Santiago, año 2021

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16.075.909-7
Director Técnico
Laboratorio Biotoscana Farma SpA

Avda. Los Militares 5001 – Piso 12
Las Condes - 7560955 – Santiago, Chile
t. + 56 2 2826 1600
lkmsa.com

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

Russell D. Cohen, MD and Sushila R. Dalal, MD

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.

(Inflamm Bowel Dis 2015;21:1719–1736)

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

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.ibdjournal.org).

Received for publication December 26, 2014; Accepted February 3, 2015.

From the Section of Gastroenterology, The University of Chicago Medicine, Chicago, Illinois.

Technical editorial and medical writing assistance was provided under the direction of the author by Sophie Bolick, PhD, Synchrony Medical Communications, LLC, West Chester, PA. Funding for this support was provided by Salix Pharmaceuticals, Inc., Raleigh, NC.

R. D. Cohen—Speakers Bureau: Abbvie, Entera Health, Salix Pharmaceuticals, Shire PLC. Consultant: Abbive, Cellgene, Entera Health, Hospira, Janssen, Prometheus, Salix Pharmaceuticals, Sandoz Biopharmaceuticals, Shire PLC, Takeda, UCB Pharma. S. R. Dalal has no conflicts of interest to disclose.

Reprints: Russell D. Cohen, MD, The University of Chicago Medicine, 5841 S. Maryland Avenue, MC 4076, Chicago, IL 60637 (e-mail: rcohen@medicine.bsd.uchicago.edu).

DOI 10.1097/MIB.0000000000000379

Published online 28 May 2015.

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 life[8] 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, preclinical 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

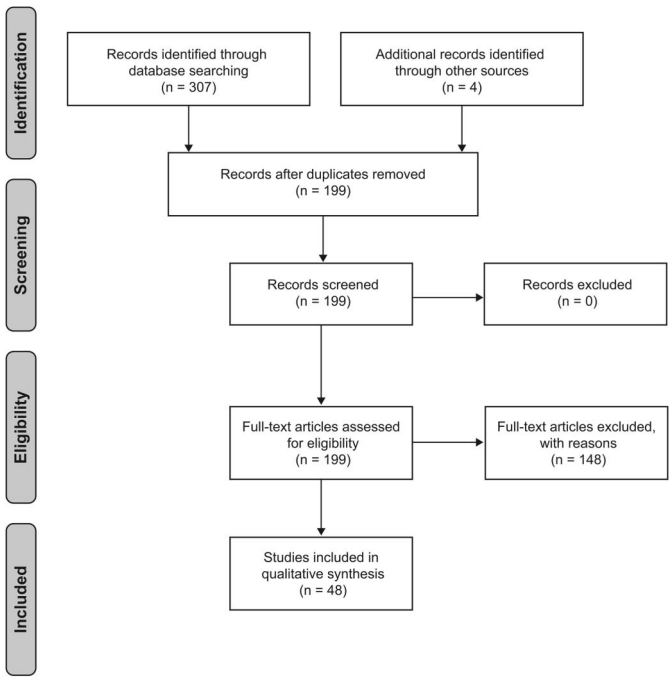

FIGURE 1. PRISMA flow diagram.

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 al[30] 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 ≥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 al[38] 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 al[37] 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% veresus 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 al[38] and Hanauer et al[37] 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 al[38] 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 al[37] 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 al[35] 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 UC[36] demonstrated that ≥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 = 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% veresus 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% ($P = 0.0001$) 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 ($P \leq 0.001$) Total histopathology score: budesonide 2 mg and 8 mg significant improvement versus PBO ($P \leq 0.05$ and $P \leq 0.001$, respectively) Remission rates: budesonide 0.5 mg 7%, budesonide 2 mg 19%, budesonide 8 mg 27% versus PBO 4%; 2 mg versus PBO ($P \leq 0.05$) and 8 mg versus PBO ($P \leq 0.001$)	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 ($P < 0.0001$) Histologic rating scores: significant improvement from baseline to wk 4 ($P < 0.002$)	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	2 mg/100 mL	8 mg/100 mL	Placebo
			N = 57	N = 56	N = 60	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		N = 21
		Baseline		464		411
		Wk 2		440		389
		Wk 4		466		447

[a]$P \leq 0.001$ 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 al[40] was designed to enroll 200 patients, the supply of enemas was limited and limited randomization to 24 patients. Biddle et al[41] 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 al[15] 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 al[15] 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 al[46] 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 Stein[47] 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 recruitment[48] and small study populations, respectively.[54]

Decreased plasma cortisol levels and abnormal adrenocorticotropic 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-aminosalicyclic 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-Aminosalicyclic 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 placebo[61] but not greater than that of

a 5-ASA enema 4 g[59] 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 enemas[51] 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 adrenocorticotropic 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 2010[71] 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.

ACKNOWLEDGMENTS

Technical editorial and medical writing assistance was provided under the direction of the author by Sophie Bolick, PhD, Synchrony Medical Communications, LLC, West Chester, PA.

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Retraction

Elevated IL-13Ra2 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

Mandal D, Levine AD. Elevated IL-13Rα2 in intestinal epithelial cells from ulcerative colitis or colorectal cancer initiates MAPK pathway. *Inflamm Bowel Dis*. 2010;16:753–764.

Digestion

Digestion 2012;86(suppl 1):36–44
DOI: 10.1159/000341947

Published online: October 5, 2012

Topical Therapies in Inflammatory Bowel Disease

Pascal Frei[a] Luc Biedermann[a] Christine N. Manser[a] Maike Wilk[a]
Michael Manz[c] Stephan R. Vavricka[a, b] Gerhard Rogler[a]

[a]Division of Gastroenterology and Hepatology, University Hospital of Zurich and [b]Division of Gastroenterology and Hepatology, Triemlispital, Zurich, and [c]Division of Gastroenterology and Hepatology, Claraspital, Basel, Switzerland

Key Words
Ulcerative colitis · Topical therapy · Enema · Foam · Aminosalicylates

Abstract
Due to misunderstandings about their effectiveness and feasibility, topical (or rectal) therapies with aminosalicylates (5-aminosalicylic acid, 5-ASA) and steroids are often underused in patients with ulcerative colitis (UC). However, many of these patients could be treated solely with rectal/topical therapies, or could benefit from them in combination with oral therapies. We review the evidence for topical therapies containing 5-ASA and budesonide in UC and discuss how these therapies can be optimized in daily practice, thereby improving compliance. Finally, we provide a brief summary of studies on the use of other topical treatments in UC, the results of which were both promising and negative.

Introduction

Ulcerative colitis (UC) is characterized by a continuous inflammation of the colonic mucosa starting from the rectum. The extent of the disease can vary from proctitis to left-sided colitis and extensive colitis or pancolitis. In most patients, only the distal colon is affected [1–3]. Fifty to sixty percent of patients have a proctosigmoiditis, 20–30% have a left-sided colitis up to the splenic flexure and only 20% have extensive colitis or pancolitis. This distribution and the mucosal inflammation enable the use of topical therapies with a good clinical response or even remission in most UC patients. Topical therapies containing budesonide and 5-aminosalicylic acid (5-ASA) can be used both for the induction and the maintenance of remission.

Topical therapies can be applied by suppositories for the rectum in the case of proctitis, and by enemas (liquid) or foam preparations in the case of proctosigmoiditis and left-sided colitis. The distribution of topical therapies has been studied by γ-scintigraphy showing a distribution of enemas up to and sometimes even further than the splenic flexure [4, 5]. Foams seem to distribute more continuously in the rectum and sigma, but they likely do not reach as far as liquid enemas [6].

Induction of Remission by Topical Therapy

In mild to moderate UC, aminosalicylates are the first-line drugs used according to evidence based guidelines.

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E-Mail karger@karger.ch
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www.karger.com/dig

Gerhard Rogler, MD, PhD
Division of Gastroenterology and Hepatology, Department of Internal Medicine
University Hospital of Zurich
Raemistrasse 100, CH–8091 Zurich (Switzerland)
Tel. +41 44 255 9519, E-Mail gerhard.rogler@usz.ch

Ulcerative proctitis is best treated in the first line with 5-ASA suppositories [7] which target the rectal mucosa better than foams or enemas [8]. However, all topical 5-ASA formulations are equally efficacious in the treatment of proctitis [9]. Suppositories with 1,000 mg 5-ASA are effective and appear to be the most feasible topical therapy [7, 10–12]. Suppositories can induce remission in about two thirds of patients with ulcerative proctitis [13]. A meta-analysis of 11 studies showed that topical 5-ASA induces remission in 67% of patients versus only 7–11% induced by placebo therapy. More than 1,000 mg topical 5-ASA did not show a greater benefit [11]. Topical 5-ASA is clearly more potent in inducing remission than topical steroids [14] which are the second-line therapy for patients who do not tolerate the topical 5-ASA therapy (this is rare). If symptoms persist despite adequate topical monotherapy with 5-ASA, topical agents should first be combined (topical steroids and 5-ASA) before switching to a combination with oral therapy [15].

Left-sided colitis should be treated with foam preparations or liquid enemas with an initial dose of at least 2 g of 5-ASA [16]. Topical formulations available in Europe are summarized in table 1. In Switzerland, topical 5-ASA is available as Asacol® liquid enemas (2 and 4 g 5-ASA in a volume of 50 and 100 ml, respectively), Salofalk® liquid enemas (2 and 4 g 5-ASA in a volume of 30 and 60 ml, respectively) or Salofalk® foam (1 g 5-ASA in a volume of 30 ml). If symptoms persist despite adequate topical monotherapy, topical therapy should first be combined (topical steroids and 5-ASA) [15]. In Switzerland, only budesonide is available as an active drug in steroid-containing enemas (Entocort® liquid enema with 2.3 mg budesonide in a volume of 115 ml or Budenofalk® rectal foam with 2 mg budesonide in a volume of 30 ml). If this does not induce remission, oral 5-ASA should be added to topical therapies [16]; this will further increase the chance of inducing remission. Under these conditions, topical therapies should not be stopped as is frequently seen in daily practice. For patients who complain about discomfort, topical therapy can be optimized. In moderate left-sided UC, it may be advisable to combine oral and topical aminosalicyates from the beginning. The combination of oral and topical 5-ASA is clearly more effective (in 88% of patients) than 4 g of rectal aminosalicyates (54%) and 2.4 g oral 5-ASA [16]. Indeed, current European Crohn's and Colitis Organization guidelines recommend initially treating mild to moderate left-sided UC with topical and oral 5-ASA [7].

In the case of extensive colitis, the treatment strategy is very similar to left-sided colitis. The combination of oral and topical 5-ASA therapy should be explored as the latter may specifically reduce the inflammation at the location, the rectum, which is mainly responsible for the patient's complaints of urgency. Indeed, the combination of topical 5-ASA with more than 2 g of oral 5-ASA has been shown to be substantially more potent in inducing remission in extensive colitis than oral 5-ASA therapy on its own [17] which induces remission in a significantly lower proportion of patients. Thus, topical 5-ASA also adds a clear benefit for the treatment of extensive colitis. The effectiveness of topical therapies should be evaluated after 2 weeks. However, if a combination of oral and topical 5-ASA is not sufficient for mild or moderately active UC, an oral/systemic steroid treatment is certainly justified. In extensive colitis, the threshold for using systemic steroids should be lower than in left-sided colitis [7].

Severe UC needs to be treated by intravenous steroids as the first-line therapy. The use of topical treatment has not been studied in severe UC, but topical application (budesonide or 5-ASA) may be considered appropriate in addition to intravenous therapy if the patient is able to retain the rectal therapy for at least 20 min [7]. Some experts, however, state that topical therapies should be avoided in the case of severe UC because they will not be tolerated by the patient. In our daily practice, this is the case in some but certainly not all the patients with severe colitis.

Maintenance of Remission by Topical Therapy

As for the induction of remission, aminosalicylates are the mainstay of therapy for the maintenance of remission in patients with UC. Topical 5-ASA is effective for proctitis and left-sided colitis [7, 13], and is possibly even more effective than oral 5-ASA [7]. Clinical trials with rectal 5-ASA preparations for the maintenance of remission have been performed with various 5-ASA formulations and dosages being administered per day, week or month, respectively [7]. Based on the data available, it can be concluded that in most patients, topical therapy is not necessary on a daily basis, but can be applied less frequently e.g. 7 days per month [18] or 2–3 times per week [19]. A clear dose-response relationship with topical 5-ASA for maintaining remission in distal UC has not been proven [7]. Probably 1 g or less of topically applied 5-ASA is sufficient to relieve inflammation in distal UC [9]. In clinical practice, finding the minimal dosage of 5-ASA for the maintenance of remission remains difficult; anyway, there should be no 'one-fits-all' approach with respect to

Table 1. Formulations for topical use in Europe and the USA

Active drug	Trade name	Formulation	Volume for foams and enemas	Countries
5-ASA	5-ASA 250 mg	supp		SRB
	Asacol 500 mg	supp		I, CZ, DK, FIN, GR, N, S, UK
	Asacol[1] 1 g	supp		I
	Asacolon 500 mg	supp		IRL
	Asamax 250 mg	supp		PL
	Asamax 500 mg	supp		I, PL
	Asazine 500 mg	supp		CH
	Canasa 1000 mg	supp		USA
	Claversal 250 mg	supp		A, B, G, P
	Claversal 500 mg	supp		A, B, E, G, P
	Colitan 250 mg	supp		PL
	Colitofalk 250 mg and 500 mg	supp		B
	Crohnax 250 mg	supp		PL
	Fivasa 500 mg	supp		F
	Laboxantryl 250 mg	supp		GR
	Mesalazin CC Pharma 500 mg	supp		G
	Mesalazine 250 mg and 500 mg	supp		N
	Mesasal 500 mg	supp		DK, N, S
	Pentasa[1] 1 g	supp		A, B, CZ, DK, E, F, FIN, G, I, IRL, N, NL, P, PL, S, SLO, UK
	Rowasa 500 mg	supp		F
	Salofalk 250 mg	supp		CH, CZ, G, GR, HR, P, PL, SLO, NL
	Salofalk 500 mg	supp		A, CH, CZ, G, HR, GR, NL, PL, SLO, SRB, UK
	Salofalk 1000 mg	supp		CH, CZ, E, G, IRL, NL, PL, SLO, UK
	Salazopyrin 500 mg	supp		N
	Asacol 1 g	foam		UK
	Asacol 2 g	foam	2 g/50 ml	CH, I, UK
	Asacol 4 g	foam	4 g/100 ml	CH, I
	Claversal 1 g	foam	1 g/60 ml	B, G, E
	Mesalazin CC Pharma 1 g	foam		G
	Mesalazin Eurim-Pharm 1 g	foam	1 g/30 ml	G
	Mesalazin-Kohlpharma 1 g	foam	1 g/60 ml	G
	Mesasal 1 g	foam	1 g/30 ml	S
	Pentacol 2 g and 4 g	foam		I
	Salofalk 1 g	foam	1 g/30 ml	A, CH, FIN, E, G, IRL, N, NL, PL, S, UK
	Asacol[1] 1 g	enema	1 g/100 ml	DK, FIN, N, S
	Asacol 2 g	enema	2 g/50 ml	B, I, N, NL, IRL, P
	Asacol 4 g	enema	4 g/100 ml	CZ, GR, I, P
	Asalex 2 g and 4 g	enema		I
	Asamax 2 g and 4 g	enema		I
	Asavixin 2 g and 4 g	enema		I
	Claversal 4 g	enema	4 g/60 ml	G
	Colitofalk 2 g and 4 g	enema	2 g/60 ml; 4 g/60 ml	B
	Enteraproct 500 mg	enema		I
	Enterasin 2 g and 4 g	enema		I
	Lextrasa 4 g	enema		I
	Mesaflor 2 g and 4 g	enema		I
	Mesaflor 500 mg	enema		I
	Pentacol 500 mg	enema		I
	Pentasa 1 g	enema	1 g/100 ml	A, B, DK, E, G, IRL, F, HR, N, NL, FIN, PL, S, SLO, UK
	Pentasa 4 g	enema		I
	Quadrasa 2 g	enema	2 g/100 ml	A, F
	Quota 2 and 4 g	enema		I
	Rowasa	enema	4 g/60 ml	USA
	Salofalk 2 g	enema	2 g/30 ml	CH, G, IRL, NL, SLO, UK
	Salofalk 4 g	enema	2 g/60 ml	NL
	Salofalk 4 g	enema	4 g/60 ml	A, CH, CZ, E, G, HR, NL, P, PL, SLO, SRB
Sulfasalazine	Salazopyrin 500 mg	supp		UK, IRL

Table 1 (continued)

Active drug	Trade name	Formulation	Volume for foams and enemas	Countries
Budesonide	Budenofalk rectal foam	foam	2 mg/20 ml	CH, DK, FIN, G, IRL, NL, S, UK
	Budo-San 2 mg	foam	2 mg/30 ml	A
	Entocort	enema	2 mg/100 ml	B, CH, G, FIN, N, NL, PL
	Entocord	enema	2 mg/100 ml	A, B, CZ, DK, E, FIN, G, GR, N, NL, P, S, UK
Hydrocortisone	Proctocort	supp	30 mg hydrocortisone acetate	USA
	Colifoam	foam	100 mg hydrocortisone/60 ml	A, B, DK, FIN, G, GR, I, IRL, S, UK
	Colofoam	foam	100 mg hydrocortisone/60 ml	F
	Cortifoam	foam	90 mg hydrocortisone acetate/? ml	USA
	Cortenema	enema	100 mg hydrocortisone/60 ml	USA
	Proctocort	creme	1%	USA
Prednisolone or similar drugs	Scheriproct	supp	1 mg prednisolone	B, CH, FIN, UK
	Neoproct suppository	supp	1 mg flucortolone-21-pivalate	CZ, DK, FIN, GR, I, S, UK
	Predsol	supp	5 mg prednisolone	UK
	Trianal	supp	0.5 mg triamcinolone	B
	Ultraproct	supp	2 mg fluocortolone	B
	Predfoam	foam	20 mg prednisolone	UK
	Prednisolone 20 rectal foam	foam	20 mg prednisolone/100 ml	UK
	Proctosteroid foam 1%	foam	10 mg triamcinolone	E
	Becloenema	enema	1 mg beclometasone	E
	Beclomethason Klysma FNA	enema	3 mg/100 ml	NL
	Beclomethason-mesalazin Klysma FNA	enema	3 mg beclometasone combined with mesalazine (1, 2, 3 or 4 g)/100 ml	NL
	Betnesol	enema	5 mg bethametasone/100 ml	F
	Pred-Klysma	enema	31.25 mg/100 ml	N
	Predenema	enema	20 mg/100 ml	UK
	Predsol	enema	20 mg prednisolone/100 ml	IRL, UK
	Rectovalone	enema	250 mg Betnesol/100 ml	F

This is a summary of topical therapies available in Europe, based on data from pharmavista.ch, information from pharmaceutical companies who were contacted by the authors and personal communications with gastroenterologists across Europe and the USA. Some names have been slightly modified (e.g. Budenofalk rectal foam is sold as 'Budenofalk Rektalschaum' in Switzerland or 'Budenofalk espuma rectal' in Spain and is listed as 'Budenofalk foam' in this table). Data should be complete for the following countries: Switzerland, Germany, France, UK, Spain, Belgium, Netherlands, Poland, Finland, Slovakia and the Czech Republic, but the authors cannot guarantee that the list of drugs is complete and correct for these and other countries. A = Austria; B = Belgium; CH = Switzerland; CZ = Czech Republic; DK = Denmark; E = Spain; F = France; FIN = Finland; G = Germany; GR = Greece; HR = Hungary; I = Italy; IRL = Ireland; N = Norway; NL = Netherlands; P = Portugal; PL = Poland; S = Sweden; SLO = Slovakia; SRB = Serbia; supp = suppository.

[1] Asacol suppositories and enemas as well as Pentasa suppositories are available in most European countries. Some countries were not specifically listed because of the lack of information on dosages of mesalazine in the specific formulations.

this maintenance. Predictive factors need to be taken into account, such as severity and the frequency of flares before the current remission. If topical therapy is not efficacious enough, combined oral and topical therapy should be considered.

Can Mucosal Healing Be Achieved by Topical Therapies only?

Many experts in the field advocate that mucosal healing should be achieved to gain an optimal prognostic benefit in IBD, irrespective of the treatment used [20]. According to a recent meta-analysis including data from 2513 patients treated with rectal 5-ASA, mucosal healing can be achieved in about 50% of UC patients treated with 5-ASA [21]. There was no evidence in this analysis that the rate of mucosal healing differs between 5-ASA foams and enemas [21]. There is further evidence for the effectiveness in inducing mucosal healing by topical 5-ASA, summarized by Sandborn et al. [22] in a recently published post hoc analysis. We conclude from their results that mucosal healing is possible when 'only' rectal 5-ASA therapies are used in distal colitis. There is no argument for a prescription of aggressive anti-TNF antibodies which give no guarantee for mucosal heal-

ing. In the ACT-2 (Active Ulcerative Colitis 2) trial, about 50% of the patients achieved mucosal healing under infliximab treatment [20]. Naturally, one has to be aware that anti-TNFs are usually given for moderate to severe UC and that these data are no head-to-head comparison.

Side Effects of Topical Therapy

Topical therapies may have disturbing side effects including leakage, problems with retention and bloating [11]. Serious complications such as rectal perforation are only described on the level of case reports [23] and can be assumed to be absolute rarities. Systemic drug-related side effects are rare. Topically applied (and orally administered) budesonide has a very low bioavailability of only 10–15% [24]; it therefore does have side effects such as cushingoid features or a measurable suppression of basal cortisol levels in the vast majority of patients [25, 26]. In contrast, with conventional systemic steroids such side effects occur often [27].

Topically applied 5-ASA does not have relevant systemic side effects. Idiosyncratic side effects such as interstitial nephritis, myocarditis or pancreatitis are very rare even when oral and systemic forms of 5-ASA are used, and there is no proven relationship between duration or cumulative dose and the risk of renal disease [28, 29]. We know of no published cases of interstitial nephritis induced by topical 5-ASA therapies. However, there is one case report on a 5-ASA-induced acute pancreatitis after the use of 5-ASA suppositories [30]. In addition, one case report has been published of a 5-ASA enema-induced relapse of acute pancreatitis in a patient who had already had a 5-ASA-induced acute pancreatitis after intake of oral 5-ASA [31]. This highlights that re-exposure to topical 5-ASA in the case of pancreatitis, myocarditis, epicarditis or interstitial nephritis and other forms of 5-ASA hypersensitivity reactions requires a very careful risk/benefit analysis.

Adherence to Topical Therapy

As is relevant for other therapies, adherence and compliance are crucial for the success of topical therapy in UC patients. Nonadherence in patients with IBD can be as high as 60% [32]. In a study on medication nonadherence in patients on 5-ASA for the maintenance of remission, the majority of patients with a relapse of UC were nonadherent [32]. Studies have shown that adherence is worse in maintenance therapies (50%) than in short-term IBD therapy [32, 33]. However, most patients with nonadherence simply forget to take their medication (because they feel better when in IBD remission) [34].

Despite problems with compliance and the fact that most patients (80%) prefer oral treatment alone [35], it is important to note that most UC patients are willing to use topical therapies [36, 37]. However, the efficacity of topical therapy is much less likely if it induces too much urgency [37–39]. A Spanish study showed that 5-ASA suppositories are well tolerated and are considered comfortable for a treatment lasting at least 1 year [5]. For enemas, it seems that urgency is associated with the higher the volume applied. Thus, most patients prefer foam preparations with less volume than liquid enema formulations [40, 41], although a Cochrane review in 2010 summarized conflicting experiences in clinical trials [12]. The urgency induced by topical therapies can be explained by the fact that the rectal compliance is clearly reduced in patients with active UC [42–44]. We advise taking 2 mg of loperamide 20–30 min before applying the enema in order to reduce urgency, although there is no evidence from clinical studies in UC for this approach. However, in a trial using loperamide in obese patients with loose stools as a side effect of orlistat treatment, loperamide had at least some effect on anorectal sphincter function [45], but no effect on rectal capacity or compliance. Furthermore, we advise lying down in a left-sided or prone position after applying topical therapy. There are no studies on how long topical therapy should be retained to be maximally effective, but even if part of the topical therapy gets evacuated, it can be assumed that enough of the drug will adhere to the mucosa [9]. So patients should be motivated to try topical therapies even if they cannot be retained for a long time.

The Doctor's Adherence to Guidelines and Evidence

A successful topical therapy not only necessitates adherence on the part of the patient, but also the doctor's adherence to evidence and guidelines. In an interesting survey among Spanish gastroenterologists, only 12–17% of gastroenterologists considered topical 5-ASA as a therapy of choice for distal colitis [46], and only 31% used the combination of oral and topical 5-ASA for extensive mild to moderate UC.

Furthermore, despite evidence that topical 5-ASA is more potent in reducing remission than topical steroids

[14], 31–47% of gastroenterologists considered rectal steroids to be as effective as topical 5-ASA [46]. In an analysis of 12 consecutive patients with UC, Reddy et al. [47] found that 75% of the patients with left-sided UC had not been on a topical therapy.

New or Rare Indications and Strategies for Topical Therapies

In patients with Crohn's proctitis or left-sided colitis, one could argue that topical steroids or 5-ASA might be useful. However, it is important to note that Crohn's disease is characterized by a transmural inflammation which may be more difficult to cure by topical application of steroids. Currently, there are no studies available on the effects of 5-ASA or steroid topical therapies in Crohn's disease, despite an extensive literature search. Furthermore, it must be kept in mind that there is also no evidence for oral 5-ASA in Crohn's colitis. Thus, topical therapies cannot be recommended for Crohn's proctitis or left-sided Crohn's colitis.

Besides topical therapies with 5-ASA and steroids, some small studies are available with conflicting results on new topical therapies in UC. The most promising alternative topical therapies include the use of probiotics and fecal transplantation, tacrolimus and alicaforsen. Several other therapeutic strategies have been reviewed by Lawrance [48] and are only mentioned briefly in this review.

- Probiotics: There is good evidence for *E*scherichia *coli* Nissle 1917 in the maintenance of remission in UC. *E. coli* Nissle was consecutively studied as a topical preparation in a double-blind study with 90 patients with moderate distal UC. Liquid enemas containing 10exp8 *E. coli* Nissle/ml were compared to placebo enemas over a treatment period of 2 weeks. A positive effect could only be demonstrated in the per protocol analysis ($p = 0.0446$), but not in the intention-to-treat analysis ($p = 0.4430$) [49].
- Fecal transplantation: Given the complexity of the fecal microbiota, it seems reasonable that the approach of fecal transplantation will be more effective than using only a single probiotic strain. Fecal transplantation has mainly been done for the treatment of recurrent *Clostridium difficile* infection, but also in patients with therapy refractory UC. More than 20 years ago, the first case of fecal transplantation in UC was published [50]. Since then, there have been various case reports showing that fecal transplantation (going by various other names such as 'stool transplant', 'fecal transfer' and 'fecal microbiota transplantation') can induce remission in UC patients [51]. In Crohn's disease, a pilot study showed no clinical or endoscopic efficacy of fecal transplantation in 4 patients [52]. Currently, at least 3 clinical trials are ongoing to study the efficacy of fecal transplantation in UC. NCT01560819 in the USA is a phase I pilot study in 10 pediatric UC and CD patients aged 7–12 years. Patients will receive 5 sessions of fecal transplantation by enema with feces from a donor chosen by the family. NCT01545908 in Canada is a phase II study for the induction of remission in active UC and aims at enrolling 130 patients. The active arm will be a fecal transplatation from a nonrelated donor and the placebo enema will be a saline enema. NTR2862 in the Netherlands ('turn trial') is a placebo-controlled trial in adults aged 18 years or older and aims at enrolling 40 patients. The active arm will be a fecal transplantation from nonspecified healthy donor by duodenal tube infusion and the placebo arm will receive their own feces.
- Tacrolimus: This is a strong immunosuppressant which is able to induce and maintain remission in severely active UC. However, high serum levels are necessary to induce remission, which predisposes to drug side effects such as tremor, headache or renal insufficiency. Interestingly, open-label studies with (not commercially available) topical tacrolimus preparations were able to induce remission in left-sided UC at a low dose of 1.8–4 mg (either as suppositories, enemas or ointments) and without leading to high serum levels of tacrolimus as is observed with oral intake [53, 54]. No relevant side effects were observed. Thirteen of 19 patients in 1 study showed a clinical improvement in disease activity after 4 weeks of local tacrolimus treatment. The other study reported clinical remission in 6 of 8 patients. These results are promising, but a commercially available topical tacrolimus preparation would be needed to allow a wide-spread use of this strategy in left-sided colitis.
- Alicaforsen: In an open-label study with nightly rectal enemas of alicaforsen, an antisense oligodeoxynucleotide against intercellular adhesion molecule 1 mRNA, 33% of patients reached remission at the end of the 6-week study period [55]. Similarly, 7 of 12 patients using alicaforsen with chronic unremitting pouchitis attained remission [56]. These results look very promising, but alicaforsen is still only a candidate as an orphan drug in Europe. Further randomized trials are clearly warranted.

Several small and early studies analyzed various other therapeutic approaches, some with promising but not convincing results to recommend their use in clinical practice. [48]

- Liquid enemas with cyclosporine initially looked promising in open-label studies [57], but were not shown to be active in placebo-controlled randomized trials [58].
- Butyrate enemas were likewise promising in open-label studies [59], but not in placebo-controlled randomized trials [60].
- Since impaired epithelial expression of peroxisome proliferator-activated receptor χ (PPARχ) ligand was described in UC, a topically administered rosiglitazone has been studied in a pilot study and was successful in IBD patients who had not been previously treated [61]. It was, however, withdrawn in 2010 due to cardiovascular side effects. We are not aware of ongoing or planned studies with other peroxisome proliferator-activated receptor γ ligands in IBD.
- Nicotine enemas containing 6 mg of nicotine have been studied in a large randomized double-blind study including 104 patients with active UC [62]. Topical nicotine 6 mg was not found to be efficacious for active UC.
- Arsenic suppositories (250 mg b.d. for 4 weeks) have been studied in only 1 small study with 10 patients [63]. In 9 of 10 patients, symptoms and endoscopic signs of proctitis resolved within 2 weeks, but 6 of 10 patients showed a relevant systemic arsenic absorption. Currently, arsenic suppositories are not often used.
- Further therapeutic strategies include the use of lidocaine, ecabet, epidermal growth factor, remapimide and thromboxane enemas [48].

Conclusions

Topical therapies are effective and feasible in proctitis and left-sided colitis for both the induction and maintenance of remission. If topical therapies are not sufficiently efficacous in left-sided UC, they should be combined with and not replaced by oral 5-ASA. Topical budesonide should be used if topical 5-ASA is not effective or in the case of intolerance to topical 5-ASA which is rare. In extensive colitis, oral and topical 5-ASA should be combined. Only in severe UC, may topical therapies be omitted due to insufficient efficacy and patient intolerance. There is insufficient evidence for the efficacy of topical therapies in Crohn's disease including Crohn's colitis. Some new topical therapeutics have recently been or are currently being studied for the treatment of UC.

Acknowledgements

The authors thank Dr. Sarah Schneeberger, pharmacist at the Kantonsapotheke Zurich, for her help in creating table 1 using pharmavista. P.F. thanks members of the young clinicians program at the UEGW 2009 who helped to collect data on topical therapy in their home countries. Our research was supported by grants from the Swiss National Science Foundation to S.R.V. (Grant No. 320000-114009/3 and 32473B_135694/1), by the Zurich Center for Integrative Human Physiology, University of Zurich and the Swiss IBD Cohort (Grant No. 3347CO-108792).

Disclosure Statement

Pascal Frei, Luc Biedermann, Maike Wilk, Christine N. Manser and Michael Manz have no conflicts of interest. Gerhard Rogler has received grant support from FALK and Tillots. Stephan R. Vavricka has received grant support from MSD, UCB, Tillots and Abbott.

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