EDITORIAL

Topical Therapy in Ulcerative Colitis: Always a Bridesmaid But Never a Bride?

See "Budesonide foam induces remission in patients with mild to moderate ulcerative proctitis and ulcerative proctosigmoiditis," by Sandborn WJ, Bosworth B, Zakko S, et al, on page 000.

Proctitis, proctosigmoiditis, and left-sided ulcerative colitis define the anatomic extent in 70% of patients at inception in the population-based IBSEN (Inflammatory Bowel South-Eastern Norway) cohort from Scandinavia.[1] Despite rather limited affected area of the colon, these patients suffer from significant morbidity and poor quality of life, because active distal disease elicits symptoms such as urgency, tenesmus, blood loss per anum, and a feeling of incomplete evacuation. Limited extent of disease makes topical anti-inflammatory therapy appealing owing to safety and efficacy. Newer preparations of effective topical therapy that are relatively small in volume and well-tolerated may increase options for treatment of such patients. In addition, topical mesalamine combined with oral mesalamine may also provide additional benefits in terms of efficacy in more extensive ulcerative colitis, as well as in more limited disease.[2–4]

Mesalamine and corticosteroid preparations are available as topical therapy. Suppositories, foam, gel, and liquid enemas are preparations used for proctitis, proctosigmoiditis, and left-sided colitis, tailoring the therapy to extent of disease, tolerability, and patient preference. Suppositories are best used for proctitis, whereas foam enema, rectal gel, and liquid enema are used for proctosigmoiditis and left-sided colitis. The formulations have different physicochemical characteristics and different extent of spread shown by scintigraphic studies, but scintigraphic studies can sometimes be challenging to interpret, difficult to conduct in patients with inflammation, and very few research centers have the experience to conduct scintigraphic studies.[5] Mesalamine suppositories can reach rectum and even distal sigmoid; foams, gels, and liquid enemas can be used to treat proctosigmoiditis and left-sided colitis. Foams and gels are well-retained and tolerated by patients and may provide a homogeneous coating of the mucosa. However, the volume of the topical therapy influences the extent of proximal spread and possible tolerability of the treatment. Larger volumes may reach more proximal colonic areas, but are also more likely not to be well-tolerated when acute inflammation reduces rectal compliance. Individuals may vary in their tolerance not simply based on the formulation and volume, but also the nature and ease of use of the delivery device and the shape of the nozzle. In addition, rare hypersensitivity reactions to topical mesalamine have been reported and these patients are appropriate for topical steroids.[6]

Some of the predominant symptoms of proctitis, such as urgency, tenesmus, and a feeling of incomplete evacuation, are not formally recorded and scored as part of clinical disease activity indices such as the Mayo score or the evolving Patient-Reported Outcome tools.[7,8] Patients with proctitis may have frequent bloody bowel movements, but not 'true' diarrhea. Many systemic therapy trials in ulcerative colitis exclude topical therapies and the effect of topical therapies on bowel frequency and consistency has not been studied rigorously. Rectal bleeding and endoscopic appearance seem to best reflect severity of proctitis and therapeutic response to topical therapies, but other patient reported parameters associated with proctitis need to be explored and incorporated into patient reported outcome tools specifically for proctitis.

In a large Swiss Inflammatory Bowel Disease Cohort Study, it was clear that topical therapy is underused even in patients where the disease extent would make such therapy the optimal choice.[9] Other studies have also expressed concern over the underuse of rectal therapies, even in distal ulcerative colitis.[10] Physicians may anticipate poor acceptability of topical therapy in their patients, but the evidence supports good acceptance by >80% of patients in clinical studies such as the PINCE study.[2] Topical therapy with mesalamine with or without oral mesalamine may lead to early cessation of rectal bleeding and possibly mucosal healing.[2] Such topical therapy may continue to maintain remission once remission has been induced.

In a previous double-blind, double-dummy, 4-week study, budesonide foam enema 2 mg/25 mL was compared with budesonide liquid enema 2 mg/100 mL in a noninferiority design study in patients with active ulcerative proctitis or proctosigmoiditis.[11] Of 541 patients, 449 were evaluable for per protocol analysis, and clinical remission rates were 60% for budesonide foam and 66% for budesonide enema within a predefined noninferiority margin of 15%. Of interest, 11% of the patients had retention problems after administration of the foam and 39% had retention problems after the enema. Overall, 84% of patients preferred the foam, 6% preferred the enema, and 10% had no preference. Budesonide foam enema and hydrocortisone foam enema have been shown to have comparable efficacy in inducing remission in patients with proctosigmoiditis; of interest, 52% of patients who did not respond to topical mesalamine responded to budesonide foam enema.[12] Mesalamine enema, however, has been shown to induce remission in a significantly higher proportion of patients compared with budesonide liquid enema 2 mg/100 mL.[13]

In the study published by Sandborn et al[14] in this issue of *Gastroenterology* budesonide foam enema 2 mg/25 mL

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Table 1. Preparations Available for Topical Therapy in Ulcerative Colitis

Formulation	Drug
Suppository	Mesalamine
	Hydrocortisone
	Beclomethasone dipropionate
Liquid enema	Mesalamine
	Hydrocortisone
	Budesonide
	Beclomethasone dipropionate
Foam enema	Mesalamine
	Budesonide
	Hydrocortisone
	Beclomethasone dipropionate
Rectal gel	Mesalamine

Not all formulations are available in different countries and there are some country-specific variation in the exact formulation, volume, and coatings.

twice daily for 2 weeks followed by 2 mg/25 mL once daily for 4 weeks was compared with placebo in a double-blind design in patients with ulcerative proctitis or proctosigmoiditis. Concomitant oral mesalamine in a stable dose was permitted. Budesonide foam enema was effective and safe in 2 phase III studies—remission at week 6 was achieved in the active arm in 38.3% and 44% compared with 25.8% and 22.4% in the placebo arm. Cessation of rectal bleeding and mucosal healing was achieved in a significantly higher proportion of patients receiving budesonide foam enema compared with placebo enema. As mentioned, bowel frequency may not be a robust parameter to track in ulcerative proctitis on topical therapy and this is seen in the study too. At week 6, approximately 14% of patients on budesonide foam did not have normal response to adrenocorticotrophic hormone challenge, showing that a small proportion of patients do have subclinical suppression of the pituitary adrenal axis.[14] Overall, however, budesonide topical treatment demonstrated minimal effects on adrenal function. In these trials, administration of even twice daily 25 mL rectal foam formulation for the initial 2 weeks had extremely high adherence (>94%) and this was not different from when the drug was administered once daily for the latter 4 weeks.

Faced with a choice from a number of formulations of topical therapy (Table 1), physicians have to make evidence based decisions while taking into account patient preferences. Gastroenterologists treating ulcerative proctitis, proctosigmoiditis, or left-sided colitis have the option of using topical mesalamine or corticosteroids, liquid enema, foam enema, rectal gel, or suppositories, and concomitant therapy with oral mesalamine.[15] Patients seem to tolerate foam enema better than liquid enema. Topical gel is also well-tolerated, although not available in many countries. In clinical practice, a 100-mL foam enema to reach splenic

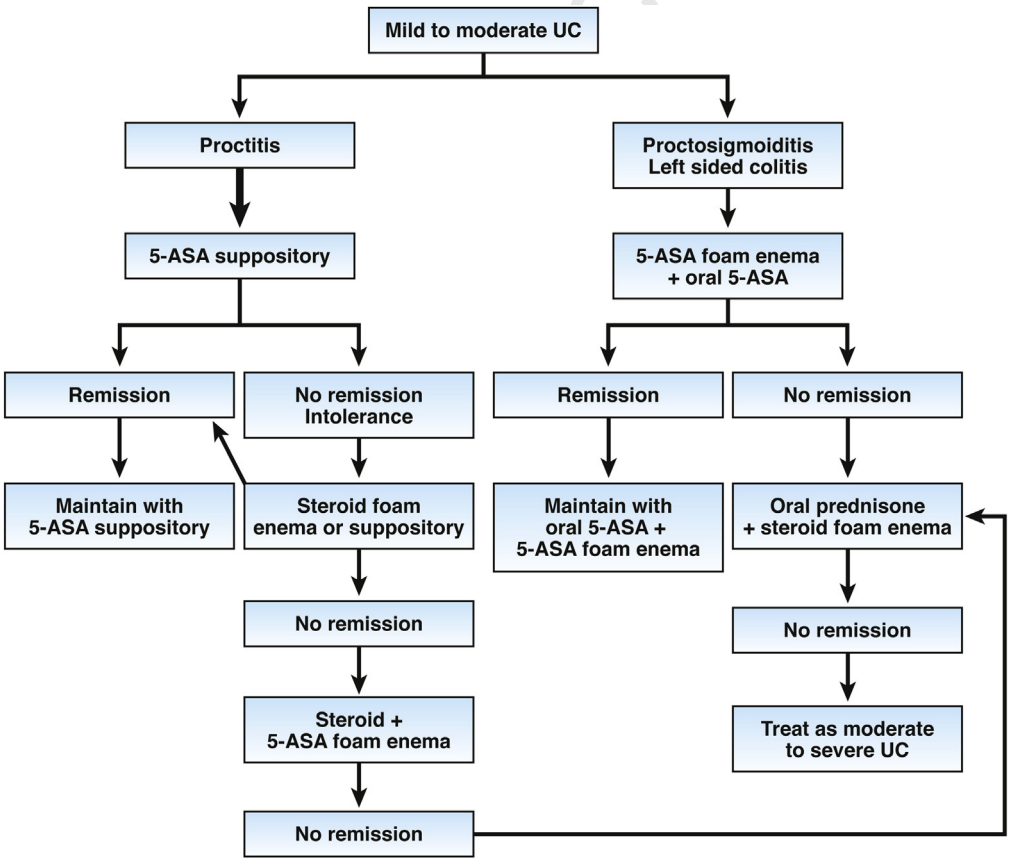

Figure 1. Algorithm for the initial management of ulcerative proctitis, proctosigmoiditis, or left-sided colitis.

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