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Budesonide Foam Induces Remission in Patients With Mild to Moderate Ulcerative Proctitis and Ulcerative Proctosigmoiditis

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BACKGROUND & AIMS: Budesonide is a high-potency, second-generation corticosteroid designed to minimize systemic adverse consequences of conventional corticosteroids. We performed 2 randomized, phase 3 trials to evaluate the ability of budesonide rectal foam, formulated to optimize retention and provide uniform delivery of budesonide to the rectum and distal colon, to induce remission in patients with ulcerative proctitis or ulcerative proctosigmoiditis. **METHODS:** Two identically designed, randomized, double-blind, placebo-controlled trials evaluated the efficacy of budesonide foam for induction of remission in 546 patients with mild to moderate ulcerative proctitis or ulcerative proctosigmoiditis who received budesonide foam 2 mg/25 mL twice daily for 2 weeks, then once daily for 4 weeks, or placebo. **RESULTS:** Remission at week 6 occurred significantly more frequently among patients receiving budesonide foam than placebo (Study 1: 38.3% vs 25.8%; $P = .0324$; Study 2: 44.0% vs 22.4%; $P < .0001$). A significantly greater percentage of patients receiving budesonide foam vs placebo achieved rectal bleeding resolution (Study 1: 46.6% vs 28.0%; $P = .0022$; Study 2: 50.0% vs 28.6%; $P = .0002$) and endoscopic improvement (Study 1: 55.6% vs 43.2%; $P = .0486$; Study 2: 56.0% vs 36.7%; $P = .0013$) at week 6. Most adverse events occurred at similar frequencies between groups, although events related to changes in cortisol values were reported more frequently with budesonide foam. There were no cases of clinically symptomatic adrenal insufficiency. **CONCLUSIONS:** Budesonide rectal foam was well tolerated and more efficacious than placebo in inducing remission in patients with mild to moderate ulcerative proctitis and ulcerative proctosigmoiditis. ClinicalTrials.gov ID: NCT01008410 and NCT01008423.

Keywords: Inflammatory Bowel Disease; Ulcerative Colitis; Budesonide; Ulcerative Proctosigmoiditis.

Ulcerative proctitis (UP) and ulcerative proctosigmoiditis (UPS) are part of the spectrum of ulcerative colitis (UC), an idiopathic chronic inflammatory disease of the colon that is believed to be immune-mediated.[1] Approximately 46% of patients with UC are diagnosed with UP or UPS.[2,3] Clinical UC symptoms include rectal bleeding, diarrhea, urgency, tenesmus, and abdominal pain.[1] Oral or rectal mesalamine is often administered as first-line therapy.[4,5] Suppositories and liquid enemas are recommended for the induction of remission in patients with mild to moderate UP, and they can be administered alone or in combination with oral mesalamine when mild to moderate disease extends beyond the rectum.[1,6,7] However, these rectal therapies have several limitations, including difficulty of administration, retention, and limited proximal spread. For example, suppositories disperse no further than the rectum, and while liquid enemas can spread to the splenic flexure, they are difficult for patients to retain and require patients to remain recumbent for a specified period of time after administration.[1,8,9]

Although active UP and UPS can be treated effectively with systemic corticosteroids,[6,10–12] their use can result in adverse effects, including mood and sleep changes, Cushingoid appearance, weight gain, fluid retention, acne, and hirsutism; longer-term use of systemic steroids can lead to more serious adverse effects, such as increased risk of infections, decreased bone density, ocular complications (eg, glaucoma, cataracts), and adrenal insufficiency.[6,13] There remains an unmet need for therapies that can target the area of active inflammation and yet have fewer systemic effects than conventional steroids.

High-potency, second-generation corticosteroids, including budesonide and beclomethasone, can be administered either rectally or orally to produce a topical anti-inflammatory effect. Budesonide has nearly 90% first-pass hepatic metabolism, thus reducing the potential for corticosteroid-related adverse events (AEs).[13–15] A randomized, double-blind, dose-ranging study of patients with active UP or distal UC receiving budesonide enema demonstrated efficacy (ie, increased rate of remission vs placebo, improved endoscopic inflammation and histology scores

Abbreviations used in this paper: **ACTH, adrenocorticotropic hormone; AE, adverse event; UC, ulcerative colitis; UP, ulcerative proctitis; UPS, ulcerative proctosigmoiditis.**

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relative to baseline) for up to 6 weeks.[16] In an active comparator study of patients with active UP, UPS, or left-sided UC, budesonide enema had a safety profile similar to that of mesalamine enema, although mesalamine enema induced remission in a significantly greater percentage of patients compared with budesonide enema (77.2% vs 63.5%, respectively; $P < .05$).[17] Beclomethasone foam and enema were shown to have efficacy and safety profiles similar to those observed for mesalamine foam and enema in patients with mild to moderate UP or UPS after 8 weeks.[18]

Budesonide foam is a new rectal formulation of budesonide that optimizes drug retention and provides uniform drug delivery to the rectum and distal colon, with a maximal spread of up to 40 cm (mean, 25.4 cm).[19] Budesonide foam had an efficacy profile comparable with that of hydrocortisone foam for treatment of UP and UPS, with no significant impact on cortisol concentrations or increased occurrence of corticosteroid-related AEs when administered for up to 8 weeks.[20] A majority of patients with active UP or UPS preferred a steroid foam formulation to a steroid enema formulation.[21] To evaluate the efficacy and safety of budesonide foam relative to placebo in patients with active, mild to moderate UP and UPS, we conducted 2 identically designed, 6-week, double-blind induction trials.

Methods

Patients

Patients aged 18 years and older with active UP or UPS extending at least 5 cm, but no further than 40 cm from the anal verge, were eligible for enrollment. Patients had mild to moderate disease, with a baseline Modified Mayo Disease Activity Index score (hereafter referred to as "Mayo score") between 5 and 10, inclusive, with subscale ratings of $\geq$2 for endoscopic appearance and rectal bleeding. The Mayo score is the sum of 4 subscale scores: stool frequency, rectal bleeding, endoscopic findings, and a physician's global assessment. Since publication of the original Mayo Disease Activity Index,[22] the endoscopy subscale was modified such that patients with any degree of friability are classified as having a subscale score of 2.

Exclusion criteria included evidence of Crohn's disease or indeterminate colitis, significant comorbid condition, a positive stool test for bacterial pathogens (*Clostridium difficile* toxin, or ovum and parasites), and adrenal insufficiency, defined as a measurement of $<$18 μg/dL serum cortisol after adrenocorticotropic hormone (ACTH) challenge. Medication restrictions included use of systemic, oral, topical, or rectal corticosteroids; laxatives; enemas; treatments for irritable bowel syndrome (eg, alosetron, lubiprostone); anticoagulants; rectal mesalamine therapies; oral mesalamine therapies at dosages of $>$4.8 g/d; narcotics; antibiotics; and antidiarrheal medications (eg, loperamide, bismuth subsalicylate).

The protocol was approved by institutional review boards and ethics committees. All patients provided written informed consent. All authors had full access to the study data and reviewed and approved the final manuscript.

Study Design

Two identically designed, phase 3, randomized, double-blind, placebo-controlled, multicenter studies (Study 1 [ClinicalTrials.gov ID: NCT01008410] and Study 2 [ClinicalTrials.gov ID: NCT01008423]) were conducted in the United States and Russia during November 2009 to March 2013 (Study 2) or to April 2013 (Study 1). Patients were assigned to a treatment group via a randomization schedule, stratified by study center, generated by an interactive voice response system/interactive web response system. Patients were randomized in a 1:1 allocation to receive budesonide rectal foam 2 mg/25 mL or placebo twice daily for 2 weeks, then once daily for 4 weeks. Concomitant use of oral mesalamine drugs at a stable dosage of up to 4.8 g/d was permitted. Each study consisted of a screening phase (completed within 7 days of randomization), a single-blind run-in/stabilization phase of 4 to 7 days, a 6-week double-blind treatment phase, and a 2-week follow-up phase (Supplementary Figure 1). Via administration of a placebo, the single-blind run-in/stabilization phase allowed patients to practice and familiarize themselves with appropriate use of the foam delivery device before the treatment phase of the study. Patients were required to meet inclusion criteria after the run-in/stabilization phase to continue in the study. A colonoscopy was required for patients newly diagnosed or without a confirmed diagnosis of UC within 12 months of the screening visit. Colonoscopy, if needed, was performed no more than 10 days, and no less than 4 days, before randomization. If a colonoscopy was not required, patients were scheduled for sigmoidoscopy 4 to 7 days before randomization. Histology results from the colonoscopy were required from patients with newly diagnosed UC, before randomization, to confirm active UP or UPS.

Assessments

The primary efficacy end point was the percentage of patients achieving remission at week 6 (defined as an endoscopy subscore $\leq$1, rectal bleeding subscore of 0, and improvement or no change from baseline in the stool frequency subscore of the Mayo score). Scores ranged from 0 to 3 for each subscore of the Mayo score (endoscopy subscore: 0 = normal or inactive disease, 1 = mild disease, 2 = moderate disease, 3 = severe disease; rectal bleeding subscore: 0 = no blood seen, 1 = streaks of blood with stool less than half the time, 2 = obvious blood with stool most of the time, 3 = blood alone passed; stool frequency subscore: 0 = normal number of stools per day for each individual patient, 1 = 1 to 2 stools more than normal, 2 = 3 to 4 stools more than normal, 3 = $\geq$5 stools more than normal; physician's global assessment subscore: 0 = normal, 1 = mild disease, 2 = moderate disease, 3 = severe disease). Endoscopic disease extent and activity were determined by local investigators.

Key secondary efficacy end points included the percentage of patients achieving a Mayo rectal bleeding subscore of 0 at week 6, the number of scheduled assessments (weeks 1, 2, 4, and 6) in which patients had a rectal bleeding subscore of 0, and the percentage of patients achieving a Mayo endoscopy subscore of 0 or 1 at week 6. Safety assessments included monitoring of AEs, clinical laboratory tests (including morning cortisol concentrations and ACTH challenge tests), and vital signs. For purposes of reporting