Efficacy, Safety and Tolerability of Rectal Therapies in Ulcerative Proctitis and Ulcerative Proctosigmoiditis

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Ulcerative colitis (UC) is a heterogeneous disease that varies in the extent of affected colon and the severity of symptoms. Studies have suggested that at the time of diagnosis, approximately 46% of patients have inflammation limited to the rectum (ulcerative proctitis) or limited to the rectum and the sigmoid colon (ulcerative proctosigmoiditis). For distal forms of UC, a number of treatment options are available, including rectal and oral formulations. Rectal therapies (i.e., suppositories, foams, enemas) may be recommended for the management of patients with distal forms of UC, either as monotherapy, or in combination with oral therapies. First-line treatment for patients with distal UC is often 5-aminosalicylic acid rectal therapies, and is supported by a history of safety and efficacy in this patient population. However, second-generation corticosteroid (i.e., budesonide, beclomethasone dipropionate) rectal therapies have also been developed to treat active distal forms of UC. Despite the demonstrated safety and efficacy of rectal therapies for the induction and maintenance of remission of UC, rectally administered agents are widely underused and associated with nonadherence to treatment. However, decreased dosing frequency and the introduction of formulations of rectal agents that improve retention may increase use of rectal therapies and help to overcome barriers associated with nonadherence. Data support the use of rectal therapies for the induction and maintenance of remission of distal forms of UC.

Pathophysiology of Ulcerative Colitis

Ulcerative colitis (UC) is a chronic inflammatory disease of the colon, characterized in most patients by alternating periods of active disease and clinical remission.[1] Common clinical symptoms of active UC include diarrhea, rectal bleeding, urgency, abdominal pain, and tenesmus. In one study, diarrhea was the most common symptom observed in patients with active UC, affecting approximately 65% of patients, with abdominal pain reported in approximately 34% of patients.[2] The majority of patients with active distal UC had rectal bleeding (i.e., 70% of patients with ulcerative proctitis [UP] vs. 33 to 37% of patients

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with more extensive disease). In another study, 96% of patients with active UC passed blood and mucus in their stool.[3] Thus, management of symptoms of active UC, which may cause concern for patients, is one of the goals of treatment.[4,5]

The prevalence of UC has been estimated between 206 and 263 per 100,000 persons in the United States, thus UC affects approximately 600,000 individuals.[6-8] While diagnosis of UC can occur anytime, age at diagnosis typically has a bimodal distribution, with the first peak observed during the 20s and 30s, and a second, smaller, peak occurring during the 60s and 70s.[9] Although it is not clear whether differences in incidence based on sex are apparent, some studies have suggested that males have slightly greater incidence of UC versus females.[9,10] In general, patients with UC have the potential for a relatively long and variable disease course, associated with a substantial economic burden. Overall total costs for UC were estimated to be $390 to $920 million in the United States (in 2010 US dollars), with mean annual direct expenditures (health insurance and patient out-of-pocket costs) estimated at $8700 per patient.[11]

Whereas the etiology of UC remains to be elucidated, both genetic and environmental factors are thought to play a role in the development of the disease. A number of susceptibility loci associated with genes involved in barrier function and inflammatory and immune responses have been implicated as potential genetic risk factors for UC.[12-18] Further, environmental exposures (e.g., hormone therapy, smoking status) have been associated with both increased and decreased risk of UC.[19-22]

Ulcerative colitis is a heterogeneous disease that varies in severity (i.e., mild to fulminant) and extent of the colon affected.[23] Inflammation typically extends proximally from the rectum along the colonic mucosa.[1] At the time of diagnosis, approximately 46% of patients had inflammation limited to the rectum (UP) or to the rectum and the sigmoid colon (ulcerative proctosigmoiditis [UPS]).[2,23,24] Disease extent is not static, as approximately 45% of patients with an initial diagnosis of UP or UPS progressed to left-sided colitis or pancolitis after 5 years,[2] and approximately 20% and 54% of patients with an initial diagnosis of UP experienced proximal extension of disease after 5 and 10 years, respectively.[25]

Most patients begin an intermittent disease course after resolution of symptoms associated with an initial disease flare.[26,27] Approximately 40 to 50% of patients with UC are in clinical remission at any given point in time, and 90% of patients experienced relapsing disease within 25 years of diagnosis.[26] However, 83% of patients with UC experienced disease relapse within 10 years; 54, 71, and 57% of patients with UP relapsed within 1 year, between 1 and 5 years, or between 5 and 10 years after diagnosis, respectively.[27] Treatment choice affects the disease course of patients with UC, both during active disease and during disease in remission.[26]

Rectal Therapies for Treatment of Ulcerative Colitis

For patients with UC, the goal of treatment is multifaceted and includes symptom resolution, mucosal healing, induction and maintenance of remission, improvement in quality of life, and prevention of infirmity, surgery, and hospitalization.[1,4,28-32] Approaches to treatment depend on the extent and severity of disease, but the initial goal of treatment is induction of clinical remission.[4,5] Mild to moderate active distal colitis is typically treated with oral 5-aminosalicylic acid (5-ASA), rectal 5-ASA or steroids, or a combination of oral and rectal therapies.[4,5] Maintenance therapy is recommended for patients with UC in remission, to reduce the risk of symptomatic relapse.[5] Rectal 5-ASA is recommended as first-line therapy for the maintenance of remission of UP, and recommended as an option for patients with left-sided colitis.[5] Oral 5-ASAs are also effective at maintaining remission as monotherapy and in combination with rectal 5-ASA.[5] Rectal therapies differ in their proximal distribution: suppositories are limited to the rectum,[33,34] whereas foams and enemas have been shown to reach to the proximal sigmoid colon and splenic flexure, respectively.[34-38] In patients with UP, suppositories may be the most effective method for targeting the rectum.[5] For the sigmoid or descending colon, enema and foams may be considered, with the greatest distribution of drug in these locations occurring within 2 hours of administration of enema or foam in patients with UPS or left-sided colitis.[35]

5-ASAs

Sulfasalazine, a combination of the antibiotic sulfapyridine with the anti-inflammatory salicylate, was developed in the 1930s as a potential treatment for rheumatoid arthritis.[39] Whereas the efficacy of sulfasalazine in rheumatoid arthritis was limited, sulfasalazine was subsequently found to have efficacy

in UC.[40,41] Sulfasalazine was widely prescribed for the treatment of UC in subsequent decades, but its use was associated with some toxicity (e.g., nausea, vomiting, anorexia, headache).[42] A seminal study by Azad Khan et al[43] demonstrated that 5-ASA was the active moiety of sulfasalazine. Sulfasalazine is not well absorbed in the small intestine and passes through to the colon, where colonic bacteria cleave the diazo bond, releasing 5-ASA and sulfapyridine.[44-47] Ingesting a pure 5-ASA moiety administered orally does not reach the colon intact,[42,48] and thus oral 5-ASAs have been developed with pH-dependent and delayed-release mechanisms to facilitate colonic delivery of active drug.[42–44] The advantage of these agents is a reduction in adverse effects compared with sulfasalazine.[49,50] However, unmodified 5-ASA can be administered rectally; for distal forms of UC, this allows direct delivery to the site of inflamed mucosa, while minimizing systemic absorption.[51]

Overall, the safety and efficacy of rectal 5-ASA for the induction and maintenance of remission of distal UC have been well established.[52,53] In randomized, double-blind, placebo-controlled studies, clinical and endoscopic remission were achieved by a greater percentage of patients with UP, UPS, left-sided UC, pancolitis, or distal UC receiving 5-ASA suppositories compared with placebo after 4 weeks (Table 1).[54-68] In addition, a once-daily dosing regimen had comparable efficacy with 2- or 3-times daily dosing of 5-ASA suppositories after 6 weeks in patients with active UP.[57-59] However, patients preferred once-daily administration compared with 3-times daily administration of suppository.[57] Furthermore, a greater percentage of patients with UP, UPS, or left-sided UC maintained remission for at least 1 year, and up to 2 years, with 5-ASA suppositories.[60-62]

In randomized, double-blind studies, 5-ASA enemas had greater efficacy than placebo in patients with active UP, UPS, or distal UC after 6 weeks.[63,64] Remission or improvement (clinical, endoscopic, or histologic) was achieved by a greater percentage of patients on 5-ASA enema therapy for 4 weeks compared with placebo.[65] Patients receiving 5-ASA enemas demonstrated improvement in the physician's global assessment score and a decrease from baseline in the mean disease activity index (DAI) score after 6 or 8 weeks.[63,64,66] In a study of patients with mild to moderate active UP and UPS receiving either 5-ASA enema or foam for 4 weeks, the majority of patients achieved clinical remission, and there was no apparent difference in the efficacy of 5-ASA enema or foam.[67] 5-ASA enemas were also efficacious for the maintenance of remission for at least 46 weeks compared with placebo in a clinical study of patients with left-sided UC.[68] Finally, in addition to demonstrated efficacy, 5-ASA suppositories and enemas had a favorable safety profile in a number of clinical studies.[54,55,57-64,66-68]

Corticosteroids

Truelove first described the efficacy of rectal corticosteroids (i.e., hydrocortisone) for the induction of remission of UC in 1956.[69] In this study, 67% of patients with mild to moderate UC receiving hydrocortisone enemas nightly for up to 3 weeks achieved clinical remission, usually within days of initiating treatment. Corticosteroids are efficiently absorbed across the colonic mucosa, with an estimated 30 to 50% of administered hydrocortisone enema absorbed through the rectal mucosa.[70,71] Thus, the potential for serious adverse effects (e.g., diminished adrenal function, hypothalamic-pituitary-adrenal [HPA] axis suppression, metabolic bone disease, ophthalmologic impairment, cushingoid features, metabolic issues) associated with long-term corticosteroid treatment must be considered.[4,72] Second-generation rectal corticosteroid therapies, including budesonide and beclomethasone dipropionate (BDP), with high first-pass hepatic metabolism (~90% for budesonide)[73] and limited systemic toxicity,[74] have since been developed.

Budesonide

Patients with active UP, UPS, left-sided UC, or distal UC achieved remission, and endoscopic and histologic improvement, following treatment with budesonide enema for 4, 6, or 8 weeks (Table 2).[75-83] However, a greater percentage of patients treated with 5-ASA enema compared with budesonide enema achieved clinical remission after 4 and 8 weeks.[77] A similar percentage of patients with active UP or UPS achieved clinical remission with budesonide foam and budesonide enema after 4 weeks.[81] However, the majority of patients preferred the foam to enema (83.6 vs. 6.2%, respectively). A significantly greater percentage of patients receiving budesonide foam achieved remission, a Mayo rectal bleeding subscore of 0, and endoscopic improvement (Mayo endoscopy subscore ≤1) after 6 weeks compared with placebo.[80] Further, a greater percentage of patients with distal UC or UP maintained remission with twice-weekly

administration of budesonide enema compared with placebo for 6 months.[76] However, it is unknown what effect increased frequency of dosing will have on the percentage of patients maintaining remission of UC. Once- or twice-daily administration of budesonide foam or enema 2 mg or 8 mg for 4, 6, or 8 weeks was safe and, notably, did not adversely affect the HPA axis in most patients with active distal UC.[75,78-80,82,83] However, in one study, twice-daily dosing with rectally administered budesonide for 8 weeks significantly increased the incidence of impaired adrenal function compared with once-daily dosing.[76] It should be noted that studies have not explored the safety profile of these agents beyond 1 year.

Several baseline factors associated with response to treatment with budesonide enemas or foams have been identified.[80-82] Less severe disease at baseline was associated with improved response to treatment, as patients with mild disease (not defined) at baseline had significantly greater odds of achieving clinical remission after 8 weeks of treatment than patients with more severe disease (odds ratio [OR], 4.25; 95% confidence interval [CI], 1.72–10.48).[82] Further, a second study demonstrated that a greater percentage of patients with less severe disease at baseline (i.e., clinical activity index [CAI] ≤8) achieved clinical remission (defined as CAI ≤4) following treatment with budesonide foam or budesonide enema for 4 weeks compared with patients with more severe disease (i.e., CAI >8; foam, 59 vs. 49%, respectively; enema, 71 vs. 47%, respectively; OR, 1.4; 95% CI, 1.01–2).[81] However, extent of disease (i.e., UP or UPS) and disease duration (i.e., ≤5 years or >5 years) had no significant association with achievement of clinical response with budesonide foam or budesonide enema after 4 weeks.[81] Finally, a significantly greater percentage of patients receiving budesonide foam achieved remission (i.e., Mayo endoscopy subscore ≤1, rectal bleeding subscore = 0, and improvement or no change in stool frequency subscore) compared with placebo when subgroup analyses of baseline disease (i.e., moderate disease, established disease, and extent of disease [UP, UPS]) and demographic (i.e., age, sex, white race, and smoking history) characteristics were conducted.[80]

The absence of exposure to previous therapeutic modalities was also associated with improved response to either budesonide foam or hydrocortisone foam, as patients who had not previously received treatment with rectal 5-ASA had significantly greater odds of achieving clinical remission compared with patients with prior exposure to rectal 5-ASA (OR, 2.97; 95% CI, 1.05–8.37).[82] However, a second study reported that a greater percentage of patients with previous response (not defined) to oral or rectal 5-ASA achieved clinical remission (CAI ≤4) after 4 weeks of treatment with budesonide foam compared with patients with no previous response to oral or rectal 5-ASA, although the findings were not significant.[81] Lastly, a randomized, double-blind, placebo-controlled study of budesonide foam found that remission was achieved with budesonide foam versus placebo regardless of a previous (baseline) 5-ASA use.[80]

Beclomethasone Dipropionate

Rectal formulations of BDP are safe and efficacious for the induction of remission of active UP, UPS, or distal UC, with improvement or induction of remission following treatment with BDP enema comparable with that of 5-ASA enema after 4 to 6 weeks (Table 3).[84-92] A comparable percentage of patients with active, distal UC receiving BDP enema or foam, or 5-ASA enema or foam, achieved remission or response at 4 or 8 weeks.[86] In both studies, patients in all groups achieved significant improvement from baseline in the DAI (total and subscale) scores and endoscopy scores after 4, 6, or 8 weeks of treatment.[84,86] The safety profiles of BDP and 5-ASA were favorable in patients with UP or UPS.[84,86]

Whereas BDP enema and 5-ASA enema induced clinical and endoscopic improvement in the majority of patients with UP, and histologic improvement in approximately half of patients, after 28 days, the combination of BDP and 5-ASA resulted in greater efficacy than monotherapy, with all patients experiencing clinical, endoscopic, and histologic improvement.[87] The efficacy of BDP enema was examined in patients with UC in 3 randomized, double-blind studies.[88-90] Mulder et al[89] found no differences in clinical, endoscopic, or histologic improvement between groups receiving BDP or prednisolone after 4 weeks, while van der Heide et al[88] demonstrated improvement from baseline only in endoscopic scores in patients receiving prednisolone enema after 4 weeks. Further, a similar percentage of patients receiving BDP and prednisolone enemas achieved clinical and endoscopic remission after 4 weeks.[90] However, in these studies, the safety profile of BDP was more favorable than that of prednisolone, with significant decreases from baseline in mean basal cortisol concentrations occurring after treatment with

prednisolone, but not BDP.[88-90]

Clinical remission, clinical response, and endoscopic improvement were achieved by a comparable percentage of patients receiving either BDP enema or betamethasone (BMT) enema in 2 randomized, double-blind studies of patients with active, distal UC after 20 to 28 days.[91,92] However, BDP had a more favorable safety profile compared with BMT, with steroid-related adverse events and suppression of adrenal function occurring with greater frequency following treatment with BMT.

Rectal and Oral Combination Therapy

Patients with more extensive active UC may benefit from a combination of oral and rectal 5-ASA therapies, as opposed to monotherapy with an oral or rectal 5-ASA (Table 4).[93-98] Rectal therapies target sites of inflammation typically affected by distal forms of UC,[24,33,35] but D'Incà et al.[93] found that mucosal concentrations of 5-ASA following the administration of both oral and rectal drugs were greater in the sigmoid colons of patients with UC compared with when oral 5-ASA had been administered alone. Thus, in patients who are refractory to rectal therapies alone, a combination of oral and rectal therapies may be warranted.[4,5]

The addition of 5-ASA enema to oral 5-ASA therapy significantly increased the rate of remission compared with oral 5-ASA therapy alone after 8 weeks in patients with extensive mild to moderate active UC.[94,95] However, the percentage of patients with extensive mild to moderate active UC achieving clinical or endoscopic remission after treatment with a combination of 5-ASA enemas plus oral 5-ASA for 6 weeks was similar to that of patients receiving 5-ASA enemas alone.[96] The majority of patients receiving either 5-ASA combination therapy or oral 5-ASA alone achieved mucosal healing after 4 weeks.[95] Resolution of rectal bleeding within 7 days of study initiation occurred in a greater percentage of patients receiving combination 5-ASA therapy versus oral 5-ASA monotherapy.

The combination of oral 5-ASA therapy and 5-ASA enemas had greater efficacy than oral 5-ASA monotherapy in 2 randomized, controlled studies of patients with UC in remission for up to 1 year.[97,98] A greater percentage of patients with UC maintained remission following treatment with a combination of oral 5-ASA therapy and weekend 5-ASA enema compared with oral 5-ASA alone.[97] Similarly, the combination of oral 5-ASAs with twice-weekly 5-ASA enemas was more efficacious for the maintenance of remission of UC after 12 months compared with oral 5-ASA monotherapy.[98] Further, the results of a case-control study of patients receiving the combination of oral 5-ASA 1.6 g/day with twice-weekly 5-ASA 2 g/50 mL enemas for a median treatment period of 6 years demonstrated that patients receiving combination therapy had a significantly lower incidence of relapse (1.59 vs. 2.76, respectively; $p = 0.034$) and fewer hospitalizations.[99] The safety profile of combination oral and rectal therapies for the induction and maintenance of remission of UC was favorable.[94,96-98]

Limitations Associated with the Use of Rectal Therapy

Rectal 5-ASAs are efficacious both for the induction and maintenance of remission in patients with mild to moderate distal UC, and rectal corticosteroids have demonstrated efficacy for the induction of remission in patients with active, distal UC. However, rectal therapies for UC are currently underused. A European study noted that a comparable percentage of patients with UP received oral or rectal therapy (29.5 vs. 25.6%, respectively); however, a greater percentage of patients with UPS received oral versus rectal treatment (42.8 vs. 6.9%, respectively).[100] The percentage of patients with UP and UPS receiving combination oral and rectal therapy was 13.2% and 17.4%, respectively. Further, during 1992–2009, the number of prescriptions for all 5-ASAs increased 72%, yet those for rectally administered 5-ASAs remained generally at the same level, with a decline in the overall 5-ASA market share from 11% to 9%.[101] Oral 5-ASAs accounted for ~70% of 5-ASA prescriptions in 2009. Patients with UC, prescribed rectal therapies at time of diagnosis, have a high rate of discontinuation of therapy, often as soon as 1 month. Data from a US health insurance database demonstrated that patients with newly diagnosed UC, or UP and UPS were commonly prescribed oral 5-ASA (53%) or 5-ASA suppositories (42%), respectively.[102] Within 1 month, approximately 40% of patients with UC discontinued treatment with oral 5-ASAs, and approximately 70% of patients with UP and UPS discontinued treatment with rectal therapy.

Underuse of rectal therapy may be related to a combination of patient preference for oral therapy and potential inconvenience and technical issues with administration of rectal agents.[103,104] An important aspect of any treatment is patient adherence.[101]

Adherence to any treatment is particularly challenging during periods of remission in patients with UC, as demonstrated by prescription refill data that estimated that only approximately 40% of patients with UC were adherent to oral 5-ASAs.[105] Other factors associated with a greater likelihood of nonadherence to treatment among patients with UC included less extensive disease and receiving >4 concomitant therapies (OR, 2.5; 95% CI, 1.4–5.7). Patients with UC receiving rectal therapy reported difficulty with use during work hours (OR, 4.4; 95% CI, 1.5–12.5; $p = 0.003$), pain and bloating (OR, 2.8; 95% CI, 1.20–6.54; $p = 0.013$), and difficulty with use (OR, 2.4; 95% CI, 1.00–5.73; $p = 0.043$) as reasons for nonadherence. Additional issues were associated with the use of rectal therapy, including retention of the medication (i.e., duration, position), leakage, and stained clothing with enemas,[106] and difficulty with administration and with anal or rectal pain that occur in some patients using suppositories.[61]

Nonadherence to treatment has implications for the course of a patient's disease, significantly increasing the risk of relapse compared with patients who are adherent to treatment (relative risk [RR], 1.4; 95% CI, 1.08–1.94; $p = 0.014$). Patient nonadherence to enemas was significantly higher compared with oral therapies (68% vs. 40%, respectively; $p = 0.001$).[107] However, in a clinical trial comparing enemas and foams, the majority of patients receiving enemas and foams reported no retention problems, unpleasant feeling, rectal or abdominal pain, or flatulence.[81] Thus, although the issue of adherence to therapy is complex, providing patients with treatment options that include less frequent dosing and simplified administration may improve adherence and, ultimately, lead to more favorable outcomes for patients.[104]

Adherence is an ongoing issue in the overall management of UC.[105,108,109] Common issues associated with nonadherence to treatment in patients with UC may be overcome by allowing for more flexible dosing regimens (i.e., weekend dosing) and addressing problems with insertion and retention with different formulations of rectal therapies. Rectal therapies (i.e., budesonide foam) have shown favorable safety profiles in clinical trials and are preferred by patients to enemas.[81,83] These therapies have the potential to provide additional safe and efficacious options for healthcare providers treating UC. The most effective way to preserve adherence is to forge a therapeutic bond with the patient and discuss the duration of therapy. Additionally, seeing patients at least every 6 months may improve adherence to both oral and rectal treatment regimens.

In conclusion, this review of published data of rectal therapies, including 5-ASAs and corticosteroids, supports that these agents are well tolerated, safe, and efficacious for the induction and maintenance of remission of distal forms of UC. Furthermore, combination oral and rectal therapy is also well tolerated and efficacious for the induction of remission in patients with mild to moderate extensive UC compared with oral therapy alone, and should be considered in appropriate patient populations. Rectal therapies are an underused, yet valuable part of the management paradigm for patients with distal forms of UC. They may be appropriate as monotherapy or in combination with oral therapy for the induction or maintenance of remission of mild to moderate UC, depending on disease extent and patient considerations. ■

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Table 1. Rectal 5-ASA Therapy for the Induction and Maintenance of UC Remission

Study Design, Dosing and Duration	Patient Population	Efficacy Outcome(s)	Safety Outcome(s)
Suppositories ***Induction of Remission***			
R, DB, PBO-C, MC[54] 5-ASA 1 g suppository (Pentasa, Ferring Pharmaceuticals, Saint-Prex, Switzerland; n = 65) vs. PBO (n = 64) qd for 4 wks	Adults with mild to moderate UC	Clinical remission[a] at wk 4 with 5-ASA or PBO: 63.1% and 17.2%, respectively ($p < 0.0001$); pts with UP, 67.6% and 22.2%, respectively (p= 0.0001) Endoscopic remission[b] at wk 4 with 5-ASA or PBO: 81.5% and 29.7%, respectively ($p < 0.0001$); pts with UP, 83.8% and 36.1%, respectively ($p < 0.0001$) Complete resolution of bleeding at wk 4: ~90% of pts receiving 5-ASA suppository	AEs: 15.4 vs. 17.2% of pts receiving 5-ASA vs. PBO, respectively AE-related discontinuations: 4.7% with PBO
R, DB, PBO-C, MC[55] 5-ASA 1.5 g/d (n = 31), 5-ASA 1 g/d (n = 32), or PBO tid (n = 31); pts received either 5-ASA 0.5 g (Asacol) or PBO suppository per dose for 4 wks	Adults with active mild to moderate UP or UPS (<20 cm)	Clinical remission[c] at wk 4 with 5-ASA 1.5 g/day, 1 g/day, or PBO: 74%, 69%, and 39%, respectively ($p < 0.01$ for both groups vs. PBO) Endoscopic response[d] at wk 4 with 5-ASA 1.5 g/day or 1 g/day vs. PBO: 55%, 59%, and 23%, respectively ($p < 0.02$ for both 5-ASA doses vs. PBO) Histologic response[d] at wk 4 with 5-ASA 1.5 g/day or 1 g/day vs. PBO: 10%, 16%, and 6%, respectively ($p < 0.01$ and $p < 0.02$, respectively)	AEs: 3.1% (i.e., transient facial erythema and mild fever)

Table 1. (Continued)

R, DB, PBO-C[56] 5-ASA 0.5 g suppository (Asacol, Giuliani Pharmaceutical Company, Milan, Italy; n = 32) vs. PBO (n = 30) tid for 1 mo	Adults with mild to moderate UC localized to distal sigmoid colon and rectum (<20 cm)	Clinical remission[e] or improvement[f] at 1 mo with 5-ASA vs. PBO: 87% vs. 33%, respectively Endoscopic remission[g] or improvement[f] at 1 mo with 5-ASA vs. PBO: 78% vs. 38%, respectively Histologic remission[h] or improvement[f] at 1 month with 5-ASA vs. PBO: 65% vs. 13%, respectively	Not reported
R, IB, MC[57] 5-ASA 1 g suppository (Salofalk, Dr. Falk Pharma, Freiburg, Germany) qd at bedtime (n = 200) vs. 5-ASA 0.5 g tid (n = 203) for 6 wks	Adults with active mild to moderate UP (≤15 cm of rectum)	Clinical remission[i] at wk 6 with 5-ASA 1 g qd and 5-ASA 0.5 g tid: 84.0% and 84.7%, respectively	AEs: 19.0% vs. 21.2% of pts receiving 5-ASA 1 g qd or 0.5 g tid, respectively Possible tx-related AEs: 2.5% vs. 3.4% of pts receiving 5-ASA 1 g qd or 0.5 g tid, respectively; resulted in study discontinuation in 2 pts receiving 5-ASA 0.5 g tid
R, MC[59] 5-ASA 1 g suppository (Canasa/ Salofalk, Axcan Pharma, Quebec, Canada) qd nightly (n = 39) vs. 5-ASA 0.5 g bid (n = 48) for 6 wks	Adults with active mild to moderate UP limited to the rectum	DAI[j] at wk 6 with 5-ASA 1 g qd and 0.5 g bid: similar between groups (p = 0.73) Decrease in DAI from baseline to wk 6: 5-ASA 1 g qd: 6.1 ± 1.5 vs. 1.3 ± 2.2, respectively 5-ASA 0.5 g bid: 6.6 ± 1.5 vs. 1.6 ± 2.3, respectively	AEs: 55% vs. 57% of pts receiving 5-ASA 1 g qd or 0.5 g bid, respectively AE-related study discontinuations: 3.8% of pts receiving 5-ASA 0.5 g bid

Table 1. (Continued)

R, MC, parallel group[58] 5-ASA 1 g suppository qd nightly (n = 39) vs. 5-ASA 0.5 g suppository bid (n = 48) for 6 wks	Adults with active mild to moderate UP limited to the rectum	Mean DAI scores after 3 and 6 wks improved vs. baseline with 5-ASA 0.5 g bid or 5-ASA 1 g qd nightly; improvement after 3 and 6 wks comparable between groups Decrease from baseline in individual components of DAI[k] after 3 and 6 wks; decrease (improvement) after 3 and 6 wks comparable between groups Remission after 3 wks with 5-ASA 0.5 g bid or 5-ASA 1 g qd: 56.3 vs. 54.1%, respectively Remission after 6 wks with 5-ASA 0.5 g bid or 5-ASA 1 g qd: 78.3% vs. 86.1%, respectively	AEs: 56.9% vs. 54.5% of pts receiving 5-ASA 0.5 g bid or 5-ASA 1 g qd, respectively AE-related study discontinuations: 3 pts (i.e., bronchospasm, increased headache intensity, worsening clinical symptoms)
Maintenance of Remission			
R, DB, PBO-C, MC[60] 5-ASA 0.5 g suppository (Rowasa, Alaven Pharmaceutical LLC, Marietta, GA; n = 31) vs. PBO (n = 34) qd for 1 yr Pts who maintained remission at yr 1 could continue receiving DB tx for 1 yr	Adults with UP in clinical and endoscopic remission with history of disease limited to rectum (≤15 cm)	Maintenance of remission[l] at 2 yrs with 5-ASA vs. placebo: 60% vs. 20%, respectively Time to relapse[m] with 5-ASA vs. PBO: significantly greater with 5-ASA ($p < 0.001$)	AEs: 23% vs. 15% of pts receiving 5-ASA vs. PBO, respectively SAEs: 3.2% of pts receiving 5-ASA (i.e., non–tx-related chest pain)
R, DB, PBO-C, MC[61] 5-ASA 1 g (Pentasa; n = 48) vs. PBO (n = 47) 3 times/wk for 12 mo 5-ASA 1 g vs. PBO qd in pts who relapsed on 5-ASA 1 g 3 times/wk	Adults with UP in remission	Time to relapse[n] with 5-ASA vs. PBO: 239 days vs. 166 days, respectively (log rank test: p = 0.067)	AEs: 12.5% vs. 10.6% of pts receiving 5-ASA vs. PBO, respectively Study discontinuations: 2.1% and 4.3% of pts receiving 5-ASA vs. PBO, respectively (i.e., anal or rectal burning)

Table 1. (Continued)

R, DB, PBO-C[62] 5-ASA 400 mg (n = 15) vs. PBO bid (n = 15) for 1 yr	Adults with UP and UPS in remission	Cumulative rate of remission[o] at 1 yr with 5-ASA vs. PBO: 92% and 21%, respectively ($p < 0.001$)	No AEs reported
Enemas ***Induction of Remission***			
R, DB, PBO-C[66] 5-ASA 1 g (n = 73), 2 g (n = 71), or 4 g (n = 73) enema (Pentasa, Ferring, Copenhagen, Denmark) qd vs. PBO (n = 70) for 8 wks	Adults with active mild to moderate UP or UPS limited to rectum or sigmoid colon (<30 cm from anal verge)	Improvement in PGA from baseline to wk 8 with 5-ASA 1 g, 2 g, and 4 g, or PBO: 67%, 65%, 75%, and 27%, respectively Decrease in mean endoscopic index from baseline to 8 wks with 5-ASA 1 g, 2 g, and 4 g, or PBO: 5.8, 5.9, 6.4, and 1.8, respectively	AEs: comparable between 5-ASA and PBO AE-related study discontinuations: 8%, 11%, 10%, and 37% of pts receiving 5-ASA 1 g, 2 g, 4 g, or PBO, respectively
R, DB, PBO-C[63] 5-ASA 4 g/60 mL enema qd (n = 29) vs. PBO (n = 30) for 6 wks	Adults with active distal UC involving 5–50 cm of the colon proximal from the anus	PGA rating "much improved" at wk 6 with 5-ASA vs. PBO: 62% and 20%, respectively ($p < 0.0001$) Decrease from baseline in mean DAI at wk 6 with 5-ASA vs. PBO: 75% and 32%, respectively ($p < 0.05$)	No significant AEs reported

Table 1. (Continued)

R, DB, PBO-C, MC[64] 5-ASA 4 g/60 mL enema qd (n = 76) vs. PBO (n = 77) for 6 wks	Adults with active UP, UPS, and distal UC involving 5–50 cm of the colon proximal from the anus	PGA rating "much improved" at wk 6 with 5-ASA vs. PBO: 63% and 29%, respectively ($p < 0.0001$) Mean DAI decreased from baseline to wk 6 with 5-ASA vs. PBO: 55% vs. 22%, respectively ($p < 0.0001$) Individual subscale scores of DAI decreased from baseline to wk 6 with 5-ASA vs. PBO: stool frequency: 0.57 vs. 0.41, respectively; rectal bleeding: 1.30 vs. 0.61, respectively ($p < 0.001$); mucosal appearance: 1.21 vs. 0.56, respectively ($p < 0.001$); and physician's assessment of disease severity: 0.97 vs. 0.30 ($p < 0.001$)	AEs: 11.8% vs. 14.3% of pts receiving 5-ASA vs. PBO, respectively
R, DB, PBO-C[65] 5-ASA 1 g (n = 27), 2 g (n = 30), 4 g/100 mL (n = 29) enema (CHIESI Pharmaceutical Company, Parma, Italy) qd vs. PBO (n = 27) for 4 wks	Adults with active mild to moderate UP, UPS, or left-sided colitis not extending beyond the splenic flexure	Clinical improvement[f] or remission[p] at wk 4 with 5-ASA 1 g, 2 g, 4 g, and PBO: 85%, 83%, 86%, and 41%, respectively Endoscopic improvement[f] or remission at wk 4 with 5-ASA 1 g, 2 g, 4 g, and PBO: 74%, 73%, 79%, and 30%, respectively Histologic improvement[f] at wk 4 with 5-ASA 1 g, 2 g, 4 g, and PBO: 63%, 70%, 76%, and 15%, respectively	Not reported
Maintenance of Remission			
R, DB, PBO-C[68] 5-ASA 1 g/60 mL enema qd (n = 12) vs. PBO (n = 13) for 48 to 52 wks, or relapse	Adults with left-sided UC in remission	Maintenance of remission[q] with 5-ASA vs. PBO: 75% vs. 15.4%, respectively, for ≥46 wks	AEs: 41.7% vs. 61.5% of pts receiving 5-ASA vs. PBO, respectively (i.e., anal canal irritation)

Table 1. (Continued)

Enemas vs. Foams			
R, C, IB, MC[67] 5-ASA 1 g/100 mL enema qd (n = 184; Pentasa) vs. 5-ASA 1 g/80 mL foam qd (n = 191) for 4 wks	Adults with active mild to moderate left-sided UC extending 5 cm from anal margin, but not beyond splenic flexure	Clinical remission[r] at wk 4 with 5-ASA enema vs. 5-ASA foam: 70.5% vs. 66.7%, respectively	AEs: 32.4% vs. 27.2% of pts receiving 5-ASA enema or 5-ASA foam, respectively AE-related study discontinuations: 6.6% vs. 7.3% of pts receiving 5-ASA enema or 5-ASA foam, respectively

[a] UCDAI score ≤2 and bleeding score = 0
[b] Rectal mucosal score ≤1
[c] No symptoms with ≤2 bowel movements/day and no visible blood in stool
[d] Change of ≥1 grade
[e] Absence of symptoms
[f] Decrease of ≥1 grade from baseline in relevant scale
[g] Repair of rectal mucosa
[h] No evidence of inflammation by biopsy
[i] DAI <4
[j] Sum of 4 subscale scores for stool frequency, rectal bleeding, mucosal appearance, and disease global assessment
[k] Stool frequency, rectal bleeding, mucosal appearance, general well-being
[l] DAI score = 0
[m] Defined as symptoms of rectal bleeding or an increase in stool frequency for ≥1 week, and inflammation by endoscopy on DAI subscales
[n] Defined as occurrence of clinical symptoms with an increase in the endoscopy score ≥1 vs. baseline, or rectal bleeding >2 times in 1 day
[o] Clinical (no blood in stools, and no diarrhea, abdominal pain, and tenesmus), endoscopic score ≤1, and histologic score ≤1
[p] Absence of symptoms of active disease
[q] Normal mucosal appearance
[r] CAI ≤2

AE adverse event, *5-ASA* 5-aminosalicylic acid, *bid* twice daily, *C* controlled, *CAI* clinical activity index, *DAI* disease activity index, *DB* double-blind, *IB* investigator-blinded, *MC* multicenter, *PBO* placebo, *PBO-C* placebo-controlled, *PGA* physician's global assessment, *pts* patients, *qd* once daily, *R* randomized, *SAE* serious adverse event, *tid* three times daily, *tx* treatment, *UC* ulcerative colitis, *UCDAI* ulcerative colitis disease activity index, *UP* ulcerative proctitis, *UPS* ulcerative proctosigmoiditis

Table 2. Budesonide Rectal Therapy for the Induction of UC Remission

Study Design, Dosing and Duration	Patient Population	Efficacy Outcome(s)	Safety Outcome(s)
Enemas			
Budesonide vs. PBO			
R, DB, PBO-C, MC[79] Budesonide enema 2 mg/100 mL (n = 20) vs. PBO (n = 21) qd at bedtime for 2 or 4 wks (dependent on tx outcome) 4-wk OL phase with budesonide enema in pts with unsatisfactory response (failure to improve)	Pts between 16 and 65 yrs of age with active UP or distal UC	Endoscopy scores improved significantly with budesonide enema for 4 wks vs. PBO ($p < 0.01$), but not 2 wks ($p = 0.07$) Histologic rating scores improved significantly with budesonide enema after 2 and 4 wks ($p < 0.05$ and $p < 0.01$, respectively) Endoscopic and histologic improvement in the 76.2% of pts receiving PBO in DB phase treated with budesonide foam in OL phase	Specific AE data published; no drug-related AEs observed in either group Plasma cortisol levels did not decrease after tx with budesonide enema
O, MC[78] Budesonide enema 2 mg/100 mL (n = 29) qd at bedtime for 4 wks	Pts between 16 and 65 yrs of age with active UP or distal UC	Endoscopy and histologic rating scores improved significantly from baseline to wk 4 ($p < 0.0001$ and $p < 0.002$, respectively)	No AEs reported Plasma cortisol levels unchanged after tx with budesonide enema for 4 wks
R, DB, PBO-C, MC[75] Budesonide enema 0.5 mg (n = 57), 2 mg (n = 56), or 8 mg/100 mL (n = 60) qd at bedtime vs. PBO (n = 60) for 6 wks	Adults with active distal UC	Remission[a] with budesonide enema 0.5 mg, 2 mg, 8 mg, or PBO: 7%, 19% ($p \leq 0.05$ vs. PBO), 27% ($p \leq 0.001$ vs. PBO), and 4% of pts, respectively Mean change in endoscopic inflammation grade improved significantly from baseline to 6 wks with budesonide enema 2 mg and 8 mg vs. PBO ($p \leq 0.001$ for both) Total histopathology score improved significantly at 6 wks with budesonide enema 2 mg and 8 mg vs. PBO ($p \leq 0.05$ and $p \leq 0.001$, respectively)	Tx-related AEs: 37%, 36%, 40%, and 30% with budesonide 0.5 mg, 2 mg, and 8 mg enema vs. PBO, respectively Adrenal insufficiency: 1.7% of pts receiving budesonide 8 mg enema Cushing's syndrome: 3.3% of pts in both the PBO and 8 mg group

Table 2. (Continued)

Induction of remission: R, DB, MC parallel group Maintenance of remission: R, PBO-C[76] Induction phase: Budesonide enema 2 mg/100 mL in evening and PBO enema in morning (n = 73) vs. budesonide enema 2 mg/mL bid (n = 76) for 8 wks, or until remission achieved Maintenance phase: Budesonide enema 2 mg/100 mL (n = 39) vs. PBO (n = 37) twice weekly for 6 mo, or relapse	Adults with active distal UC	Induction phase: Remission[b] with budesonide qd vs. bid: 33% vs. 41% of pts, respectively, at 4 wks vs. 51% vs. 54% of pts, respectively, at 8 wks Maintenance phase: Relapse[c] with budesonide vs. PBO after 8, 16, and 24 wks: 15% vs. 24%, 31% vs. 27%, and 41% vs. 51%, respectively	Induction phase: AEs: 66% vs. 71% with budesonide enema qd vs. bid, respectively Impaired adrenal function at 8 wks: 8% vs. 33% of pts receiving budesonide enema qd vs. bid, respectively, (p = 0.001) Maintenance phase: AEs: 72% vs. 65% of pts in budesonide enema vs. PBO, respectively Normal adrenal function after tx: similar between groups

Table 2. (Continued)

Budesonide vs. 5-ASA			
R, C, MC[77] Budesonide enema 2 mg/100 mL (n = 118; Entocort, AstraZeneca, Wedel, Germany) vs. 5-ASA enema 4 g/60 mL (n = 119; Salofalk, Dr Falk Pharma GmbH, Freiburg, Germany) for 8 wks	Adults with active mild to moderate left-sided UC	Clinical remission[d] with budesonide enema or 5-ASA enema: 63.5% vs. 77.2%, respectively, after 4 wks ($p < 0.05$); and 64.4% and 77.4%, respectively, after 8 wks ($p < 0.05$)	AEs: 55% vs. 34% with budesonide enema or 5-ASA enema, respectively ($p < 0.002$) AE-related study discontinuations: 3.1% vs. 2.4% with budesonide enema vs. 5-ASA enema, respectively No AEs associated with systemic corticosteroid effects reported after 8 wks
Foams			
R, O, AC, MC[82] Budesonide foam 2 mg/20 mL qd at bedtime (n = 122; Budenofalk, Dr Falk Pharma GmbH) vs. hydrocortisone acetate foam 100 mg/15 mL qd at bedtime (n = 129; Colifoam, Block Drug Company Inc, Ratingen, Germany) for 8 wks	Adults with active UP or UPS distal to the sigmoid colon	Clinical remission[e] with budesonide or hydrocortisone foam: 53% vs. 52%, respectively, at wk 8 Pts receiving budesonide or hydrocortisone foam had similar decreases from baseline in mean DAI (7.2 ± 1.9 to 3.6 ± 3.1, vs. 7 ± 2 to 3.9 ± 3.4, respectively), and decrease from baseline in the mean number of weekly stools (31 to 19, vs. 30 to 22, respectively) Endoscopic improvement[f] with budesonide or hydrocortisone foams: 59% vs. 50%, respectively Histologic improvement[f] with budesonide or hydrocortisone foams: 48% vs. 50%, respectively	AEs: 30% vs. 39% with budesonide or hydrocortisone foam, respectively Adrenal suppression (serum cortisol <138 nmol/L) in 3% vs. 0% with budesonide or hydrocortisone foam, respectively

Table 2. (Continued)

R, DB, MC, PBO-C[80] Budesonide foam 2 mg/25 mL (n = 267; Uceris rectal foam, Salix Pharmaceuticals, Inc., Raleigh, NC, USA) vs. PBO (n = 279) bid for 2 wks, then qd for 4 wks	Adults with mild to moderate active UP or UPS extending ≥5 cm and ≤40 cm from anal verge	Remission[9] with budesonide foam or PBO: 41.2% vs. 24.0%, respectively, at wk 6 ($p < 0.0001$) Rectal bleeding subscore = 0 with budesonide foam or PBO: 48.3% vs. 28.3%, respectively, at wk 6 ($p < 0.0001$) Endoscopy subscore ≤1 with budesonide foam or PBO: 55.8% vs. 39.8%, respectively, at wk 6 ($p = 0.0002$)	AEs: 45.9% vs. 36.3% with budesonide foam or PBO, respectively; decreased blood cortisol concentrations (17.2% vs. 2.2%, respectively), adrenal insufficiency (3.7% vs. 0.7%), headache (2.2% vs. 2.5%), nausea (2.2% vs. 0.7%), and UP (0% vs. 2.2%) were the most common AEs 96.6%, 85.2%, 84.0%, 92.8%, and 94.2% of pts receiving budesonide foam had normal morning serum cortisol concentrations at baseline and wks 1, 2, 4, and 6, respectively

Table 2. (Continued)

Foams vs. Enemas			
R, DB, DD, MC[81] Budesonide foam 2 mg/25 mL (Budenofalk, Dr Falk Pharma GmbH) plus PBO enema (n = 265) vs. budesonide enema 2 mg/100 mL plus PBO foam (n = 268) for 4 wks Administration of foam and enema alternated between morning and evening	Adults with active UP or UPS involving ≤40 cm of colon proximal from anus	Clinical remission[h] with budesonide foam or budesonide enema: 59.5% vs. 65.7%, respectively Endoscopic remission with budesonide foam or budesonide enema: 52% vs. 54%, respectively Histologic remission with budesonide foam or budesonide enema: 51% and 57%, respectively	32% and 33% of pts receiving budesonide foam or budesonide enema, respectively, reported AEs; headache, UC deteriorated, nausea, and abdominal pain were the most common AEs reported Low serum cortisol concentrations (<150 nmol/L): 2 pts vs. 3 pts receiving budesonide foam vs. budesonide enema, respectively
R, O, C, MC[83] Budesonide foam (Dr Falk Pharma GmbH) 2 mg/50 mL (n = 22) vs. BMT enema 5 mg/100 mL (n = 16) bid for 2 wks, then qd at bedtime for 2 wks	Adults with active distal UC not extending beyond the left colonic flexure	Remission[h] with budesonide foam vs. BMT enema: 40.9% vs. 81.3%, respectively, after 4 wks Decrease in mean CAI after 4 wks with budesonide foam vs. BMT enema: 63.8% and 76.6% of pts, respectively	AEs: 32% vs. 44% with budesonide foam or BMT enema, respectively Steroid-related AEs (i.e., leukocytosis, dizziness, visual disturbance, facial edema, increased appetite): 17% vs. 44% with budesonide foam or BMT enema, respectively Low serum cortisol levels after 4 wks: 22% vs. 87% of pts receiving budesonide foam or BMT enema, respectively

Table 2. (Continued)

[a] ≤3 bowel movements/day, no blood in stools, no symptoms of urgency, abdominal pain, or painful evacuations, and a sigmoidoscopic inflammation grade score = 0 for previous 2 days

[b] No clinical symptoms (no blood in stools and <3 bowel movements/day) and endoscopy score ≤1

[c] Clinical symptoms (blood in stools and ≥3 bowel movements/day) and endoscopy score ≥2

[d] CAI <4

[e] DAI ≤3

[f] Decrease ≥1 point

[g] Mayo endoscopy subscore ≤1, rectal bleeding subscore = 0, and improvement or no change from baseline in stool frequency subscore

[h] CAI ≤4

AE adverse event, *5-ASA* 5-aminosalicylic acid, *AC* active-controlled, *BDP* beclomethasone dipropionate, *bid* twice daily, *BMT* betamethasone, *C* controlled, *CAI* clinical activity index, *DAI* disease activity index, *DB* double blind, *DD* double dummy, *MC* multicenter, *O* open, *OL* open label, *PBO* placebo, *PBO-C* placebo-controlled, *pts* patients, *qd* once daily, *R* randomized, *tx* treatment, *UC* ulcerative colitis, *UP* ulcerative proctitis, *UPS* ulcerative proctosigmoiditis

Table 3. Beclomethasone Dipropionate Rectal Therapy for the Induction of UC Remission

Study Design, Dosing and Duration	Patient Population	Efficacy Outcome(s)	Safety Outcome(s)
BDP vs. 5-ASA			
R, SB, C, parallel group, MC[84] BDP 3 mg/60 mL enema (Clipper, *n* = 111) vs. 5-ASA 1 g/100 mL enema (Pentasa, Ferring, Copenhagen, Denmark; *n* = 106) qd nightly for 6 wks	Adults with active mild to moderate UP, UPS, and left-sided UC	Remission[a]: 36.7% vs. 29.2% with BDP or 5-ASA enemas, respectively; improvement[b]: 45.5% vs. 58.4%, respectively, after 6 wks Mean decrease in DAI score from baseline to wk 6 after BDP or 5-ASA enemas (4.44 and 4.31, respectively; 95% CI -0.50–0.65) Mean decrease in endoscopic scores from baseline to week 6 after tx with BDP or 5-ASA enemas (1.28 and 1.21, respectively; p = NS between groups)	AEs: 10.8% vs. 12.6% with BDP or 5-ASA enemas, respectively Morning plasma cortisol levels unchanged from baseline after 6 wks of BDP No difference between groups in plasma cortisol levels at baseline or after 6 wks

Table 3. (Continued)

R, DB, MC, parallel group[86] BDP 3 mg enema (n = 26) or foam (n = 24) vs. 5-ASA 2 g enema (n = 22) or foam (n = 20) qd nightly for 8 wks	Adults with active mild to moderate distal UC	Remission[c]: 24% vs. 28% with BDP vs. 5-ASA enema or foam, respectively, after 4 wks, and 36% vs. 52%, respectively, after 8 wks Response[d]: 77%, 79%, 77%, and 80% with BDP enema or foam vs. 5-ASA enema or foam, respectively, after 4 wks, and 92%, 78%, 99%, and 82%, respectively, after 8 wks Significant decrease from baseline in median DAI subscale scores: Number of daily liquid stools after BDP enema or foam, or 5-ASA enema or foam after 4 wks (BDP, $p < 0.0001$; 5-ASA, $p < 0.01$) or 8 wks(BDP and 5-ASA, $p < 0.0001$) Presence of visible blood in stools after BDP enema or foam, or 5-ASA enema or foam after 4 or 8 wks ($p < 0.0001$ for both groups at both time points) Endoscopic score with 5-ASA enema or foam tx after 4 wks ($p < 0.01$) or 8 wks ($p < 0.0001$); decrease from baseline following BDP tx reached significance after 8 wks ($p < 0.0001$) PGA following tx with BDP enema or foam, or 5-ASA enema after 8 wks ($p < 0.01$); for 5-ASA foam ($p < 0.05$)	AEs: 33% vs. 25% with BDP enema or foam vs. 5-ASA enema or foam, respectively Serum cortisol levels within normal range: 86% vs. 81% of pts receiving BDP at baseline and after 8 weeks, respectively AE-related study discontinuations: 6% vs. 7.5% with BDP foam vs. 5-ASA foam, respectively

Table 3. (Continued)

R, DB, MC[87] BDP 3 mg/100 mL enema (n = 20), 5-ASA 2 g/100 mL enema (n = 21), or BDP 3 mg plus 5-ASA 2 g/100 mL enema (n = 19) qd nightly for 4 wks	Adults with UC or UP limited to distal 20 cm of colon	Clinical improvement[e]: 70%, 76%, and 100% with BDP, 5-ASA, or BDP plus 5-ASA, respectively (BDP plus 5-ASA vs. BDP or 5-ASA, p = 0.09) Endoscopic improvement[f]: 75%, 71%, and 100% with BDP, 5-ASA, or BDP plus 5-ASA, respectively (BDP plus 5-ASA vs. BDP or 5-ASA, p = 0.021) Histologic improvement[g]: 50%, 48%, and 100% with BDP, 5-ASA, or BDP plus 5-ASA, respectively (BDP plus 5-ASA vs. BDP or 5-ASA, p = 0.009)	No AEs reported
BDP vs. Prednisolone			
R, DB[88] BDP 1 mg/40 mL enema (n = 10) vs. prednisolone 30 mg/40 mL enema (n = 8) qd nightly for 4 wks	Adults with UC limited to distal 20 cm of colon	Improvement from baseline in clinical and histologic scores in both groups, while endoscopic scores decreased from baseline only in prednisolone group	Mean basal and stimulated cortisol concentrations significantly decreased from baseline in prednisolone group (p = 0.001 and p = 0.05, respectively), and remained unchanged in BDP group (p = NS for both comparisons)
R, DB[89] BDP 3 mg/40 mL enema (n = 8), BDP 2 mg/40 mL enema (n = 7), or prednisolone 30 mg/40 mL enema (n = 8) qd nightly for 28 days	Adults with UC limited to distal 20 cm of colon	No differences between groups in overall clinical improvement[e], endoscopic improvement[f], or histologic improvement[h]	Fasting cortisol concentrations decreased significantly from baseline after tx with prednisolone (0.47 µmol/L vs. 0.22 µmol/L, respectively; $p < 0.05$), but not in either BDP group Stimulated cortisol concentrations did not differ before and after tx for any tx group

Table 3. (Continued)

R, DB, MC[90] BDP 3 mg/60 mL enema (n = 80) vs. prednisolone 30 mg/60 mL enema (n = 77) qd nightly for 4 wks	Adults with distal UC limited to distal 15–50 cm of colon	Clinical and endoscopic remission: 29% and 25% with BDP and prednisolone, respectively, after 4 wks Endoscopic scores significantly decreased from baseline in both groups after 2 wks (BDP, $p < 0.05$; prednisolone, $p < 0.001$) and 4 weeks ($p < 0.001$) Histologic scores significantly decreased from baseline in both groups after 4 wks ($p < 0.001$)	AEs: 10% vs. 8% with BDP or prednisolone, respectively Mean plasma cortisol concentrations significantly decreased from baseline in prednisolone group ($p < 0.05$), but were unchanged from baseline with BDP after 4 weeks; plasma cortisol levels were ≥138 nmol/L Plasma cortisol concentrations with ACTH stimulation remained within normal range at baseline and after 4 weeks in both groups
BDP vs. BMT			
R, DB[91] BDP 0.5 mg/100 mL enema (n = 9) vs. BMT 5 mg/100 mL (n = 9) qd nightly for 20 days	Adults with active, distal UC	Clinical remission[i] or improvement: 88.9% and 77.8% with BDP or BMT, respectively, after 20 days Improvement from baseline of clinical, endoscopic, and histologic scores comparable between groups	Suppression of adrenal function: 0% vs. 77.8% with BDP or BMT, respectively Basal plasma cortisol concentrations were below normal range in 11.1% and 77.8% of pts in BDP and BMT groups, respectively; 55.6% of pts receiving BMT had basal plasma cortisol concentrations <55 nmol/L Mean basal and stimulated post-tx cortisol concentrations were significantly decreased in pts receiving BMT vs. BDP

Table 3. (Continued)

R, C, DB[92] BDP 0.5 mg/100 mL enema (n = 20) or BMT 5 mg/100 mL enema (n = 20) qd nightly for 28 days	Adults with UC limited to distal ≤45 cm of colon	Clinical response comparable between groups, with blood in stool resolving sooner after tx with BMT enema vs. BDP enema ($p < 0.05$) Histologic improvement greater with BMT enema vs. BDP enema ($p < 0.01$) Endoscopic histologic improvement and remission similar between groups	Steroid-related AEs reported in BMT group included moon face, leg edema, and severe acne; no steroid-related AEs reported after tx with BDP Fasting plasma cortisol concentrations decreased significantly from baseline after BMT tx (499 nmol/L vs. 80 nmol/L, respectively), but were comparable with baseline after tx with BDP Significant decrease in plasma cortisol concentrations after ACTH stimulation with BMT tx ($p < 0.01$), but not BDP tx

[a] DAI score = 0
[b] Decrease in DAI score ≥3 points
[c] DAI score <3
[d] Decrease ≥1 point in DAI score
[e] Defined as decrease from baseline >2 [89] or ≥2 [87] in clinical score
[f] Defined as decrease from baseline >3 [89] or ≥3 [87] in endoscopic score
[g] Defined as decrease from baseline ≥2 in histologic score
[h] Decrease from baseline >8 in histologic score
[i] ≤3 bowel movements/day, no evidence of blood in stool, and no symptoms

AE adverse event, *5-ASA* 5-aminosalicylic acid, *ACTH* adrenocorticotropic hormone, *BDP* beclomethasone dipropionate, *BMT* betamethasone phosphate, *C* controlled, *CI* confidence interval, *DAI* disease activity index, *DB* double blind, *MC* multicenter, *NS* not significant, *PGA* physician's global assessment, *qd* once daily, *R* randomized, *SB* single blind, *tx* treatment, *UC* ulcerative colitis, *UP* ulcerative proctitis, *UPS* ulcerative proctosigmoiditis

Table 4. Combination Rectal and Oral Therapies for the Induction and Maintenance of Remission of UC

Study Design, Dosing and Duration	Patient Population	Efficacy Outcome(s)	Safety Outcome(s)
R, DB, DD, MC[96] Oral 5-ASA (Salofalk, Dr. Falk Pharma, Freiburg, Germany) 2 g bid plus PBO enema qd (oral group; *n* = 67) vs. oral 5-ASA 1 g bid plus 5-ASA 2 g/60 mL enema (Salofalk) qd (combined group; *n* = 63) for 6 wks	Adults with active mild to moderate UC involving ≥15 cm of colon (excluding pts with UP)	Clinical remission[a] or improvement[b]: 82% and 87% with oral tx vs. combined tx, respectively, (*p* = 0.56) after 6 wks Time to clinical remission or improvement: 21.5 d vs. 19.8 d for oral tx vs. combined tx, respectively (*p* = 0.307) Endoscopic remission: 58% vs. 71% with oral tx vs. combined tx, respectively, after 6 wks (*p* = 0.21)	AEs: 8% vs. 6% with oral tx vs. combined tx, respectively AE-related study discontinuations: 1.5% vs. 1.6% with oral tx vs. combined tx, respectively
R, DB, PBO-C, MC[94] Oral 5-ASA (Pentasa, Ferring, Copenhagen, Denmark) 1 g bid plus 5-ASA 1 g/100 mL enema (*n* = 71) or PBO enema (*n* = 56) qd nightly for 4 wks Oral 5-ASA administered for 8 wks	Adults with mild to moderate extensive UC extending beyond the splenic flexure	Remission[c]: 44% and 34% with 5-ASA enema vs. PBO enema, respectively, (*p* = 0.3079) after 4 wks, and 64% and 43%, respectively, (*p* = 0.0298) after 8 wks	AEs: 34% vs. 50% with 5-ASA or PBO enema, respectively SAEs affecting the GI system: 4% vs. 2% with 5-ASA or PBO enema, respectively (unrelated to tx) AE-related study discontinuations: 12.7% and 19.6% with 5-ASA or PBO enema, respectively

Table 4. (Continued)

R, DB, PBO-C, MC[95] 5-ASA 1 g/100 mL (Pentasa) enema (n = 71) or PBO enema (n = 56) qd for 4 wks Oral 5-ASA (Pentasa) 2 g bid for 8 wks	Adults with extensive mild to moderate UC (inflammation extending beyond the splenic flexure)	Remission[c]: 44% vs. 34% with 5-ASA combination tx vs. oral 5-ASA alone, respectively, after 4 wks, and 64% and 43%, respectively, after 8 wks (p = 0.03) Mucosal healing[d]: 95% vs. 83% with 5-ASA combination tx or oral 5-ASA alone, respectively, after 4 wks (p = 0.052) Cessation of rectal bleeding achieved by 35% and 25% of pts receiving 5-ASA combination tx or 5-ASA oral tx alone, respectively, within 7 days; for pts with cessation of bleeding, the mean duration of rectal bleeding was 21.0 and 24.4 days following 5-ASA combination tx or oral 5-ASA alone, respectively	Not reported
R, DB, MC[98] 5-ASA 4 g/100 mL enema twice weekly plus oral 5-ASA 1.6 g/d (n = 36) vs. PBO enema twice weekly plus oral 5-ASA 1.6 g/d (n = 36) for 12 mo	Adults with UC in remission	Relapse: 39% vs. 69% with combination tx or oral tx alone, respectively, after 12 mo (p = 0.02)	No AEs reported

Table 4. (Continued)

R, C[97] 5-ASA 1 g enema twice weekly (Saturday and Sunday) with oral 5-ASA 3 g/d (n = 11) vs. oral 5-ASA 3 g/d (n = 13) Mean observation, 305 days (SD, 162 days)	Adults with UC in remission	Relapse[e]: 18.2% vs. 76.9% with weekend 5-ASA enema plus oral 5-ASA vs. oral 5-ASA alone, respectively (HR, 0.19; 95% CI, 0.04–0.94)	No AEs reported

[a] CAI <4
[b] Decrease from baseline >50% in CAI
[c] UCDAI score <2
[d] DAI endoscopic mucosal appearance subscale score ≤1
[e] CAI ≥6 and endoscopic index >3

AE adverse event, *5-ASA* 5-aminosalicylic acid, *bid* twice daily, *C* controlled, *CAI* clinical activity index, *CI* confidence interval, *DAI* disease activity index, *DB* double-blind, *DD* double dummy, *GI* gastrointestinal, *HR* hazard ratio, *MC* multicenter, *PBO* placebo, *PBO-C* placebo-controlled, *pts* patients, *qd* once daily, *R* randomized, *SAE* serious adverse event, *SD* standard deviation, *tx* treatment, *UC* ulcerative colitis, *UP* ulcerative proctitis, *UCDAI* ulcerative colitis disease activity index

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