

Systematic Review: Rectal Therapies for the Treatment of Distal Forms of Ulcerative Colitis

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Background: Many therapeutic options are available for patients with distal forms of ulcerative colitis (UC). Rectal therapies (e.g., suppositories, foams, gels, and enemas) may be recommended either alone or in combination with oral treatment. Compared with oral therapies, rectal therapies are underused in patients with distal forms of UC, although rectal therapies have favorable efficacy and safety profiles.

Methods: This systematic review identified 48 articles for inclusion after a comprehensive PubMed search and the identification of additional relevant articles through other sources. Inclusion criteria were clinical studies examining efficacy and safety of 5-aminosalicylic acid, corticosteroid, and non-5-aminosalicylic acid rectal therapies (suppositories, foams, gels, and enemas) that induce or maintain remission in patients with ulcerative proctitis, ulcerative proctosigmoiditis, or left-sided colitis (i.e., distal forms of UC). The quality of the evidence presented was evaluated using the GRADE system.

Results: Overall, a greater percentage of patients with distal forms of UC receiving 5-aminosalicylic acids or corticosteroid rectal formulations derived greater therapeutic benefit after treatment compared with patients receiving placebo. Furthermore, most uncontrolled studies of rectal therapies reported that patients with distal forms of UC had marked improvement from baseline after treatment. The overall safety profile of rectal therapies was favorable. Treatment with second-generation corticosteroids, such as budesonide and beclomethasone dipropionate, did not increase the incidence of steroid-related adverse effects.

Conclusions: The current literature supports the use of rectal therapies for both induction and maintenance of remission in patients with distal forms of UC.

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Key Words: suppository, enema, foam, corticosteroid, 5-ASA

Ulcerative colitis (UC) affects approximately 600,000 individuals in the United States.^{1–3} Approximately, 63% of patients with UC are diagnosed with ulcerative proctitis (UP), ulcerative proctosigmoiditis (UPS), or left-sided colitis (i.e., distal forms of UC).^{4,5} The American College of Gastroenterology Practice Guidelines, published in 2010, identified topical or oral formulations of 5-aminosalicylic acid (5-ASA) and topical corticosteroids, as recommended treatment for patients with mild-to-moderate distal forms

of UC.⁶ The authors considered combination therapy with topical and oral 5-ASA agents to be superior to monotherapy and found a clear role for topical mesalamine agents in patients who have disease refractory to oral 5-ASA or topical corticosteroids.

The distribution of drug in rectal therapies varies by mode of delivery: the medication dispersion of suppositories is limited to the rectum, foam extends to the sigmoid and descending colon, and enemas may reach all the way to the splenic flexure.⁷ Compared with oral therapies, rectal therapies offer a number of advantages, including direct delivery of drug to inflammation sites in the distal colon, rapid response of patients to treatment, once-daily dosing, and reduced systemic drug exposure.^{6,8} However, despite the potential advantages of rectal therapies, these agents are underused for the treatment of patients with distal forms of UC.^{6,9} For example, one study reported that although oral therapy was used in 29.5%, 42.8%, and 35.6% of patients with UP, UPS, or left-sided colitis, respectively, rectal therapy was only used by 25.6% of patients with UP, 6.9% with UPS, and 6.7% with left-sided colitis.⁹ Although the number of 5-ASA prescriptions increased by 6-fold between 1992 and 2009, the percentage of prescriptions for rectal 5-ASAs declined from 11% to 9%. This is potentially because of difficulties with the administration of rectal therapy (e.g., leakage and bloating) and inconvenience, particularly among patients requiring multiple daily doses, as well as patient and health care provider reluctance to use rectal therapies.^{8,10,11} These limitations are countered by evidence that use of rectal therapy was the

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strongest predictor of patient adherence to treatment after 3 months,¹² and a number of short- and long-term clinical studies of rectal therapies have demonstrated that most patients with UC are compliant with treatment.^{13–17} Providing patients with a targeted therapy that also offers rapid relief of clinical symptoms has the potential to quickly and effectively improve quality of life⁸ and maintain clinical and endoscopic remission of UC.^{18,19}

This systematic review was conducted to examine the current state of the literature regarding the efficacy and safety of rectal therapies for the management of distal forms of UC (i.e., UP, UPS, and left-sided colitis). A number of meta-analyses and systematic reviews have examined the therapeutic modalities available for patients with UC, but these studies either were not restricted to rectal therapies^{20,21} or were limited to an evaluation of a particular class of therapy.²² The current review examines rectal therapies, including suppository, foam, gel, and enema formulations of 5-ASAs, corticosteroids, and non-5-ASA agents, and provides ratings for the quality of the evidence.

METHODS

Literature Search

Studies were identified by conducting a PubMed search of English-language articles using the following key words: “suppository,” “foam,” “gel,” “enema,” “ulcerative colitis,” “steroid,” “mesalamine,” “5-aminosalicylate,” “hydrocortisone,” “hydrocortisone acetate,” “immune modulators,” “antibiotic,” “clotrimazole,” and “antifungal.” Articles were restricted to those involving adult humans and included comparative studies, meta-analyses, and reviews (including systematic reviews) published between January 1, 2004, and December 31, 2013. A separate PubMed search of clinical trials (phase I–IV), controlled clinical trials, and randomized controlled trials was not time-restricted. Reference lists in all relevant studies and review articles were examined to identify additional articles for inclusion. Clinical studies of pouchitis or cuffitis and case reports were excluded from the review.

Efficacy outcomes analyzed in the current systematic review were limited to those defined as primary efficacy outcomes in the identified publications. When no primary efficacy outcome was defined, efficacy outcomes included the findings presented, especially those findings that overlapped with efficacy outcomes of other studies for comparative purposes. Safety outcomes were also evaluated, including adverse events (AEs), drug-related AEs, and AEs that resulted in patients discontinuing from the studies.

Rating the Quality of the Evidence

An adaptation of the GRADE system was used to determine the quality of evidence for the efficacy of rectal therapies for inducing or maintaining UC remission.²³ The quality of the evidence was categorized as “high,” “moderate,” “low,” or “very low.” Study design was the primary factor used to rank the quality of evidence, with randomized placebo-controlled trials providing the strongest evidence, followed by, in decreasing

strength of evidence, randomized, active-controlled studies, other controlled studies, and, finally, observational studies. Additional factors considered in determining the quality of the evidence were study limitations (e.g., lack of blinding), inconsistency of results (e.g., variability in results), indirectness of the evidence (e.g., lack of head-to-head trials, differences in study outcomes), and imprecision (e.g., small sample size, large confidence intervals).

RESULTS

Identification of Studies

A total of 307 articles were identified by searching PubMed, and an additional 4 articles were identified through other sources. After removal of duplicates, a total of 199 studies were evaluated for inclusion in this systematic review, with 48 studies finally identified for qualitative assessment (Fig. 1). Review articles, pre-clinical studies (e.g., animal or cell line models), studies of patients with Crohn’s disease, studies of oral or intravenous therapies, and studies that failed to mention rectal therapy were removed from further qualitative analysis. No studies of hydrocortisone rectal therapies or corticosteroid suppositories or gels met the final inclusion criteria for this review. Similarly, no studies of antimicrobial agents were eligible for qualitative analysis.

5-ASA Rectal Therapies

5-ASA Suppositories

The efficacy and safety of 5-ASA suppositories for the treatment of patients with distal UC (i.e., UP, UPS, and left-sided

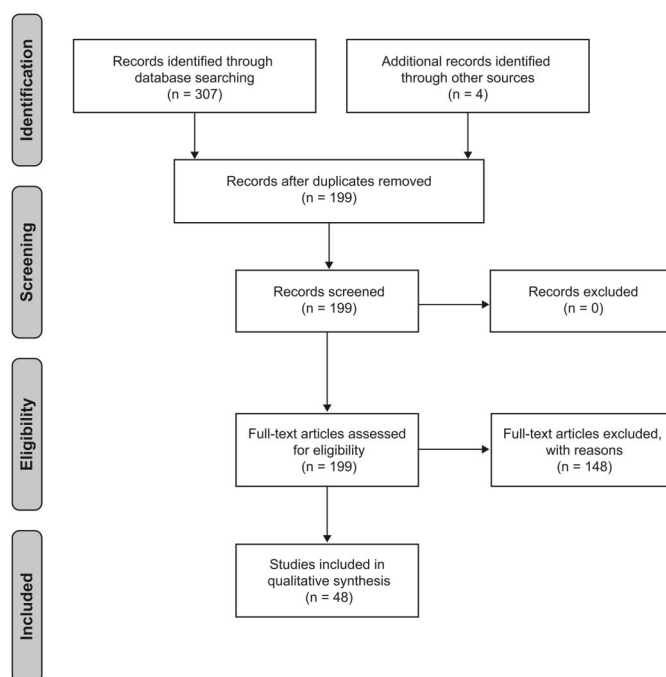


FIGURE 1. PRISMA flow diagram.

UC) were evaluated for induction^{13,24–27} or maintenance of remission (Table 1).^{13,16,17,24–28} Induction of remission after treatment with 5-ASA suppositories in patients with active distal UC was examined in 3 randomized, double-blind, placebo-controlled studies.^{24–26} Although definitions of remission differed among studies, clinical and endoscopic remission were achieved by a greater percentage of patients receiving 5-ASA suppositories compared with placebo.^{24–26} In patients with mild-to-moderate distal UC, dose-ranging studies support the use of once-daily administration of 5-ASA suppositories for the induction of clinical remission.^{13,27} Coupled with the consistency of the evidence-supporting induction of remission, the quality of the evidence ranks **high** for the use of 5-ASA suppositories to induce remission in patients with distal UC.

Regarding maintaining remission, 3 randomized, double-blind, placebo-controlled studies of patients with UP or UPS in remission qualified for inclusion in this review.^{16,17,28} Compared with placebo, remission was maintained in a significantly greater percentage of patients receiving 5-ASA suppositories, regardless of whether patients received 5-ASA 0.4 g twice daily for 1 year,²⁸ 5-ASA 0.5 g once nightly for up to 2 years,¹⁶ or 5-ASA 1 g 3 times weekly for up to 1 year.¹⁷ The quality of the evidence is **moderate** for 5-ASA suppositories in the maintenance of remission in patients with UC, given that the differences in dosing regimens limit comparisons among studies.

The safety profile of 5-ASA suppositories was favorable for both induction and maintenance of remission in patients with distal UC. The percentage of patients reporting AEs was comparable between 5-ASA suppositories and placebo groups in randomized, double-blind, placebo-controlled trials.^{16,17,24} The most common AEs reported by patients receiving 5-ASA suppositories affected the gastrointestinal (e.g., flatulence, diarrhea, abdominal pain) and nervous (e.g., headache) systems.^{13,16,27} Transient facial erythema, mild fever, and nasopharyngitis were other AEs reported by patients receiving 5-ASA suppositories.^{24,26}

5-ASA Foams

5-ASA rectal foam formulations also have been shown to be efficacious for the induction of clinical remission (defined by clinical activity index ≤ 4) in 2 randomized studies of patients with active mild-to-moderate distal forms of UC.^{29,30} In one study,³⁰ clinical remission (defined as above, with a decrease from baseline in clinical activity index ≥ 2 points) was achieved in a significantly greater percentage of patients receiving 5-ASA 1 g/60 mL foam once daily after 6 weeks compared with placebo (64.8% versus 40.4%, respectively; $P = 0.008$). In the second study,²⁹ rates of clinical remission were comparable in patients receiving once-daily treatment with 5-ASA 1 g/60 mL foam (low volume) or 5-ASA 1 g/120 mL foam (high volume; 75.5% versus 72.5%, respectively) after 6 weeks. Thus, 5-ASA 1 g/60 mL foam induced clinical remission in a greater percentage of patients compared with placebo and had comparable efficacy with high-volume foam. The quality of evidence for the treatment of patients with active UC using 5-ASA foams is **moderate**, because data are

limited to these 2 studies of differing design (i.e., 1 placebo-controlled study and 1 active-controlled study). Although clinical remission outcomes for 5-ASA 1 g/60 mL foam were comparable, additional prospective studies are warranted to confirm these findings. The safety profile of 5-ASA foam was favorable with the most common AEs reported affecting the gastrointestinal and nervous systems (data were not further detailed).^{29,30} Pokrotnieks et al³⁰ reported that 1 patient in each group discontinued the study due to an AE (5-ASA foam group: hallucinations; placebo group: diarrhea and abdominal cramps).

5-ASA Gels

The efficacy of 5-ASA gels was reported in 1 small, open-label study of 6 patients with distal UC.³¹ Patients received a single dose of 5-ASA 4 g/60 mL rectal gel, which after 48 hours was followed by nightly administration of rectal gel for 4 days. Disease activity index (DAI) score was used to measure the extent of disease and includes qualitative rating scales of stool frequency, rectal bleeding, mucosal appearance, and physician's global assessment subscales to provide a score ranging from 0 (normal) to 12 (severe disease).³² In this study, after 5 doses, the mean baseline DAI score of 6.5 (SD, 2.1) decreased to a mean posttreatment DAI score of 3.0 (SD, 0.9; $P = 0.0009$); each patient had $\geq 50\%$ improvement in DAI score from baseline. The AEs reported by more than 1 patient were abdominal pain, headache, dizziness, and mouth ulceration. As suggested earlier, the quality of this evidence is **low**, because the study was limited to 6 patients, lacked a control arm, and evaluated patients after only a few doses.

5-ASA Enemas

Eight randomized clinical studies (Table 2) examined 5-ASA enemas for the induction of remission in patients with active distal forms of UC.^{32–39} Two studies examined 5-ASA enemas for the maintenance of remission in patients with left-sided UC or UP in remission.^{40,41}

Induction of remission. Once-daily 5-ASA enemas have demonstrated efficacy in a number of randomized, double-blind, placebo-controlled clinical studies of patients with active distal forms of UC.^{32,37–39} Definitions of clinical response varied between the studies, but in 3 studies, physician's global assessment improved from baseline for 5-ASA doses ranging from 1 to 4 g compared with placebo enema for up to 8 weeks of treatment (see Fig., Supplemental Digital Content 1, <http://links.lww.com/IBD/A812>).^{32,37,39}

Campieri et al³⁸ evaluated clinical outcome (defined by criteria of Truelove and Richards)⁴² in patients with active mild-to-moderate UC that received enemas containing either placebo or 1, 2, or 4 g of 5-ASA. Compared with placebo, clinical, endoscopic, and histologic improvement or remission occurred in a greater percentage of patients receiving any dose of 5-ASA and at a similar frequency across dose groups. Improved endoscopic outcomes also were observed by Hanauer et al³⁷ in patients

TABLE 1. Efficacy and Safety of 5-ASA Suppositories in Patients with UC

Study and Study Design	Disease State	Treatment	Duration of Treatment	Primary Efficacy Endpoint	Efficacy Outcomes	Safety Outcomes
Induction of Remission						
Watanabe et al ²⁴ R, DB, PBO-C, MC	UC	5-ASA 1 g (n = 65) versus PBO (n = 64) qd	4 wk	Rate of endoscopic remission (percentage of patients with rectal mucosal score ≤ 1) at wk 4	Rate of endoscopic remission: 5-ASA 81.5% versus PBO 29.7% ($P < 0.0001$)	AEs: 5-ASA 15.4% versus PBO 17.2% Most common AE: nasopharyngitis (5-ASA 7.7% versus PBO 6.3%) Discontinued due to AEs: 5-ASA 0% versus PBO 4.7%
Andus et al ¹³ R, IB, MC	Active mild-to-moderate UP	5-ASA 1 g qhs (n = 200) versus 5-ASA 0.5 g tid (n = 203)	6 wk	Clinical remission (defined as DAI < 4 at wk 6)	Clinical remission: 5-ASA 1 g qhs 84.0% versus 5-ASA 0.5 g tid 84.7%	AEs: 5-ASA 1 g qhs 19.0% versus 5-ASA 0.5 g tid 21.2% Most common AEs: headache, nasopharyngitis, and UC Possible tx-related AEs: 5-ASA 1 g qhs 2.5% versus 5-ASA 0.5 g tid 3.4% 2 patients receiving 5-ASA 0.5 g tid discontinued study due to possible tx-related AEs (flatulence, pruritus, defecation urgency, constipation)
Lamet et al ²⁷ R, MC	Active mild-to-moderate UP	5-ASA 1 g qd nightly (n = 39) versus 5-ASA 0.5 g bid (n = 48)	6 wk	Clinical efficacy at wk 6 by DAI (sum of 4 subscales of stool frequency, rectal bleeding, mucosal appearance, and disease global assessment)	No significant difference between tx groups in DAI at wk 6 ($P = 0.73$) Baseline versus wk 6: 5-ASA 0.5 g bid, 6.6 ± 1.5 versus 1.6 ± 2.3 , respectively; 5-ASA 1 g qd 6.1 ± 1.5 versus 1.3 ± 2.2 , respectively	55% and 57% of patients receiving 5-ASA 1 g qd versus 0.5 g bid, respectively, reported AEs Most common AEs were flatulence, diarrhea, abdominal pain, and headache 3.6% of patients receiving 5-ASA 0.5 g bid discontinued the study due to AEs
Campieri et al ²⁵ R, DB, PBO-C	Mild-to-moderate distal UC	5-ASA 0.5 g (n = 32) versus PBO (n = 30) tid	1 mo	Clinical remission (absence of symptoms) or improvement, endoscopic remission (repair of rectal mucosa) or improvement, histologic remission (no inflammation in biopsy) or improvement Improvement defined as decrease of ≥ 1 grade from baseline in relevant scale	Clinical remission or improvement: 5-ASA 87% versus PBO 33% Endoscopic remission or improvement: 5-ASA 78% versus PBO 38% Histologic remission or improvement: 5-ASA 65% versus PBO 13%	Not reported

TABLE 1 (Continued)

Study and Study Design	Disease State	Treatment	Duration of Treatment	Primary Efficacy Endpoint	Efficacy Outcomes	Safety Outcomes
Campieri et al ²⁶ R, DB, PBO-C, MC	Active mild-to-moderate UP or UPS	5-ASA 1.5 g/d (n = 31), 5-ASA 1 g/d (n = 32), or PBO (n = 31) tid; patients received either 5-ASA 0.5 g or PBO suppository per dose	4 wk	Clinical remission (no symptoms with ≤ 2 bowel movements per day and no visible blood in stool), endoscopic and histologic response (defined as change of ≥ 1 grade)	Remission rates: 5-ASA 1.5 g/d 74%, 5-ASA 1 g/d 69%, versus PBO 39% ($P < 0.01$ for both 5-ASA groups versus PBO) Endoscopic response: 5-ASA 1.5 g/d 55%, 5-ASA 1 g/d 59% versus PBO 23% ($P < 0.02$ for both 5-ASA groups versus PBO) Histologic response: 5-ASA 1.5 g/d 10%, 5-ASA 1 g/d 16% versus PBO 6% (5-ASA 1.5 g/d versus PBO, $P < 0.01$; 5-ASA 1 g/d versus PBO, $P < 0.02$)	AEs: 3.1% (transient facial erythema and mild fever)
Maintenance of remission						
Hanauer et al ¹⁶ R, DB, PBO-C, MC	UP in clinical and endoscopic remission	5-ASA 0.5 g (n = 31) versus PBO (n = 34) qd	1 yr 2 yr	Maintenance of remission (DAI score = 0); time to relapse (defined as symptoms of rectal bleeding or an increase in stool frequency for ≥ 1 wk, and inflammation by endoscopy on DAI subscales)	Maintenance of remission at 24 mo: 5-ASA 60% versus PBO 20% Time to relapse: significantly greater with 5-ASA versus PBO ($P < 0.001$)	AEs: 5-ASA 23% versus PBO 15% Most common AEs with 5-ASA: rectal disorder (9.7%), abdominal pain (6.5%), and headache (6.5%) SAEs: 5-ASA 3.2% (ie, chest pain not related to 5-ASA tx)
Marteau et al ¹⁷ R, DB, PBO-C, MC	UP in remission	5-ASA 1 g (n = 48) versus PBO (n = 47) tiw 5-ASA 1 g versus PBO qd in patients who relapsed on 5-ASA 1 g tiw	12 mo	Time to relapse (defined as occurrence of clinical symptoms with an increase in endoscopy score ≥ 1 versus baseline, or rectal bleeding > 2 times in 1 d)	Time to relapse: 5-ASA 239 d versus PBO 166 d (log rank test: $P = 0.067$)	AEs: 5-ASA 12.5% versus PBO 10.6% Common AEs with 5-ASA: anal or rectal pain or difficulty with administration of the suppository, asthenia, hypotension, moderate leukopenia, mild hair loss Common AEs with PBO: anal or rectal pain or difficulty with administration of the suppository Discontinued due to AEs: 5-ASA 2.1% versus PBO 4.3% (anal or rectal burning)

TABLE 1 (Continued)

Study and Study Design	Disease State	Treatment	Duration of Treatment	Primary Efficacy Endpoint	Efficacy Outcomes	Safety Outcomes
D'Arienzo et al ²⁸ R, DB, PBO-C	UP, UPS in remission	5-ASA 400 mg (n = 15) versus PBO bid (n = 15)	1 yr	Maintenance of complete remission (defined as clinical signs [no blood in stools and no diarrhea, abdominal pain, tenesmus], endoscopic score ≤ 1 , and histologic score ≤ 1)	Cumulative remission rate at 1 yr: 5-ASA 92% versus PBO 21% ($P < 0.001$)	No AEs reported

bid, twice daily; DB, double blind; IB, investigator-blinded; MC, multicenter; PBO, placebo; PBO-C, placebo-controlled; qd, once daily; qhs, once daily at bedtime; R, randomized; SAE, serious adverse event; tid, 3 times daily; tiw, 3 times per week; tx, treatment; UP, ulcerative proctitis; UPS, ulcerative proctosigmoiditis.

with active mild-to-moderate UC after treatment with 5-ASA enema compared with placebo. Both Campieri et al³⁸ and Hanauer et al³⁷ demonstrated that treatment with 5-ASA enemas for 4 and 8 weeks improved histologic outcomes in an apparent dose-dependent manner; however, histologic sampling and grading differed between the 2 studies. Campieri et al³⁸ examined biopsy samples taken from the posterior rectal wall (5–10 cm from the anus) for edema, inflammatory infiltrate, crypt abscess, mucus depletion, gland architecture, and ulceration, while Hanauer et al³⁷ graded biopsy samples taken 5 to 15 cm from the anal verge on a scale of 0 to 3 (0, normal colonic mucosa; 1, inactive inflammatory bowel disease; 2, low-grade active inflammatory bowel disease; and 3, high-grade active inflammatory bowel disease).

In evaluations of disease severity after treatment, mean DAI scores significantly decreased from baseline after 6 week treatment with 5-ASA 4 g compared with placebo in 2 studies.^{32,39} When 5-ASA enemas are used in combination therapy with oral 5-ASA, there is also a suggestion of benefit. Marteau et al³⁵ reported similar 4-week remission rates in patients with active mild-to-moderate UC receiving oral 5-ASA 2 g twice daily with either 5-ASA 1 g or placebo enemas; however, week 8 remission rates were superior in patients receiving combination 5-ASA therapy for the first 4 weeks versus patients who had not (64% versus 43%, respectively; $P = 0.03$). Overall, 5-ASA enemas administered at doses ranging between 1 and 4 g using a number of different clinical, endoscopic, and histologic outcome measures have demonstrated efficacy superior to placebo.^{32,39}

In a noninferiority study conducted by Cortot et al,³⁴ the percentage of patients with active mild-to-moderate left-sided UC achieving clinical remission was similar after 4 weeks of treatment with either 5-ASA 1 g/100 mL liquid enema or 5-ASA 1 g/80 mL foam enema. A study comparing the efficacy of 6 weeks of oral 5-ASA 2 g (twice daily in combination with placebo enema nightly) with oral 5-ASA 1 g and 2 placebo tablets (twice daily in combination with 5-ASA 2 g/60 mL enema nightly) in patients with active mild-to-moderate UC³⁶ demonstrated that $\geq 85\%$ of patients in both groups achieved clinical improvement or remission. Finally, patients with active UC receiving 5-ASA 1 g for 4 weeks in combination with oral 5-ASA 2 g twice daily for 8 weeks achieved significant improvement from baseline in health-related quality of life after 4 weeks of treatment and maintained improvement in health-related quality of life after 8 weeks of treatment (oral dosing only) when compared with patients who received placebo enemas with the same dose of oral 5-ASA.³³

The quality of the evidence is rated **high** for the use of 5-ASA enemas to induce remission in patients with active UC because of the number of placebo-controlled studies demonstrating clinical efficacy based on a combination of different outcomes, including clinical response and endoscopic and histologic findings.^{32,37–39} Furthermore, the addition of 5-ASA enemas to oral 5-ASA therapy improved efficacy and health-related quality of life beyond that of treatment with oral 5-ASAs alone.³³ The safety profile of 5-ASA enemas was favorable, because the percentage

TABLE 2. Efficacy and Safety of 5-ASA Enemas for the Treatment of Patients with UC

Study and Study Design	Disease State	Treatment	Duration of Treatment	Primary Efficacy Endpoint	Efficacy Outcomes	Safety Outcomes
Induction of Remission						
Connolly et al ³³ R, DB, C, MC	Active mild-to-moderate UC	5-ASA 1 g/100 mL enema plus oral 5-ASA 2 g bid (n = 71) versus PBO enema (n = 56) plus oral 5-ASA 2 g bid	Enemas: 4 wk; Oral tx: 8 wk	HRQOL by EQ-5D	Increase from baseline in HRQOL index score: wk 4, 5-ASA enema 0.128 versus PBO enema 0.076 ($P < 0.05$); wk 8, 5-ASA enema 0.137 versus PBO enema 0.099 ($P = \text{NS}$)	Not reported
Cortot et al ³⁴ R, C, IB, MC	Active mild-to-moderate left-sided UC	5-ASA 1 g/100 mL enema qd (n = 179) versus 5-ASA 1 g/80 mL foam qd (n = 189)	4 wk	Clinical remission (CAI ≤ 2)	Clinical remission at wk 4: 5-ASA 1 g/100 mL enema 70.5% versus 5-ASA 1 g/80 mL foam 66.7%	AEs: 5-ASA 1 g/100 mL enema 32.4% versus 5-ASA 1 g/80 mL foam 27.2% Most common AEs: GI disorders Discontinuation due to AEs: 5-ASA 1 g/100 mL enema 6.6% versus 5-ASA 1 g/80 mL 7.3% (i.e., GI disorders)
Marteau et al ³⁵ R, DB, PBO-C, MC	Mild-to-moderate UC extending beyond splenic flexure	Oral 5-ASA 2 g bid plus 5-ASA 1 g/100 mL enema (n = 71) or PBO enema (n = 56) qhs Oral 5-ASA administered for 8 wk	4 wk (oral/enema combination) 8 wk (oral only)	Remission at 4 wk of ITT population (UCDAI score < 2)	Rate of remission: wk 4, 5-ASA enema 44% versus PBO enema 34% ($P = 0.31$); wk 8, 5-ASA enema 64% versus PBO enema 43% ($P = 0.03$)	AEs: wk 8, 5-ASA enema 34% versus PBO enema 50% Most common AEs: 5-ASA, diarrhea (4%), headache (4%), and vomiting (3%); PBO, abdominal pain (4%) SAEs: 5-ASA 4% versus PBO 2% (affecting the GI system and unrelated to tx) Discontinued due to AEs: 5-ASA 12.7% versus PBO 19.6%

TABLE 2 (Continued)

Study and Study Design	Disease State	Treatment	Duration of Treatment	Primary Efficacy Endpoint	Efficacy Outcomes	Safety Outcomes
Vecchi et al ³⁶ R, DB, DD, MC	Mild to moderate UC flare	Oral 5-ASA 2 g bid plus PBO enema qd (oral group; n = 67) versus oral 5-ASA 1 g bid plus 2 tablets PBO bid plus 5-ASA 2 g/60 mL enema qd (combined group; n = 63)	6 wk	Rate of clinical remission (CAI <4) or improvement (decrease from baseline >50% in CAI); time to clinical remission or improvement	Clinical remission or improvement: oral 5-ASA 85% versus oral/enema 5-ASA combination 91% ($P = 0.50$) Time to clinical remission or improvement: oral 5-ASA 21.5 d versus oral/enema 5-ASA combination 19.8 d ($P = 0.31$)	AEs: oral 5-ASA 8% versus oral/enema 5-ASA combination 6% Discontinued due to AEs: oral 5-ASA 1.5% (headache and fever) versus oral/enema 5-ASA combination 1.6% (flu-like syndrome)
Hanauer ³⁷ R, DB, PBO-C, MC	Active mild-to-moderate UP or UPS	5-ASA 1 g (n = 73), 2 g (n = 71), or 4 g/100 mL (n = 73) enema qd versus PBO (n = 70)	8 wk	Clinical response (PGA; mean change from baseline in endoscopic index)	Improvement from baseline in PGA at wk 8: 5-ASA 1 g 67%, 5-ASA 2 g 65%, 5-ASA 4 g 75%, versus PBO 27% ($P < 0.01$) Mean decrease from baseline in endoscopic index at wk 8: 5-ASA 1 g 5.8, 5-ASA 2 g 5.9, 5-ASA 4 g 6.4, versus PBO 1.8 ($P < 0.01$)	AEs: comparable between 5-ASA and PBO groups Discontinued due to tx failure: 5-ASA 1 g 8%, 5-ASA 2 g 11%, 5-ASA 4 g 10%, versus PBO 37%
Campieri et al ³⁸ R, DB, PBO-C	Active mild-to-moderate UP, UPS, and left-sided coliti	5-ASA 1 g (n = 27), 2 g (n = 30), 4 g/100 mL (n = 29) enema qd versus PBO (n = 27)	4 wk	Clinical, endoscopic, and histologic disease activity	Clinical improvement or remission: 5-ASA 1 g 85%, 5-ASA 2 g 83%, 5-ASA 4 g 86%, versus PBO 41% Endoscopic improvement or remission: 5-ASA 1 g 74%, 5-ASA 2 g 73%, 5-ASA 4 g 79%, versus PBO 30% Histologic improvement: 5-ASA 1 g 63%, 5-ASA 2 g 70%, 5-ASA 4 g 76%, versus PBO 15%	Not reported
Sutherland and Martin ³⁹ R, DB, PBO-C	Active distal UC	5-ASA 4 g/60 mL enema qd (n = 29) versus PBO (n = 30)	6 wk	Response to tx (PGA; DAI)	PGA rating "much improved" at wk 6: 5-ASA 62% versus PBO 20% ($P < 0.0001$) Decrease from baseline in mean DAI at wk 6: 5-ASA 75% versus PBO 32% ($P < 0.05$)	Few minor AEs reported

TABLE 2 (Continued)

Study and Study Design	Disease State	Treatment	Duration of Treatment	Primary Efficacy Endpoint	Efficacy Outcomes	Safety Outcomes
Sutherland et al ³² R, DB, PBO-C, MC	Active distal UC, UP, and UPS	5-ASA 4 g/60 mL enema qd (n = 76) versus PBO (n = 77)	6 wk	Response to tx (PGA, DAI, DAI individual subscales)	PGA rating “much improved” at wk 6: 5-ASA 63% versus PBO 29% ($P < 0.0001$) Decrease from baseline in mean DAI at wk 6: 5-ASA 55% versus PBO 22% ($P < 0.0001$) Decrease from baseline in DAI subscale score at wk 6: Stool frequency: 5-ASA 0.57 versus PBO 0.41 Rectal bleeding: 5-ASA 1.30 versus PBO 0.61 ($P < 0.001$) Mucosal appearance: 5-ASA 1.21 versus PBO 0.56 ($P < 0.001$) Physician’s assessment of disease severity: 5-ASA 0.97 versus PBO 0.30 ($P < 0.001$)	AEs: 5-ASA 11.8% versus PBO 14.3% AEs with 5-ASA: headache and mild hair loss AEs with PBO: headache, nausea and vomiting, rash, arthralgia, periorbital edema, and diarrhea
Maintenance of Remission						
Yokoyama et al ⁴⁰ R, C	Left-sided UC, UC, and UP in remission	5-ASA 1 g enema twice weekly, with oral 5-ASA 3 g/d (n = 11) versus oral 5-ASA 3 g/d (n = 13)	Mean observation: 305 d (SD, 162 d)	Relapse (CAI ≥ 6 and endoscopic index > 3)	Relapse: 5-ASA enema plus oral 5-ASA 18.2% versus oral 5-ASA alone 76.9% (HR, 0.19; 95% CI, 0.04–0.94)	No AEs reported
Biddle et al ⁴¹ R, DB, PBO-C	Left-sided UC in remission	5-ASA 1 g/60 mL enema qd (n = 12) versus PBO (n = 13)	48–52 wk, or until relapse	Clinical and endoscopic maintenance of remission	Maintenance of remission for ≥ 46 wk: 5-ASA 75% versus PBO 15% ($P < 0.005$)	Anal canal irritation: 5-ASA 41.7% versus PBO 61.5%

AE, adverse event; bid, twice daily; C, controlled; CAI, Clinical Activity Index; CI, confidence interval; DB, double blind; DD, double-dummy; GI, gastrointestinal; HR, hazard ratio; HRQOL, health-related quality of life; IB, investigator-blinded; MC, multicenter; NS, not significant; PBO, placebo; PBO-C, placebo-controlled; PGA, physician’s global assessment; qd, once daily; qhs, once nightly; R, randomized; tx, treatment; UCDAI, ulcerative colitis disease activity index; UP, ulcerative proctitis; UPS, ulcerative proctosigmoiditis.

TABLE 3. Efficacy and Safety of Corticosteroid Foam and Enemas in Patients with UC

Study and Study Design	Disease State	Treatment	Duration of Treatment	Primary Efficacy Endpoint	Efficacy Outcomes	Safety Outcomes
Foam						
Gross et al ¹⁵ R, DB, DD, MC	Active UP or UPS	Budesonide 2 mg/25 mL foam and PBO enema (n = 265) versus budesonide 2 mg/100 mL enema and PBO foam (n = 268)	4 wk	Clinical remission (CAI ≤ 4) at wk 4	Clinical remission: budesonide foam 60% versus budesonide enema 66%	AEs: budesonide foam 32% versus budesonide enema 33% Most common AEs: headache, UC deteriorated, nausea, and abdominal pain Serum cortisol levels <150 nmol/L: budesonide foam 0.8% versus budesonide enema 1.1%
Hammond et al ⁴⁶ R, C, MC	Active distal UC	Budesonide 2 mg/50 mL foam (n = 22) versus betamethasone 5 mg/100 mL enema (n = 16) bid for 2 wk, then qd for 2 wk	4 wk	Change from baseline in mean LQI	Decrease from baseline in mean LQI: betamethasone enema 2.1 versus budesonide foam 2.9 ($P < 0.09$)	AEs: budesonide foam 31.8% versus betamethasone enema 43.8% Corticosteroid-related AEs: budesonide foam 17.4% versus betamethasone enema 43.8% Decreased plasma cortisol levels: budesonide foam 22% versus betamethasone enema 87%
Enemas						
Hartmann et al ⁴⁷ R, C, MC	Active mild-to-moderate left-sided UC	Budesonide 2 mg/100 mL enema (n = 118) versus 5-ASA 4 g/60 mL enema (n = 119)	8 wk	Clinical remission (CAI <4) at wk 4 and 8	Clinical remission: wk 4, budesonide enema 63.5% versus 5-ASA enema 77.2% ($P < 0.05$); wk 8, budesonide enema 64.4% versus 5-ASA enema 77.4% ($P < 0.05$)	AEs: budesonide enema 55% versus 5-ASA enema 34% ($P < 0.002$) Most common AEs with budesonide enema: nausea and vomiting, common cold, headache/migraine, increased CRP, and worsening UC Most common AEs with 5-ASA enema: nausea and vomiting, and abdominal pain Discontinuation due to AEs: budesonide enema 3.1% versus 5-ASA enema 2.4%
Biancone et al ⁴⁸ R, DB, MC, parallel group	Active mild-to-moderate distal UC	BDP 3 mg enema or foam versus 5-ASA 2 g enema or foam qd nightly	8 wk	Rate of remission (DAI score <3) at wk 4	Rate of remission: BDP 24% versus 5-ASA 28%	AEs: BDP 33% versus 5-ASA 25% Discontinuation due to AEs: BDP foam 6% (eg, bloody stools, diarrhea) versus 5-ASA foam 7.5% (eg, abdominal pain, bowel tenderness) Serum cortisol levels within normal range: BDP at baseline 86% versus BDP after 8 wk 81%

TABLE 3 (Continued)

Study and Study Design	Disease State	Treatment	Duration of Treatment	Primary Efficacy Endpoint	Efficacy Outcomes	Safety Outcomes
Gionchetti et al ⁴⁹ R, SB, C, parallel group, MC	Active mild-to-moderate UC, UP, and UPS	BDP 3 mg/60 mL enema (n = 111) versus 5-ASA 1 g/100 mL enema (n = 106) qd nightly	6 wk	Change in DAI score from baseline to wk 6	Decrease from baseline in DAI score: BDP 4.44 versus 5-ASA 4.31 (95% CI, -0.50–0.65)	AEs: BDP 10.8% versus 5-ASA 12.3% Morning plasma cortisol levels with BDP enema: baseline and 6 wk levels comparable
Lindgren et al ⁵⁰ Part 1 (induction of remission): R, DB, MC parallel group Part 2 (maintenance of remission): R, PBO-C	Active distal UC and UP	Part 1 (induction of remission): budesonide 2 mg/100 mL enema qhs and PBO enema qam versus budesonide 2 mg/100 mL enema bid Part 2 (maintenance of remission): budesonide 2 mg/100 mL enema versus PBO enema twice weekly	Part 1: remission, or 8 wk Part 2: relapse, or 6 mo	Part 1: rate of remission (ie, no clinical symptoms [eg, no blood in stools and <3 bowel movements/24 h] and endoscopy score ≤1) Part 2: rate of relapse (ie, clinical symptoms [eg, blood in stools and ≥3 bowel movements/24 h] and endoscopy score ≥2)	Part 1: rate of remission: wk 4, budesonide enema qhs 33% versus budesonide enema bid 41%; wk 8, budesonide enema qhs 51% versus budesonide enema bid 54% Part 2: rate of relapse: wk 8, budesonide enema 15% versus PBO 24%; wk 16, budesonide enema 31% versus PBO 27%; wk 24, budesonide enema 41% versus PBO 51%	Part 1: AEs: budesonide enema qd 66% versus budesonide enema bid 71% Most common AEs: flatulence, abdominal pain, fatigue, respiratory infection, and nausea Impaired adrenal function: budesonide enema qd 8% versus budesonide enema bid 33% (<i>P</i> = 0.0001) Part 2: AEs: budesonide enema 72% versus PBO 65% Most common AEs: abdominal pain, nausea, flatulence, and diarrhea Normal adrenal function: similar percentage of patients after tx
Hanauer et al ⁵¹ R, DB, PBO-C, MC	Active distal UC extending to splenic flexure	Budesonide 0.5 mg (n = 57), 2 mg (n = 56), or 8 mg/100 mL enema (n = 60) qhs versus PBO (n = 60)	6 wk	Mean change from baseline in endoscopic inflammation grade, sum score of histopathology (all 3 components), and remission (defined as ≤3 bowel movements/d; no blood in stool; no urgency, abdominal pain, or painful evacuations; and a 0 score for endoscopic inflammation grade for previous 2 d)	Endoscopic inflammation grade: budesonide 2 mg and 8 mg significant improvement in mean change from baseline versus PBO (<i>P</i> ≤ 0.001) Total histopathology score: budesonide 2 mg and 8 mg significant improvement versus PBO (<i>P</i> ≤ 0.05 and <i>P</i> ≤ 0.001, respectively) Remission rates: budesonide 0.5 mg 7%, budesonide 2 mg 19%, budesonide 8 mg 27% versus PBO 4%; 2 mg versus PBO (<i>P</i> ≤ 0.05) and 8 mg versus PBO (<i>P</i> ≤ 0.001)	AEs: budesonide 0.5 mg 37%, budesonide 2 mg 36%, budesonide 8 mg 40%, versus PBO 30% Most common AEs: headache, back pain, dyspepsia, and nausea Adrenal insufficiency: budesonide 8 mg 1.7% Cushing syndrome: budesonide 8 mg 6.7% versus PBO 3.3%
Danielsson et al ⁵² OL, MC	Active distal UC or UP	Budesonide 2 mg/100 mL enema (n = 29) qhs	4 wk	Endoscopic rating scores, histologic rating scores	Endoscopy scores: significant improvement from baseline to wk 4 (<i>P</i> < 0.0001) Histologic rating scores: significant improvement from baseline to wk 4 (<i>P</i> < 0.002)	No AEs reported Plasma cortisol levels: no significant change

TABLE 3 (Continued)

Study and Study Design	Disease State	Treatment	Duration of Treatment	Primary Efficacy Endpoint	Efficacy Outcomes	Safety Outcomes
Danielsson et al ⁵³ R, DB, PBO-C, MC	Active distal UC or UP	Budesonide 2 mg/100 mL enema (n = 20) versus PBO (n = 21) qhs	2 or 4 wk (dependent on tx outcome) 4-wk OL phase with budesonide in patients with unsatisfactory response (failure to improve)	Endoscopy rating scores, histologic rating scores, and laboratory variables	Endoscopy scores: significant improvement with budesonide at wk 4 versus PBO ($P < 0.01$), but not at wk 2 ($P = 0.07$) Histologic rating scores: significant improvement with budesonide at wk 2 ($P < 0.05$) and 4 ($P < 0.01$) 4/20 (20%) patients in budesonide group and 16/21 (76%) patients in PBO group entered OL phase ($P < 0.001$)	No AEs reported Plasma cortisol levels: no decrease
Cobden et al ⁵⁴ R, DB, DD	Active mild-to-moderate distal UC	Prednisolone metabenzoate 20 mg/100 mL enema bid plus oral PBO tablets (n = 19) versus PBO enemas bid plus oral 5-ASA 0.8 g qid (n = 18)	4 wk	Stool frequency, urgency score, tenesmus score, rectal bleeding score	Decrease from baseline in median stool frequency: prednisolone enema 1.5 versus oral 5-ASA 1.2 ($P = NS$) Decrease from baseline in median urgency score: prednisolone enema 39 versus oral 5-ASA 35 ($P = NS$) Decrease from baseline in median tenesmus score: prednisolone enema 9 versus oral 5-ASA 5 ($P = NS$) Median decrease in rectal bleeding score: prednisolone enema 0.9 versus oral 5-ASA 1.0	Not reported

AE, adverse event; bid, twice daily; BDP, beclomethasone dipropionate; C, controlled; CAI, Clinical Activity Index; CI, confidence interval; CRP, C-reactive protein; DB, double-blind; DD, double dummy; LQI, life quality index; MC, multicenter; NS, not significant; OL, open label; PBO, placebo; PBO-C, placebo-controlled; qam, once in morning; qd, once daily; qhs, once nightly; qid, 4 times daily; R, randomized; SB, single-blind; tx, treatment; UP, ulcerative proctitis; UPS, ulcerative proctosigmoiditis.

TABLE 4. Effect of Treatment with Budesonide Enemas on Plasma Cortisol Concentrations

Study	Study Duration	Time Point	Plasma Cortisol Concentration (Nmol/L)			
Hanauer et al ⁵¹	6 wk	Budesonide Enema Dose				
			0.5 mg/100 mL N = 57	2 mg/100 mL N = 56	8 mg/100 mL N = 60	Placebo N = 60
			Basal			
		Baseline	415	382	369	407
		Wk 6	393	322	246 ^a	385
			ACTH-stimulated			
		Baseline	721	683	698	729
		Wk 6	702	583 ^a	529 ^a	739
Danielsson et al ⁵²	4 wk		N = 29			
		Baseline	481			
		Wk 2	398			
		Wk 4	430			
Danielsson et al ⁵³	4 wk		N = 20			
		Baseline	464			
		Wk 2	440			
		Wk 4	466			
			N = 21			
		Baseline	411			
		Wk 2	389			
		Wk 4	447			

^a*P* ≤ 0.001 versus placebo.

ACTH, adrenocorticotropic hormone.

of patients with active UP, UPS, or distal UC reporting AEs was comparable between 5-ASA and placebo groups.^{32,37,39} Similarly, in 2 studies of patients receiving 5-ASA or placebo enemas in combination with oral 5-ASAs, the percentage of reported AEs also was comparable between groups.^{35,36}

Maintenance of remission. The efficacy and safety of 5-ASA enemas also was examined for the maintenance of remission in patients with UC (Table 2). Compared with placebo, treatment with a 5-ASA enema resulted in a greater percentage of patients maintaining long-term remission.⁴¹ The combination of 5-ASA enemas and oral 5-ASA treatment also resulted in a lower rate of relapse compared with use of oral 5-ASA alone.⁴⁰ However, the quality of the evidence for the use of 5-ASA enemas for maintaining UC remission is **low**, because only 2 studies were used as the basis for this assessment.^{40,41} Also, although the study conducted by Yokoyama et al⁴⁰ was designed to enroll 200 patients, the supply of enemas was limited and limited randomization to 24 patients. Biddle et al⁴¹ also examined efficacy in a small number of patients, and the small study population reduced the quality of the evidence.²³ In both studies of UC remission maintenance, anal canal irritation was the sole AE reported by patients with left-sided colitis who received 5-ASA or placebo for up to 1 year.⁴¹

Corticosteroids

Traditional corticosteroids (prednisone, hydrocortisone) have prohibitive side-effects that limit their long-term use. Second-generation corticosteroids, such as budesonide and beclomethasone

dipropionate (BDP), are associated with minimal steroid-related effects.^{43–45} The low incidence of systemic effects observed with these agents is attributed to their low systemic bioavailability (i.e., budesonide has approximately 90% first-pass metabolism in the liver; BDP undergoes rapid hepatic inactivation). The rectal formulations of corticosteroids evaluated in clinical studies include both foams and enemas. Foam formulations have improved retention compared with enemas; studies of enemas often cite “inconvenient administration,” including issues with leakage.⁴⁴ Studies examining the efficacy and safety of corticosteroid foams and enemas for the induction of remission of UC are summarized in Table 3.^{15,46–54}

Corticosteroid Foams

Two studies examined clinical remission (defined as clinical activity index score ≤4) after treatment with corticosteroid foams for 4 weeks in patients with active UC (Table 3).^{15,46} Gross et al¹⁵ demonstrated that the majority of patients receiving either budesonide foam 2 mg/25 mL or budesonide enema 2 mg/100 mL achieved clinical remission with no difference between groups. Both budesonide foam and enema were considered well tolerated, with headache, worsening UC, nausea, and abdominal pain as the most commonly reported AEs. Decreased morning cortisol levels (≤150 nmol/L) were exceptionally rare and observed in a similar number of patients receiving budesonide foam or enema (0.7% versus 1.1%, respectively). In a study performed by Hammond et al, although treatment with betamethasone enema 5 mg/100 mL was more efficacious than budesonide foam 2 mg/50 mL for the induction of clinical remission, a greater percentage of patients receiving

TABLE 5. Efficacy and Safety of 4-ASA Enemas for the Treatment of Patients With UC

Study and Study Design	Disease State	Treatment	Duration of Treatment	Primary Efficacy Endpoint	Efficacy Outcomes	Safety Outcomes
Ginsberg et al ⁵⁶ R, DB, PBO-COL (patients receiving PBO in whom tx failed)	Left-sided UC	4-ASA 2 g/60 mL enema (n = 12) versus PBO (n = 13)	8 wk OL (3 mo)	Clinical, endoscopic, and histologic improvement (improvement ≥ 1 grade of ≥ 2 variables [blood, mucus, urgency] and improvement ≥ 1 grade in both endoscopic appearance and histologic inflammation)	Clinical, endoscopic, and histologic improvement from baseline at wk 4: 4-ASA 83% versus PBO Clinical, endoscopic, and histologic improvement at mo 3: 81.8% of patients who entered OL tx phase	Not reported
Gandolfo et al ⁵⁷ R, DB, PBO-COL (all patients)	Active distal UC	4-ASA 2 g/100 mL enema bid (n = 18), 4-ASA 1 g/100 mL bid (n = 12), PBO bid (n = 17) OL: 4-ASA 2 g/100 mL bid (n = 35)	2 wk OL (1 yr)	Symptom severity (0 = absent, 1 = mild, 2 = moderate, 3 = severe) Symptoms evaluated were blood in stool, mucus in stool, tenesmus, abdominal pain, loss of appetite, fatigue, weight loss, and malaise; stool consistency (1 = formed, 2 = semiformed, 3 = liquid)	Decrease in symptom severity score from baseline: 4-ASA 1 g 7.18–3.18, $P = 0.05$; 4-ASA 2 g 8.82–5.24, $P = NS$; versus PBO 9.94–7.47, $P = NS$ Patients in OL phase with improvement at 1 yr: 77% (cumulative total)	AEs: 4-ASA 2 g 0%, 4-ASA 1 g 25%, versus PBO 23.5% AEs with 4-ASA 1 g: fever, diarrhea, and abdominal discomfort AEs with PBO: incontinence, postprandial heartburn, anorexia weight loss, epigastric discomfort, and palmar rash
Selby et al ⁵⁸ R, DB, C	Mild-to-moderate distal UC	Part 1: 4-ASA 1 g/100 mL enema qd (n = 15) versus PBO (n = 15) Part 2: 4-ASA 2 g/100 mL enema qd (n = 10) versus PBO (n = 12)	2 wk	Clinical response (stool number and consistency, passage of blood or mucus, abdominal pain, and patient general well-being); endoscopic response (grade 0–3)	Clinical improvement: 4-ASA 1 g and 2 g 80% versus PBO 41% ($P < 0.005$) Endoscopic improvement: 4-ASA 1 g and 2 g 72% versus PBO 30% ($P < 0.005$)	AEs: none reported

4-ASA, 4-aminosalicylic acid; 5-ASA, 5-aminosalicylic acid; bid, twice daily; C, controlled; DB, double-blind; NS, not significant; OL, open label; PBO, placebo; PBO-C, placebo-controlled; R, randomized; tx, treatment; UC, ulcerative colitis.

the betamethasone enema reported steroid-related AEs (e.g., leukocytosis, dizziness, visual disturbances, morning facial edema, and increased appetite) than patients receiving budesonide foam (43.8% versus 17.4%, respectively). Additionally, plasma cortisol levels were decreased in a greater percentage of patients receiving the betamethasone enema (87% versus 22%, respectively).⁴⁶

Based on these 2 randomized controlled studies, which used the same definition of clinical remission, the quality of the evidence is **moderate** for the use of budesonide foam to achieve clinical remission in patients with active distal forms of UC. Although findings were similar, Gross et al¹⁵ did not evaluate the primary efficacy outcome using the intent-to-treat population but rather the per-protocol population, which was determined to be a study limitation using the GRADE system.²³ In addition, the small number of patients included in Hammond et al⁴⁶ limited statistical analyses of the findings.

Corticosteroid Enemas

Eight studies evaluating the efficacy and safety of corticosteroid enemas for the treatment of patients with UC were included (Table 3).^{47–54} In 2 randomized, placebo-controlled, double-blind studies of patients with active distal forms of UC, endoscopic appearance significantly improved after 4 and 6 weeks of treatment with budesonide enema 2 mg.^{51,53} Similarly, histology scores significantly improved after 2, 4, and 6 weeks of treatment with budesonide enema 2 mg when compared with placebo. The rate of remission at week 6 appeared to be dose-dependent with budesonide enema when evaluated at doses of 0.5 to 8 mg.⁵¹ In a separate study, twice-daily dosing of budesonide enema 2 g was not shown to have superior induction nor maintenance of remission when compared with once-daily dosing, while adrenal impairment was much more prevalent (32% versus 4.8%, respectively; $P = 0.001$).⁵⁰

Studies comparing the efficacy of corticosteroid enemas with other active treatments have reported mixed results.^{47–49,54} Hartmann and Stein⁴⁷ demonstrated that a smaller percentage of patients with active left-sided UC receiving daily budesonide enema 2 mg achieved clinical remission after 4 and 8 wk compared with patients receiving 5-ASA enema 4 g. However, remission was induced in a comparable percentage of patients with active distal forms of UC who received either BDP enema 3 mg or 5-ASA enema 2 g for 4 and 8 weeks.⁴⁸ Similarly, once-daily treatment with BDP enema 3 mg or 5-ASA enema 1 g for 6 weeks in patients with active distal forms of UC resulted in comparable percentages of patients in both groups achieving clinical remission.⁴⁹ Furthermore, after 4 weeks of either prednisolone metabenzoate enema 20 mg twice daily plus oral placebo, or placebo enema plus oral 5-ASA 0.8 g 4 times a day, a comparable percentage of patients with active distal forms of UC achieved clinical and histologic remission.⁵⁴

Overall, the quality of the evidence is **high** for the use of rectally administered budesonide enema to induce remission in patients with distal forms of UC although the data do not appear to support its administration to maintain remission. The quality of

the evidence available for BDP enema and prednisolone enema is **low**; categorization of these formulations was hindered by a low rate of recruitment⁴⁸ and small study populations, respectively.⁵⁴

Decreased plasma cortisol levels and abnormal adrenocorticotrophic hormone stimulation test results are typically associated with treatment with systemic corticosteroids, which adversely affect the hypothalamic–pituitary–adrenal axis.⁵⁵ However, results after treatment with budesonide or BDP enemas indicate that plasma cortisol levels remained within the normal range for most patients (Tables 3 and 4).^{48,49,51–53} Furthermore, AE profiles in these studies suggest that budesonide and BDP enemas are safe for the treatment of patients with UP, UPS, or left-sided colitis (i.e., distal forms of UC).^{47–53}

Other Agents

A number of other agents have been examined for their efficacy and safety in the treatment of patients with active UP, UPS, and left-sided UC, including 4-aminosalicylic acid (4-ASA),^{56–58} alicaforsen,^{59–62} nicotine,⁶³ the human recombinant proteins trefoil family factor 3,⁶⁴ epidermal growth factor,⁶⁵ cyclosporine,⁶⁶ the peroxisome proliferator-activated receptor- γ (PPAR- γ) agonist rosiglitazone,⁶⁷ rebamipide,⁶⁸ and tacrolimus.⁶⁹

4-Aminosalicylic Acid

Efficacy and safety outcomes after treatment with 4-ASA enemas, which are currently marketed in Europe,⁷⁰ were assessed in 3 randomized, double-blind, placebo-controlled clinical studies of patients with active UC^{56–58} (Table 5), the results of which suggest that patients with active distal forms of UC derive clinical and endoscopic benefit after treatment for 2 to 8 weeks.^{56–58} Overall, 4-ASA enemas had a favorable safety profile in these clinical studies,^{56,58} with 2 studies reporting no AEs and the third study reporting fever, diarrhea, and abdominal discomfort in few patients treated with 4-ASA 2 g enemas.⁵⁷

The quality of the evidence for the use of 4-ASA enemas for the treatment of patients with active distal forms of UC is ranked **moderate**, because although patients received therapeutic benefit after treatment with 4-ASA in 3 randomized placebo-controlled studies, these clinical studies examined small patient populations (range, 25–52 patients). Furthermore, the patient populations varied across the studies. Two studies permitted concomitant use of oral therapies for UC, and in the third study, which did not permit concomitant use of oral therapy, 1 or more patients were exempted from this requirement.^{56–58} Larger, randomized, placebo-controlled studies with similar inclusion criteria are needed to support the findings of these smaller studies.

Alicaforsen

Alicaforsen, an experimental antisense oligodeoxynucleotide inhibitor of intercellular adhesion molecule 1, was examined in clinical studies of patients with active mild-to-moderate distal forms of UC and pancolitis.^{59–61} Overall, the mean decrease from baseline in DAI after a 6-week treatment with alicaforsen enema was greater than that of placebo⁶¹ but not greater than that of

a 5-ASA enema 4 g⁵⁹ in either the randomized clinical studies or the open-label study.⁶⁰ An additional randomized, double-blind, placebo-controlled, dose-ranging study of patients with active mild-to-moderate UC demonstrated significant improvement from baseline in DAI in a dose-dependent manner after once-daily treatment with alicaforsen 6, 30, 120, and 240 mg for 4 weeks ($P = 0.003$).⁶² The quality of the evidence is **moderate** for alicaforsen for the treatment of patients with active UC based on study design variability. Additional studies of similar design and endpoints are needed to support the findings presented here. The safety profile of alicaforsen is favorable with reported AEs primarily affecting the gastrointestinal system and occurring in an inverse dose-dependent manner.^{59–62}

Less Common Agents

Efficacy and safety findings of other noncorticosteroid agents (e.g., nicotine, trefoil family factor 3, epidermal growth factor, cyclosporine, rosiglitazone, rebamipide, and tacrolimus) have been reported in clinical studies (see Table, Supplemental Digital Content 2, <http://links.lww.com/IBD/A813>).^{63–69} However, the quality of the evidence is **low** for the use of these agents, because the results presented for each agent are limited to single small studies. The results of these small studies need to be confirmed by additional, well-designed, larger, prospective studies.

DISCUSSION

Rectal therapies are highly efficacious in the treatment of patients with active mild-to-moderate distal forms of UC.⁶ Treatment with 5-ASA suppositories or enemas, or corticosteroid foam or enemas, may often be used instead of, or in addition to, oral 5-ASAs. The findings of this systematic review support the use of rectal therapies as well-tolerated efficacious agents for inducing and maintaining remission in patients with mild-to-moderate distal forms of UC.

The efficacy of suppositories, foam, and enemas was shown for various durations (e.g., 2 wk–8 wk),^{24–26,32,37,39,52,53} and different dosages (e.g., once daily compared with twice daily).^{13,27,50} Overall, efficacy was demonstrated as early as 2 weeks but also was seen with longer durations of treatment.^{24–26,37,39,52,53} Once-daily treatment was found to be as efficacious as a regimen of multiple daily doses.^{13,27,50} A significantly greater percentage of patients receiving 5-ASA suppositories,^{25,26} 5-ASA enemas,^{35,38} or budesonide enemas⁵¹ achieved remission compared with patients receiving placebo. In addition, endoscopic and histologic improvement were demonstrated after treatment with 5-ASA suppositories,^{24–26} 5-ASA enemas,^{32,37,38} and budesonide enemas^{51–53} in placebo-controlled clinical studies. Randomized controlled studies support the use of 5-ASA rectal suppositories^{16,28} and 5-ASA enemas^{40,41} for the maintenance of remission, but no data support the use of rectal corticosteroids for the maintenance of remission.

Overall, rectal therapies had favorable safety profiles, with the frequency of AEs comparable with the rate of those reported with placebo in most studies.^{16,17,24,26,28,32,36,37,39,51,57} Some studies

even reported a greater percentage and number of AEs with placebo when compared with active treatment.^{30,41} Based on plasma cortisol concentrations and adrenocorticotrophic hormone challenge tests, the incidence of steroid-related AEs (including potential effects on the hypothalamic–pituitary–adrenal axis) was low after treatment with budesonide compared with other corticosteroids.^{51–53}

In this review, a number of rectal therapies provided significant treatment benefit compared with placebo, both in patients with active disease and in those with UC in remission.^{16,17,24–26,28,30,32,33,35,37,39,41,50,51,53,56,58,65} Furthermore, rectal therapies examined in non–placebo-controlled studies have demonstrated increased efficacy over baseline for the induction of remission of active UC.^{13,36,48,49,52,54} Overall, the findings of the current systematic review are in agreement with those of 2 earlier systematic reviews by Marshall et al,^{22,71} as well as a previous analysis demonstrating improved efficacy with rectal corticosteroid therapy compared with placebo.⁷² This current review builds on the Cochrane reviews by Marshall et al, which were published in 2010⁷¹ and 2012,²² which comprehensively examined rectal 5-ASAs for the induction and maintenance of remission of UC, respectively.

In conclusion, the findings of this comprehensive review provide a detailed overview of the current landscape of the literature regarding widely used and emerging rectal therapies for the treatment of patients with UC. Overall, most rectal therapies, regardless of formulation, were shown to be well tolerated and efficacious for both the treatment of active UC and for the maintenance of UC remission. Avoiding systemic corticosteroid exposure by using non–steroid-containing agents or therapies with second-generation corticosteroids, such as budesonide and BDP, should be emphasized when selecting topical therapies for patients with these conditions.

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RETRACTION

Elevated IL-13Rα2 in Intestinal Epithelial Cells From Ulcerative Colitis or Colorectal Cancer Initiates MAPK Pathway: RETRACTION

At the request of the authors, the Editors and Publisher retract the article “Elevated IL-13Rα2 in intestinal epithelial cells from ulcerative colitis or colorectal cancer initiates MAPK pathway” by Mandal and Levine published in *Inflammatory Bowel Diseases* (Vol. 16, pp. 753–764, May 2010). This article has been retracted at the request of the corresponding author and the author’s institution, Case Western Reserve University. In a formal university process, the institution reviewed the data and figures associated with this article and concluded that the figures cannot be validated by original data.

REFERENCE

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