53: 799–800
18. Bratthand R: Overview of newer glucocorticosteroid preparations for inflammatory bowel disease. Can J Gastroenterol, 1990; 4: 407–14
19. Brunner M, Vogelsang H, Greinwald R et al: Colonic secretory and positional pharmacokinetics of budesonide foam in patients with mildly to moderately active ulcerative colitis. Aliment Pharmacol Ther, 2005; 22: 463–70
20. Watanabe M, Nishino H, Sameshima Y et al: Randomised clinical trial: Evaluation of the efficacy of mesalamine (mesalazine) suppositories in patients with ulcerative colitis and active rectal inflammation – a placebo-controlled study. Aliment Pharmacol Ther, 2013; 38: 264–73
21. Naganuma M, Aoyama N, Tada T et al: Complete mucosal healing of distal lesions induced by twice-daily budesonide 2-mg foam promoted clinical remission of mild-to-moderate ulcerative colitis with distal active inflammation: Double-blind, randomized study. J Gastroenterol, 2018; 53: 494–506
22. Lichtiger S, Present DH, Kombluth A et al: Cyclosporine in severe ulcerative colitis refractory to steroid therapy. N Engl J Med, 1994; 330: 1841–45
23. Schroeder KW, Tremaine WJ, Istrup DM: Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med, 1987; 317: 1625–29
24. Sandborn WJ, Sands BE, Wolf DC et al: Repifermin (keratinocyte growth factor-2) for the treatment of active ulcerative colitis: A randomized, double-blind, placebo-controlled, dose-escalation trial. Aliment Pharmacol Ther, 2003; 17: 1355–64

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25. Rutgeerts P, Sandborn WJ, Feagan BG et al: Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med, 2005; 353(23): 2462–76

26. Naganuma M, Aoyama N, Suzuki Y et al: Twice-daily budesonide 2-mg foam induces complete mucosal healing in patients with distal ulcerative colitis. J. Crohns Colitis, 2016; 10: 828–36

27. Bosworth BP, Sandborn WJ, Rubin DT, Harper JR: Baseline ural 5-ASA use and efficacy and safety of budesonide foam in patients with ulcerative proctitis and ulcerative proctosigmoiditis: Analysis of 2 phase 3 studies. Inflamm Bowel Dis, 2016; 22: 1881–86

28. van der Valk ME, Mangen MJ, Leenders M et al: Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNF alpha therapy: Results from the COIN study. Gut, 2014; 63: 72–79

29. Gomollón F, Dignass A, Annese V et al: 3rd European Evidence-Based Consensus on the Diagnosis and Management of Crohn’s Disease 2016: Part 1: Diagnosis and medical management. J Crohns Colitis, 2017; 11: 3–25