A Comprehensive Review of Topical Therapies for Distal Ulcerative Colitis

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Abstract: Patients with ulcerative colitis (UC) limited to distal segments of the colon and rectum are often poorly represented in large clinical therapeutic trials, yet they constitute up to two-thirds of all UC patients. The propensity of UC to be most severe distally has also resulted in many oral or systemic therapies with lower levels of therapeutic success and mucosal healing in the distal regions of the colon. Topically administered mesalamine and corticosteroid agents have been utilized for decades in patients with distal UC but are often poorly accepted by patients and their prescribing physicians due to difficulties in administration and embarrassment. Formulation advances in the mesalamine preparations have led to the addition of topical 5-aminosalicylic acid (5-ASA) foams and gels to the existing options of liquid enemas and suppositories. Comparable advances in the use of topical corticosteroids have also taken advantage of the development of topical budesonide and similar safer corticosteroid preparations that promise clinical efficacy while delivering fewer systemic corticosteroid side effects. Combination therapy with oral and topical 5-ASA agents, or with topical 5-ASA and topical corticosteroid compounds, has further expanded the armamentarium for prescribers. Novel topical applications of currently existing therapies such as tacrolimus and cyclosporine show varying degrees of promise; the growing area of biologic and novel small molecules raises the possibility of a new wave of topically applied therapies for patients with distal UC and ulcerative proctitis.

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) characterized by inflammation of the rectal and colonic mucosa. UC involves the rectum in 95% of cases and may extend continuously to more proximal parts of the large intestine. The extent of the disease is typically categorized as ulcerative proctitis (endoscopically visualized disease up to the rectosigmoid junction), left-sided colitis (extending from the sigmoid to the splenic flexure), or extensive colitis (extending beyond the splenic flexure).[1] Some classification systems may also list ulcerative

proctosigmoiditis, whereby the inflammation involves the rectum and the sigmoid colon.

The extent of disease is not always stable, and the risk for proximal progression of the disease has been shown in approximately 50% of patients.[2] Nevertheless, distal disease is much more common than extensive colitis, involved in approximately two-thirds of UC patients.[1,3,4] The clinical course of UC is highly variable and ranges from a single mild episode to potentially life-threatening severe continuous disease. Approximately 25% of all UC patients will eventually undergo colectomy.[5] The different treatment options are usually determined by the severity and extent of the disease.[6] More distal disease will enable the option to treat with rectally administered local therapies, allowing for direct delivery of the drug to inflammation sites in the distal colon and reduced systemic drug exposure.[6,7] However, these agents are often underused in this population of patients,[7,8] mostly due to patients' preferences but also due to health care provider bias or unfamiliarity with these products.[6,9,10] Topical therapies may be administered alone in patients with distal disease or together with oral therapies (combination therapy) in patients with more extensive disease, in which case the therapies are often withdrawn once a patient has achieved a satisfactory clinical response or remission. Failure of topical therapies may require advancement to combination with oral therapies or to systemically active agents.

This article examines the current state of the literature regarding the efficacy and safety of different topical treatment options for patients with distal UC. Similar reviews of oral and systemic options for patients with UC provide more in-depth summaries of their use.[11-17] Figure 1 shows a strategy to assist in the choice of an initial and subsequent topical treatment in these patients.

Topical Treatments

5-Aminosalicylic Acid

Suppositories Sulfasalazine- or mesalamine-based compounds, or 5-aminosalicylic acids (5-ASAs), have been used for treating UC patients for several decades and are first-line therapy for patients with ulcerative proctitis. The first placebo-controlled trial in UC was performed in 1965.[18] Thereafter, the effect of 5-ASA drugs given topically on mild to moderate distal UC was assessed thoroughly. Induction of remission was demonstrated in several randomized, controlled studies in which both clinical[19] and endoscopic[20] remission were achieved in approximately 80% of the patients. This was also shown in a Cochrane review from 2010, demonstrating rectal 5-ASA superiority in comparison to placebo for inducing clinical, endoscopic, and histologic improvement and remission, with an odds ratio of 6 to 8 compared to placebo.[21] The dose and frequency were not constant in all studies. Nevertheless, at least for ulcerative proctitis, the use of 5-ASA suppositories in the range of 500 mg to 1 g[22,23] has led to these doses being recommended for the induction of clinical remission in several international guidelines.[24,25] Regarding the efficacy of maintaining remission, several other randomized, double-blind, placebo-controlled studies confirmed the usefulness of the 5-ASA agents for periods of up to 2 years.[26-28] The same effect was also shown in a Cochrane review, indicating significant advantage over placebo in maintaining clinical and endoscopic remission.[29] Again, no dose-response relationship was observed. For patients achieving remission with this treatment, some clinicians advocate continuing the same dose as a maintenance long-term therapy[24]; however, remission rates with 2 to 3 weekly treatments have also been shown to be comparable to daily use.[27,28] The safety profile of 5-ASA suppositories has been comparable to placebo in randomized, placebo-controlled trials, with the most common adverse events related to gastrointestinal intolerance.[30]

Enemas Mesalamine enemas are first-line therapy for patients with left-sided UC or proctosigmoiditis. The yield of 5-ASA enemas was evaluated in several randomized, placebo-controlled studies more than 30 years ago.[31,32] Once-daily enema demonstrated clinical, endoscopic, and histologic remission in the majority of patients experiencing mild to moderate left-sided colitis. More recently, the effect on patient-reported, health-related quality of life was demonstrated in patients with active UC receiving 1 g of 5-ASA for 4 weeks in combination with oral 5-ASA.[33] The clinical and endoscopic improvements occurred as early as 15 days after administering the drug (78% and 67%, respectively),[34] with better effects seen in 4 to 6 weeks. A post-hoc analysis[35] of 2 previously published studies[32,36] demonstrated the early effect of this drug. In the first study, 31.4% of patients in the treatment arm reported no rectal bleeding vs 5.5% in the placebo arm by day 2 (P<.0006). By week 3, both studies demonstrated significantly higher rates of remission (48.6% and 57.9% in the treatment groups vs 9.6% and 18.2% in the placebo groups, respectively).

The minimal dose needed to achieve effect was also studied thoroughly in several clinical trials.[34,37] Doses of 1, 2, and 4 g were assessed in mild to moderate UC patients. Compared with placebo, clinical, endoscopic, and histologic improvement or remission occurred in a greater percentage of patients receiving any dose of 5-ASA with a similar frequency across dose groups. One study demonstrated a small difference favoring the dose of 4 g, although the benefit did not reach statistical significance.[34] The efficacy of 5-ASA enemas was also examined

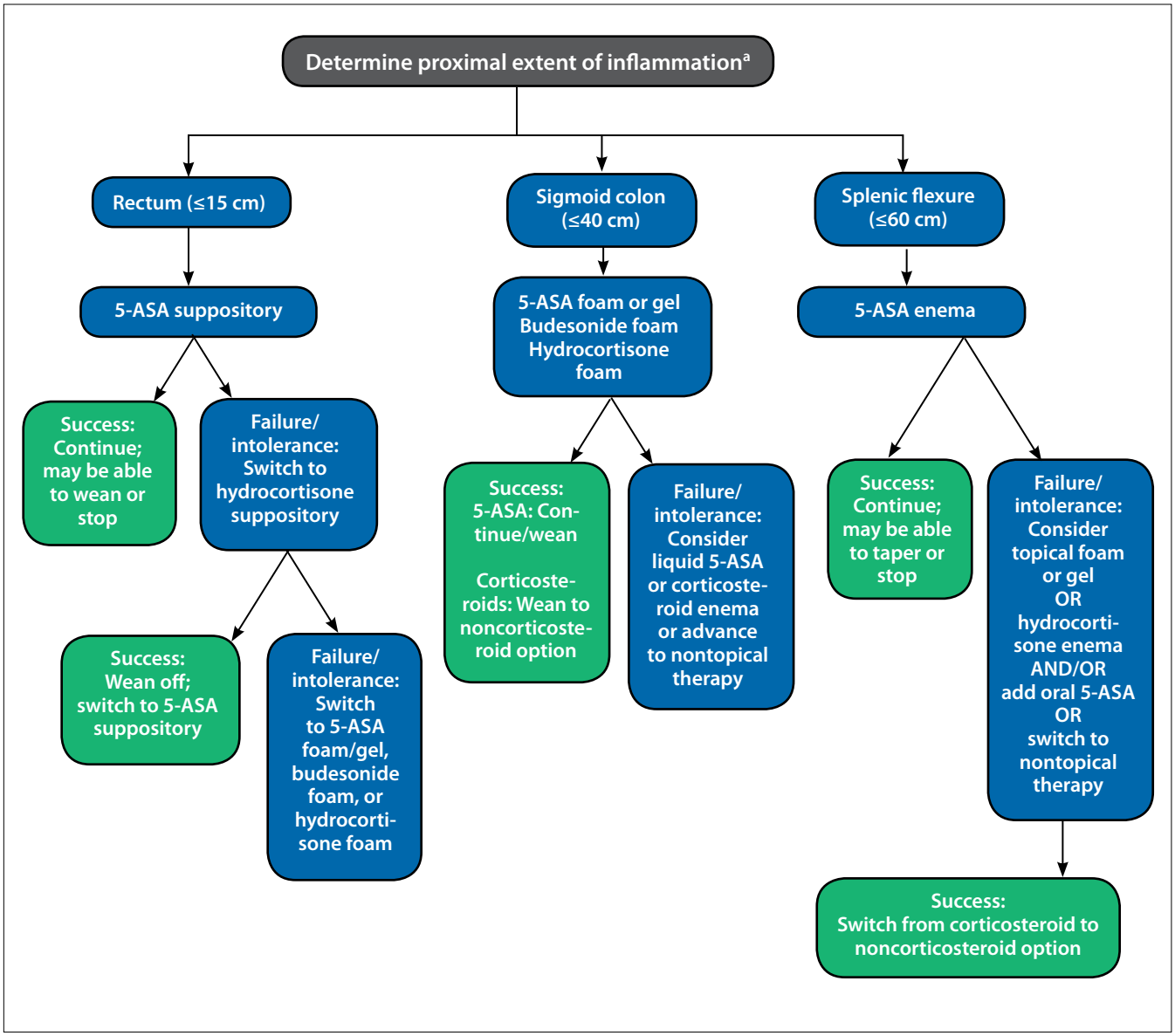

Figure 1. Decision tree for initial and subsequent topical therapies in patients with mild to moderately severe ulcerative proctitis, proctosigmoiditis, or left-sided ulcerative colitis.

5-ASA, 5-aminosalicyclic acid.

[a]As measured from anal verge on sigmoidoscopy or colonoscopy.

for the maintenance of remission in patients with mild to moderate distal UC, mostly in addition to oral treatment. Both 5-ASA enema alone[38] and the combination of 5-ASA enemas with oral 5-ASA[39] resulted in a lower rate of relapse compared to placebo or use of oral 5-ASA alone. These studies demonstrated a very low relapse rate of 18.2% to 25.0% after 1 year of treatment, although the small treatment group size may limit the reliability of these findings.

Foams Mesalamine foams or gels may be considered first-line therapy in patients with ulcerative proctosigmoiditis in countries where these formulations are available. In an effort to improve drug delivery to the inflamed mucosa as well as patient adherence to treatment, foam enema formulations of mesalamine have been developed. A study comparing patient acceptance of a liquid and a foam enema containing 5-ASA in 233 patients with active distal UC showed a significantly higher proportion of patients

receiving the foam enema accepting treatment compared to liquid enemas, as the foam formulations were more comfortable, more practical, and easier to retain, and interfered less with daily living.[40] Two randomized, controlled studies have evaluated the efficacy of foam formulation of 5-ASA for patients with mild to moderate distal UC. Pokrotnieks and colleagues evaluated the efficacy of low-volume 5-ASA foam (1 g/30 mL; total volume, 60 mL) in a group of 111 patients with mild to moderately active ulcerative proctitis, proctosigmoiditis, or left-sided UC.[41] Clinical remission was more frequent in the foam group than in the placebo group (65% vs 40%; $P<.008$).[41] High-volume (1 g/60 mL; total volume, 120 mL) 5-ASA foam has been shown to be therapeutically equivalent to a standard 5-ASA enema (4 g), achieving 64.9% and 69.5% remission after 4 weeks of treatment, respectively.[42] Endoscopic remission was similar as well (33.3% vs 33.9%, respectively). The tolerability of the 2 formulations was also comparable. When evaluating 330 patients for efficacy and safety, clinical remission rates at week 6 were 77% on low-volume foam vs 77% on high-volume foam ($P=.00002$ for noninferiority). The low-volume foam was associated with a lower frequency of severe discomfort, pain, and retention issues.[43]

Gels Another treatment formulation is mesalamine rectal gel preparation. A randomized, controlled trial compared daily 2-g gel enemas vs 2-g foam for induction of remission in 103 patients with mild to moderate left-sided UC or proctosigmoiditis.[44] After 4 weeks of treatment, clinical remission was achieved by 76% of mesalamine gel–treated patients and 69% of foam-treated patients ($P=.608$). Endoscopic remission rates at week 4 were 51% and 52% for the gel and foam enemas, respectively ($P=.925$). The patients receiving the gel formulation reported less difficulty in retaining the product, less discomfort with administration, and less bloating.

Comparison Between Oral and Topical 5-Aminosalicylic Acid

Several studies have investigated the advantage of topical mesalamine over the oral formulation in patients with mild to moderate distal UC for induction of therapy. Nevertheless, no significant difference was found between the 2 treatment options, both in an individual study[36] and in a meta-analysis combining the data.[45] For maintenance therapy, when intermittent topical 5-ASA was compared to oral therapy, the relapse rate was significantly lower with the topical therapy (relative risk [RR], 0.38-0.64).[45,46]

Besides its use as monotherapy, topical treatment with 5-ASA can be used as an adjunct treatment option to augment efficiency of oral therapy. In a 2012 meta-analysis, Ford and colleagues demonstrated a significant reduction in the risk of failure to achieve remission with combined therapy compared with oral 5-ASA alone (RR, 0.65).[45] In addition, one of the studies included in the meta-analysis demonstrated shorter mean time to remission in the combined therapy arm.[36] There was no significant difference in the rate of adverse events between patients receiving combination and oral 5-ASAs.

Corticosteroids

Corticosteroids have traditionally been used in patients with IBD due to their anti-inflammatory effects, speed of onset, and low cost. Traditional corticosteroids (eg, prednisone, prednisolone, hydrocortisone) can be administered by intravenous, oral, or topical routes, the latter including suppositories, foams, and enemas. The systemic use of corticosteroids poses significant risk for both short- and long-term side effects, including diabetes, adrenal insufficiency, and osteoporosis.[47] As a result, mesalamine-based products are preferred, particularly for long-term therapy. Topically applied corticosteroids offer the advantages of a more targeted treatment with fewer systemic effects.

New second-generation corticosteroids have lower bioavailability due to extensive first-pass metabolism in the liver, resulting in reduced systemic side effects[48] and adrenal suppression.[49,50] Two main products are available, beclomethasone dipropionate (BDP) and budesonide,[51] which are delivered in enema, foam, or suppository configurations.

Enemas Two randomized, controlled, double-blind studies of patients with active distal UC have demonstrated endoscopic and histologic response to budesonide enema (2 mg) after 4 weeks[49] and 6 weeks.[52] In the latter study, a dose-response relationship was also shown. Remission was achieved in 19% of patients in the 2-mg budesonide group ($P<.05$) and in 27% of patients in the 8-mg budesonide group ($P<.001$) compared with 4% in the placebo group.[52] Doses lower than 2 mg have not shown benefit over placebo. BDP enema (3 mg) was as effective as prednisolone (30 mg) in inducing clinical remission (29% vs 25%, respectively) and response (40% vs 47%, respectively).[48] When compared with 5-ASA, BDP has achieved similar results, with a clinical remission rate of 36.7% in the BDP group and 29.2% in the 5-ASA group.[53] Comparing 5-ASA to budesonide yielded a statistically significant benefit to the former in achieving clinical remission. Week 4 remission was 63.5% for budesonide enemas and 77.2% for mesalamine enemas ($P<.05$).[54]

Foams Similar to 5-ASA products, the need for better adherence and comfort, especially in the setting of

inflamed colonic mucosa, has advanced the development of foam formulation in addition to enema. A 2006 randomized, controlled trial evaluated clinical response in 541 patients to either budesonide foam or enema.[55] Clinical remission rates were 60% for budesonide foam and 66% for enema (P=.02 for noninferiority). Both formulations were safe and no drug-related serious adverse events were observed. Because of better tolerability and easier application, most patients (84%) preferred the foam formulation. In addition, a comparison of budesonide foam with classic corticosteroid rectal foam therapies demonstrated similar efficacy (remission rates of approximately 50%).[56]

Budesonide foam also has additive treatment effects in patients already receiving oral mesalamine. Foam addition to oral mesalamine (dose <4.8 g) yielded better success in achieving clinical remission defined by a Mayo score of 1 or less, no rectal bleeding, and either no change or an improvement in stool frequency.[57]

Combination 5-Aminosalicylic Acid and Topical Corticosteroid Therapies

The combination of topical mesalamine and corticosteroids may be of benefit as well to either treatment separately. BDP (3 mg) and mesalamine (2 g) enemas produced significantly better clinical, endoscopic, and histologic results than either agent alone, with endoscopic improvement in 100% of patients treated with the combination vs 75% treated with BDP and 71% in the 5-ASA group.[58] Combinations of mesalamine and corticosteroids in enemas and suppositories may be offered by various compounding pharmacies that can customize the combinations and concentrations of each agent. Figure 2 displays various strategies for treating patients with refractory distal colitis.

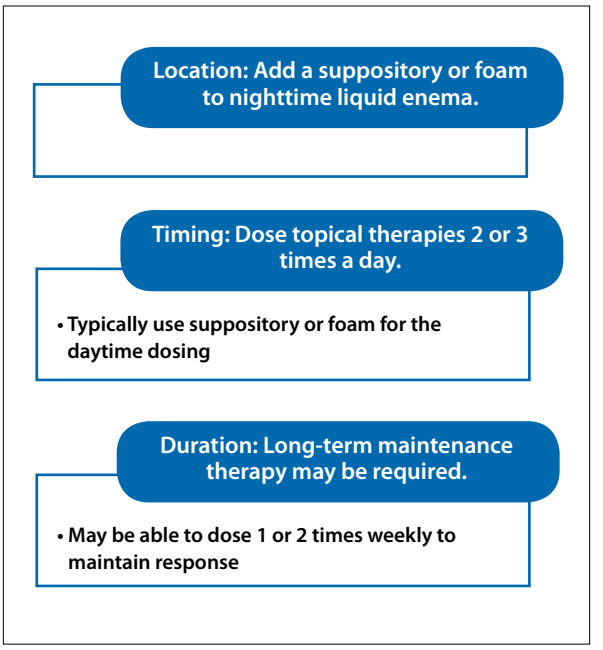

Figure 2. Strategies for refractory distal colitis utilizing topical therapies.

Other Therapeutic Approaches

Tacrolimus Suppositories

Tacrolimus delivered as a topical ointment has been studied in a few small trials. Lawrance and Copeland reported remission with reduction or cessation of corticosteroids in 6 of 8 patients with refractory ulcerative proctitis or proctosigmoiditis limited to 30 cm after 8 weeks of therapy.[30] Lawrance and colleagues subsequently conducted a double-blind, randomized, placebo-controlled trial of rectal tacrolimus (0.5 ng/mL) for 8 weeks; the benefit of the drug over placebo was so apparent (clinical response in 73% vs 10%; P=.004) that the study was stopped after just 20 patients due to ethical concerns.[59] Mucosal healing was seen in 73% vs 10% on placebo, and clinical remission occurred in 45% vs 0% of patients, respectively. These benefits were observed with no safety findings.

More recently, Jaeger and colleagues reported on a retrospective analysis of 23 patients with ulcerative proctitis refractory to combined topical and systemic therapies who received tacrolimus suppositories (2 g) twice daily.[60] The authors reported that 52.3% of patients achieved clinical remission, defined as a clinical activity index score of less than 4. Mean serum tacrolimus levels were 5.5 ng/mL, suggestive of systemic absorption. Adverse events were reported in 1 patient with elevated serum creatinine (fully reversible after cessation of therapy), hand tremor, headache, and fatigue.

Cyclosporine Enemas

Cyclosporine is widely heralded as an extremely effective agent for UC when given intravenously; there are far less data on topical administration in patients with distal colitis. Although open-label experiences have reported response rates of 50% or higher with nightly retention enemas,[61,62] a placebo-controlled trial failed to show benefit vs placebo.[63]

Nicotine Enemas and Other Experimental Therapies

Investigations into the potential protective role of nicotine in patients with UC included open-label and placebo-controlled studies of nicotine enemas in patients with distal colitis. Although an initial open-label study had promising results with clinical, endoscopic, and histologic score improvements,[64] there was no benefit seen

in a subsequent 6-week, 104-patient, placebo-controlled trial with nicotine enemas.[65]

Multiple other experimental therapies have been studied in patients with distal UC but are beyond the scope of this review; as the use of biologic and novel small-molecule agents continues to expand, there will hopefully be further dedicated studies of their efficacy in this patient population.

Conclusion

Patients with distal UC are often an overlooked population with IBD, as its characterization tends to translate into undertreatment and continued patient symptoms. Coupled with the higher rate of more debilitating symptoms arising from the rectum and distal colon, this has resulted in unnecessary patient suffering. The advent of various formulations of rectally applied 5-ASA and corticosteroids, along with the substitution of traditional corticosteroids with safer agents such as budesonide, has resulted in more topical options for patients with distal colitis. The application of alternative agents, such as tacrolimus, as well as upcoming anticipated studies with some of the newer biologic and novel small-molecule agents being developed for IBD, raise the possibility of further advances in the field, higher patient satisfaction, and better health.

Dr Cohen serves on the speakers bureau for AbbVie and Takeda; serves as a consultant for AbbVie, Celgene, Janssen, Pfizer, and Takeda; and has conducted clinical trials for AbbVie, Boehringer Ingelheim, Celgene Corp, Crohn's & Colitis Foundation of America, Genentech, Gilead, Hollister, Medimmune, Pfizer, Receptos, Schwarz Pharma, Seres Therapeutics, and Takeda. His spouse serves on the Board of Directors for Aerpio Therapeutics, Novus Therapeutics, and Vital Therapies, Inc. Dr Weisshof serves on the speakers bureau for AbbVie, Takeda, and Janssen.

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