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Baseline Oral 5-ASA Use and Efficacy and Safety of Budesonide Foam in Patients with Ulcerative Proctitis and Ulcerative Proctosigmoiditis: Analysis of 2 Phase 3 Studies

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Background: Rectal budesonide foam is a second-generation corticosteroid efficacious for active mild to moderate ulcerative proctitis and ulcerative proctosigmoiditis. This subgroup analysis examined the impact of baseline oral 5-aminosalicylic acid (5-ASA) on the efficacy and safety of budesonide foam in patients with mild to moderate ulcerative proctitis or ulcerative proctosigmoiditis.

Methods: Patients received budesonide foam 2 mg/25 mL twice daily for 2 weeks, then once daily for 4 weeks, or placebo, with or without continued stable dosing of baseline oral 5-ASAs, for remission induction at week 6 (primary endpoint) in 2 identically designed, randomized, double-blind, phase 3 studies.

Results: Of the 267 and 279 patients randomized to treatment with budesonide foam or placebo (pooled population), 55.1% and 55.2%, respectively, reported baseline 5-ASA use. A significantly greater percentage of patients achieved remission with budesonide foam versus placebo, either with (42.2% versus 31.8%, respectively; $P = 0.03$) or without (40.0% versus 14.4%; $P < 0.0001$) baseline 5-ASA use at week 6. A significantly greater percentage of patients achieved a Modified Mayo Disease Activity Index rectal bleeding subscale score of 0 at week 6, regardless of baseline 5-ASA use (5-ASA, 50.3% versus 35.7%; $P = 0.003$: no 5-ASA, 45.8% versus 19.2%; $P < 0.0001$). The frequency of adverse events was comparable between groups, regardless of baseline 5-ASA use.

Conclusions: Budesonide foam was efficacious and safe for induction of remission of mild to moderate ulcerative proctitis and ulcerative proctosigmoiditis in patients receiving oral 5-ASA at baseline and those who were not (Clinicaltrials.gov: NCT01008410 and NCT01008423).

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Key Words: budesonide foam, corticosteroid, ulcerative proctitis, ulcerative proctosigmoiditis, 5-aminosalicylic acid

Ulcerative colitis (UC), a chronic inflammatory bowel disease, extends proximally from the rectum through the length of the colon.[1] Ulcerative proctitis (UP) involves inflammation limited to the rectum distal to the rectosigmoid junction, whereas ulcerative proctosigmoiditis (UPS) involves rectal and sigmoid inflammation without involvement of the descending colon. UC has been estimated to affect approximately 0.3% of the US population, or 960,000 patients; 46% of patients have UP or UPS.[2,3]

Current guidelines recommend rectal corticosteroids as second-line therapy for the induction of remission of patients with UP or UPS.[4–6] Rectal therapies have a limited proximal distribution, with suppositories localized to the rectum, and foams and enemas capable of spreading to the sigmoid colon and splenic flexure, respectively.[7–11] A combination of rectal and oral therapy is generally more efficacious than either alone for the induction of remission of UC, even in patients with extensive UC.[4,5] This may be related to uniform drug distribution across affected segments in the colon.[12]

Rectal budesonide foam is a second-generation corticosteroid that provides uniform delivery of budesonide to the distal colon for the treatment of UP and UPS.[13] Budesonide foam has been shown to be safe and efficacious for the treatment of patients with active UP or UPS in 2 identically designed, randomized, double-blind, placebo-controlled studies.[14] More than half of patients in each of these studies used 5-aminosalicylic acids (5-ASAs) concomitantly with budesonide foam. In this study, the impact of baseline use of oral 5-ASA on the efficacy and

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safety of budesonide foam for the induction of remission of UP and UPS was examined in patients with mild to moderate disease.

MATERIALS AND METHODS

Patients

Details of the patient population, along with inclusion and exclusion criteria, have been previously described.[14] In brief, patients ≥18 years of age with active UP or UPS extending ≥5 cm, but no further than 40 cm, from the anal verge were eligible for enrollment in the studies (Clinicaltrials.gov: NCT01008410 and NCT01008423). Patients had a baseline Modified Mayo Disease Activity Index (MMDAI) score ≥5 but ≤10, with subscale ratings ≥2 for rectal bleeding and endoscopic appearance. The MMDAI score is the sum of 4 subscale scores: stool frequency, rectal bleeding, endoscopic appearance, and physician's global assessment. Since publication of the original MMDAI,[15] the endoscopic appearance subscale was modified to classify patients with any degree of friability with a subscale score of 2. Exclusion criteria included the use of systemic, oral, topical, or rectal corticosteroids or laxatives or enemas (other than mesalamine) during the preceding 14 days. Concomitant use of a stable oral 5-ASA regimen was permitted at doses up to 4.8 g/d. Rectal 5-ASA use was discontinued during the run-in phase of the study (i.e., 4–7 days before randomization) and was not permitted during the studies.

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

Details of the study design have been previously described.[14] In brief, 2 identically designed, phase 3, randomized, double-blind, placebo-controlled, multicenter studies were conducted in the United States and Russia (BUCF3001 [Clinicaltrials.gov identifier NCT01008410] and BUCF3002 [Clinicaltrials.gov identifier NCT01008423]). Each study was comprised of a 2-week screening phase, a run-in/stabilization phase of 4 to 7 days, a 6-week treatment phase, and a 2-week follow-up phase (Fig. 1). During the run-in phase, patients received single-blind placebo rectal foam twice daily, to familiarize themselves with study drug administration. In the treatment phase of each study, patients were randomized 1:1 to receive budesonide rectal foam 2 mg/25 mL twice daily for 2 weeks, then once daily for 4 weeks, or matching placebo. A colonoscopy was required for patients with newly diagnosed UC or without a confirmed diagnosis of UC within 12 months of the screening visit. Colonoscopy, if necessary, was performed no greater than 10 days and no less than 4 days before randomization. For patients not meeting the requirement for colonoscopy, a sigmoidoscopy was scheduled 4 to 7 days before randomization.

Assessments

Subgroup analyses for the primary, key secondary, and safety endpoints were performed for patients with baseline oral 5-ASA use (i.e., at the time the first study dose [budesonide foam or placebo] was received) during the studies. The primary efficacy endpoint was the percentage of patients achieving remission (defined as MMDAI endoscopy subscale score ≤1, MMDAI rectal bleeding subscale score 0, and improvement or no change from baseline in MMDAI stool frequency subscale score) at week 6. Scores ranged from 0 to 3 for each MMDAI subscale (endoscopy subscale score: 0 = normal or inactive disease, 1 = mild disease, 2 = moderate disease, 3 = severe disease; rectal bleeding subscale score: 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 subscale score: 0 = normal number of stools per d for each individual patient, 1 = 1 to 2 stools more than normal, 2 = 3 to 4 stools more than normal, 3 = ≥5 stools more than normal; physician's global assessment subscale score: 0 = normal, 1 = mild disease, 2 = moderate disease, 3 = severe disease). Endoscopic disease extent and activity were determined by local investigators.

Key secondary efficacy endpoints included the percentage of patients achieving an MMDAI rectal bleeding subscale score of 0 and the percentage of patients achieving an MMDAI endoscopy subscale score ≤1 at week 6. Safety endpoints included monitoring of adverse events (AEs), laboratory parameters (including morning cortisol concentrations and adrenocorticotropic hormone challenge tests), and vital signs.

Statistical Analyses

The intent-to-treat population included all patients randomized to treatment. The safety population included all patients in the intent-to-treat population who received ≥1 dose of study drug. Pooled data were analyzed using the Cochran–Mantel–Haenszel test adjusted for study and country. The last observation carried forward method was used for missing data.

RESULTS

Patient Disposition and Demographics

Of the patients receiving budesonide foam (n = 267) and placebo (n = 279) in the pooled intent-to-treat population, 147 (55.1%) and 154 (55.2%) patients, respectively, reported baseline 5-ASA use during the double-blind treatment phase of the studies. There were no significant differences in demographic and baseline characteristics across groups, regardless of baseline 5-ASA use (Table 1). Most patients in each group had UPS (range, 59.2%–79.9%). Most patients had moderate UC at baseline (MMDAI score 7–10).

Efficacy

Significant treatment effects favored budesonide foam versus placebo for the percentage of patients achieving remission

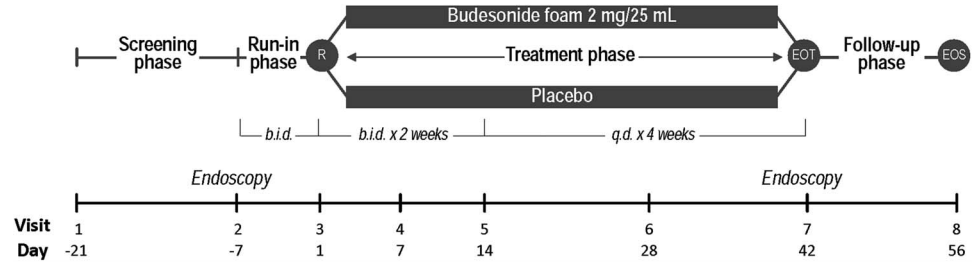

FIGURE 1. Study design. b.i.d., twice daily; EOS, end of study; EOT, end of trial; q.d., once daily; R, randomization.

(primary endpoint), as well as patients with an MMDAI rectal bleeding subscale score of 0 at week 6 (key secondary endpoint),[14] regardless of whether patients reported baseline 5-ASA use (Fig. 2). Treatment with budesonide foam induced remission in a significantly greater percentage of patients with or without baseline oral 5-ASA use compared with placebo at week 6 (5-ASA, 42.2% versus 31.8%, respectively; $P = 0.03$: no 5-ASA, 40.0% versus 14.4%; $P < 0.0001$). A significantly greater percentage of patients receiving budesonide foam achieved an MMDAI rectal bleeding subscale score of 0, regardless of baseline oral 5-ASA use at week 6 (5-ASA, 50.3% versus 35.7%; $P = 0.003$: no 5-ASA, 45.8% versus 19.2%; $P < 0.0001$). A significant treatment effect for achieving an MMDAI endoscopy subscale score of 0 or 1 was observed in patients receiving budesonide foam versus placebo without baseline use of oral 5-ASAs (55.8% versus 31.2%; $P = 0.0004$); however, while treatment with budesonide foam was

TABLE 1. Demographic and Baseline Characteristics (Intent-to-treat Population)

	Budesonide Foam 2 mg/25 mL		Placebo	
Parameter	5-ASA (n = 147)	No 5-ASA (n = 120)	5-ASA (n = 154)	No 5-ASA (n = 125)
Age, mean (SD), yr	45.4 (13.9)	41.7 (13.2)	42.6 (13.8)	40.6 (12.5)
Male sex, n (%)	62 (42.2)	61 (50.8)	64 (41.6)	51 (40.8)
Race, n (%)				
White	130 (88.4)	104 (86.7)	146 (94.8)	112 (89.6)
Other	17 (11.6)	16 (13.3)	8 (5.2)	13 (10.4)
Duration of disease, mean (SD), yr	5.7 (7.5)	4.0 (5.3)	5.1 (6.5)	3.4 (5.0)
Extent of disease, n (%)[a]				
Proctitis	28 (19.0)	44 (36.7)	31 (20.1)	50 (40.0)
Proctosigmoiditis	117 (79.6)	76 (63.3)	123 (79.9)	74 (59.2)
Missing	2 (1.4)	0	0	1 (0.8)
Baseline MMDAI total score, mean (SD)	8.0 (1.2)	7.7 (1.2)	8.0 (1.2)	7.9 (1.3)
Severity of disease[b], n (%)				
Mild	14 (9.5)	14 (11.7)	15 (9.7)	19 (15.2)
Moderate	132 (89.8)	105 (87.5)	139 (90.3)	106 (84.8)
Severe	1 (0.7)	1 (0.8)	0	0
Baseline MMDAI rectal bleeding subscore, n (%)				
0	0	1 (0.8)	0	0
1	2 (1.4)	2 (1.7)	0	3 (2.4)
2	125 (85.0)	103 (85.8)	137 (89.0)	99 (79.2)
3	20 (13.6)	14 (11.7)	17 (11.0)	23 (18.4)
Baseline MMDAI endoscopy subscore, n (%)				
0	0	0	0	0
1	0	0	0	0
2	126 (85.7)	111 (92.5)	138 (89.6)	116 (92.8)
3	21 (14.3)	9 (7.5)	16 (10.4)	9 (7.2)

[a]Proctitis was defined as disease limited to the rectum (up to ~15 cm); proctosigmoiditis was defined as disease limited to the rectum and sigmoid colon (up to ~40 cm).
[b]Mild (MMDAI score, 4–6), moderate (MMDAI score, 7–10), severe (MMDAI score, 11–12).

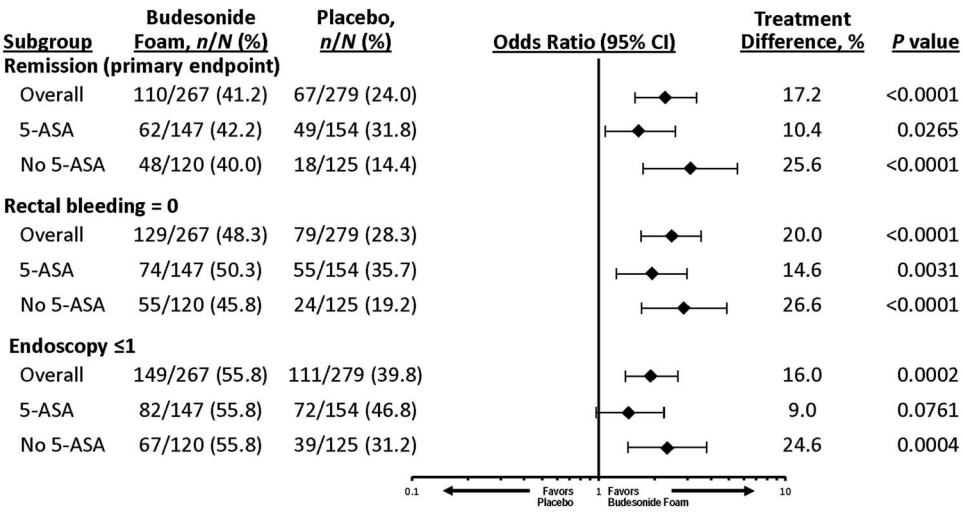

FIGURE 2. Patients achieving primary and key secondary outcome measures at week 6.

favored compared with placebo, the treatment difference for the subgroup of patients with baseline oral 5-ASA use did not reach statistical significance (55.8% versus 46.8%; $P = 0.08$). Furthermore, although the rates of response for the 2 subgroups of patients (baseline 5-ASA use versus no 5-ASA use) were comparable across the primary and key secondary efficacy endpoints, the treatment effect favoring budesonide foam was relatively greater in the subgroup of patients without baseline 5-ASA use. Patients with baseline oral 5-ASA use had greater response rates with placebo compared with patients without baseline oral 5-ASA use.

Safety

The safety profile of budesonide foam was comparable between patients with and without baseline oral 5-ASA use during the studies (Table 2). Most AEs were mild or moderate in intensity. The most common AEs (≥2% in the budesonide foam group) occurred with comparable frequency in patients with and without baseline 5-ASA use: blood cortisol decreased (20% versus 14%, respectively), adrenal insufficiency (3% versus 4%), headache (3% versus 2%), and nausea (1% versus 3%).

DISCUSSION

The overall results of the 2 identically designed, randomized, placebo-controlled studies demonstrated that a significantly greater percentage of patients with active, mild to moderate UP or UPS receiving budesonide foam achieved remission at week 6 (primary efficacy endpoint) compared with placebo (41.2% versus 24.0%, respectively; $P < 0.0001$).[14] Furthermore, a significantly greater percentage of patients receiving budesonide foam

TABLE 2. Summary of AEs (Safety Population)

	Budesonide Foam 2 mg/25 mL		Placebo	
AE, n (%)	5-ASA (n = 147)	No 5-ASA (n = 121)	5-ASA (n = 154)	No 5-ASA (n = 124)
Any AE	64 (43.5)	59 (48.8)	56 (36.4)	45 (36.3)
Serious AE	4 (2.7)	1 (0.8)	1 (0.6)	2 (1.6)
AE leading to discontinuation	16 (10.9)	10 (8.3)	10 (6.5)	2 (1.6)
Most common AEs[a]				
Decreased blood cortisol	29 (19.7)	17 (14.0)	3 (1.9)	3 (2.4)
Adrenal insufficiency[b]	5 (3.4)	5 (4.1)	1 (0.6)	1 (0.8)
Nausea	2 (1.4)	4 (3.3)	2 (1.3)	0
Headache	4 (2.7)	2 (1.7)	2 (1.3)	5 (4.0)
Abdominal pain	1 (0.7)	3 (2.5)	2 (1.3)	2 (1.6)
Fatigue	0	3 (2.5)	0	2 (1.6)

[a]AEs reported in ≥2% of patients in either budesonide subgroup.
[b]Adrenal insufficiency was defined as having a serum cortisol concentration of ≤18 μg/dL at 30 minutes after adrenocorticotropic hormone challenge.

achieved secondary outcome measures of rectal bleeding resolution (48.3% versus 28.3%; $P < 0.0001$) and endoscopic improvement (55.8% versus 39.8%; $P = 0.0002$).[14] The results of this analysis suggest that budesonide foam was efficacious and safe for induction of remission of mild to moderate UP or UPS in patients receiving oral 5-ASA at baseline and those who were not. These findings are comparable with the overall findings of Sandborn et al.[14] Furthermore, baseline oral 5-ASA use had no apparent effect on the safety profile of budesonide foam. The AE profile was comparable with that reported by Sandborn et al.[14]

Baseline oral 5-ASA use has been reported in a number of clinical studies of rectal therapies for the induction of remission of mild to moderate distal forms of UC; however, these studies did not perform further efficacy or safety analyses in patients with baseline use of oral 5-ASAs.[16–18] In a double-blind, double-dummy, randomized, comparative study of budesonide foam and budesonide enema in patients with active UP or UPS, response or lack of response to oral 5-ASA therapy had no significant effect on the percentage of patients in clinical remission with either treatment after 4 weeks.[16] Furthermore, results of a randomized, double-blind, placebo-controlled study of patients with extensive mild to moderate UC demonstrated that concomitant treatment with oral and rectal 5-ASAs improved efficacy compared with oral 5-ASAs alone after 4 and 8 weeks.[19] These studies suggest that baseline oral 5-ASA use does not aberrantly affect the efficacy of rectal therapies in patients with UP or UPS.

Rectal 5-ASAs are currently the first-line treatment for patients with active, mild to moderate UP or UPS.[4–6] Pooled analysis demonstrated that treatment with rectal 5-ASAs was associated with significant symptomatic improvement, endoscopic improvement, and histologic improvement, as well as symptomatic remission, endoscopic remission, and histologic remission, compared with placebo in patients with distal forms of UC.[12] However, the second-generation corticosteroid budesonide foam has demonstrated efficacy and safety in patients with mild to moderate UP and UPS,[14] thus providing patients who fail treatment with rectal 5-ASAs a safe and efficacious therapeutic option.[20] Furthermore, patients with UP or UPS preferred foam to enema (83.6% versus 6.2%, respectively) in a head-to-head comparison study of these budesonide formulations.[16] The findings of this study further support the use of budesonide foam in patients with active mild to moderate UP or UPS, regardless of baseline oral 5-ASA use.

Limitations of this study include the fact that further analyses stratified by the various formulations of 5-ASA and by the range of 5-ASA doses were not conducted because of sample size limitations. Although the combination of oral and rectal 5-ASA therapies had greater efficacy than oral or rectal 5-ASA monotherapy for the treatment of mild to moderate UP or UPS,[4] it is possible that some patients in this study had recently discontinued rectal 5-ASA monotherapy. Whereas the findings of this analysis favored treatment with budesonide foam, regardless of whether patients were using 5-ASAs, additional prospective studies are warranted to further examine the potential benefit of oral 5-ASAs or other oral agents (e.g., budesonide multi-matrix) in combination with budesonide foam in patients with mild to moderate UP or UPS. In conclusion, budesonide foam was efficacious and well tolerated for the induction of remission in patients with active, mild to moderate UP and UPS receiving oral 5-ASAs at baseline, as well as in those who were not.

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