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Title:

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Journal:

Dig Dis 2016

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Digestive Diseases

Dig Dis 2016;34:122–124
DOI: 10.1159/000443026

Oral or Topical 5-ASA in Ulcerative Colitis

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Key Words
5-Aminosalicylic acid · Mesalamine · Mesalazine · Ulcerative colitis

Abstract
Aminosalicylates (5-ASAs) are foundational therapies for patients with mild-moderate active ulcerative colitis (UC) and to maintain remissions. A variety of oral and topical formulations have been evaluated in both active and quiescent disease in both extensive and distal UC. This review summarizes data on pharmacokinetics and applications of oral and topical 5-ASA therapies in active and quiescent, extensive colitis and distal disease, both as monotherapies and in combination and reviews dosing and dosing intervals for oral 5-ASA in both active disease and to maintain remissions.

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Aminosalicylates (5-aminosalicylic acid, 5-ASA) remain the foundational therapies for induction and maintenance of remission for patients presenting with mild-moderate ulcerative colitis (UC). In contrast to many of the newer, targeted biologic medications (e.g., anti-TNF or anti-integrin therapies) 5-ASA is pluripotent with numerous anti-inflammatory properties including inhibition of cyclooxygenase, lipoxygenase, platelet activating factor, interleukin 1, nuclear factor kappa beta, peroxisome proliferator-activated receptor-gamma and B lymphocytes and is a scavenger of oxygen radicals.

5-ASA has been extensively evaluated in a variety of formulations since its original development as sulfasalazine [1]. Due to inter- and intra-individual variations in intestinal pH in active and quiescent disease the pharmacologic properties of differing formulations overlap substantially as pertains to the absorption and urinary excretion of 5-ASA and acetylated 5-ASA [2]. All the mesalamine compounds showed comparable ranges of systemic absorption, plasma pharmacokinetics, urinary excretion of total 5-ASA and fecal excretion of 5-ASA. Hence, we suggested that the selection of a 5-ASA therapy for UC should be based on other factors such as demonstrated efficacy, dose-response, toxicity of the parent compound (e.g., sulfasalazine), compliance issues related to dosage forms and costs.

Given the different indications in UC (induction and maintenance of remission) and the varied formulations of 5-ASA (mesalamine (oral and topical), olsalazine, balsalazide, sulfasalazine), there have been numerous clinical trials assessing efficacy versus placebo and comparative efficacy between formulations. Randomized controlled trials of different oral formulations in

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0257–2753/16/0342–0122$39.50/0

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mild-moderate active UC have demonstrated consistent benefits versus placebo [3]. The meta-analyses concluded that mesalamine is more effective than placebo to induce remission in UC and is better tolerated than sulfasalazine. Of interest, there has often been a numerical, but not statistically significant advantage to sulfasalazine in comparative trials; but sulfasalazine side effects often limit tolerability. Overall, despite the varied delivery systems for 5-ASA to the colon, efficacy appears to be similar when comparable concentrations of 5-ASA are delivered.

Since 5-ASA requires topical contact with the mucosa and is available in both oral and topical formulations, it is reasonable to determine 'optimal' approaches to both extensive and distal colitis for induction and maintenance of mild-moderate UC. Somewhat surprising, despite the limited proximal distribution of 5-ASA suspensions, Marteau et al. [4] demonstrated that a combination of oral 5-ASA, 2 g bid and rectal 5-ASA, 1 g suspension (Pentasa® formulations) was superior at inducing clinical remissions compared with oral 5-ASA alone. This finding suggests that healing of the rectum can improve clinical outcomes even in the presence of more proximal colitis.

Given the topical benefits of 5-ASA in distal UC [5], the question arises as to whether oral, topical or combination therapies are most efficacious in patients with active or quiescent distal UC. Several recent meta-analyses have addressed these questions. Ford et al. [6] have reviewed 5 studies comparing oral and topical therapy in active UC and concluded a numerical, but not statistically significant advantage for topical 5-ASA suspensions compared with oral therapies. Of note, there were no dose comparisons. However, consistent with the findings in extensive colitis, combining oral and topical therapy for patients with active, distal UC was superior to oral therapy alone.

Ford et al. [7], in a separate meta-analysis reviewed 3 clinical trials that compared oral versus topical 5-ASA in patients with quiescent distal UC and demonstrated that topical therapy was superior to oral therapy at preventing relapses. Despite these findings, most patients would prefer oral therapy to topical therapy on a long-term basis.

In summary, while there is no difference in outcomes with oral or topical therapy for patients with active distal UC, the series of meta-analyses suggest that topical therapy is more effective than oral therapy for maintenance therapy. In both distal and extensive UC, combining oral and topical therapy has had benefits compared with either, alone.

As mentioned previously, it is important to consider dosing, in particular, with oral 5-ASA therapies [8]. To date, there have not been dosing differences between 1 and 4 g administrations of topical 5-ASAs [5]. In comparison with sulfasalazine that has well-known dose-related side effects attributed to the sulfapyridine moiety [3], there does not appear to be dose-related toxicity up to 4.8 g of oral 5-ASA [1]. Ford et al. [3] compared controlled trials of 'high dose' (above 2 g/day) versus 'low-dose' 5-ASA formulations in the induction of remission in mild-moderate active UC. They concluded from the randomized controlled trials of 5-ASA versus placebo that utilizing greater than 2 g/day were more effective than trials comparing 'low dose' 5-ASA to placebo.

One of the issues within the spectrum of mild-moderate UC has been the definition and descriptions of what entails 'mild' versus 'moderate' disease. In the 'ASCEND' trial comparing 2.4 versus 4.8 g of Asacol®, a pre-specified subgroup analysis of patients entering with a 'physicians global assessment' (PGA) of UC disease activity scored as '1' versus '2' according to the 'Mayo Score' [9], while patients with mild disease (PGA 1) responded equally well to 2.4 or 4.8 g/day, the patients in the moderate subgroup (PGA 2) had improvements in both clinical symptoms and clinical remissions with 4.8 g dosing compared with 2.4 g daily. Another means of discriminating patients with mild versus moderate disease activity is to evaluate patients who had received prior therapies. Sandborn et al. [10] reviewed a pharmacy database and demonstrated that patients who had previously received oral 5-ASA, topical 5-ASA or steroids, oral steroids or more than 2 medications fared better with 4.8 versus 2.4 g/day of 5-ASA. Similarly, in the analysis of a multi-matrix (MMX) formulation of oral 5-ASA, patients with mild-moderate disease who were randomized to either 2.4 g, 4.8 g of MMX mesalamine or placebo who were naïve to prior therapies responded better to the lower dose; however, patients who had received prior therapy with oral 5-ASA had a significantly better response to the 4.8 g dose [11].

Despite the absence of well-controlled dose-ranging studies of 5-ASA to prevent relapse in UC, Ford et al. [3] compared randomized controlled trials of 5-ASAs versus placebo in the prevention of relapse and found that groups of patients receiving greater than 2 g/day of 5-ASA had better outcomes of than patients receiving lower doses. Analyzing outcomes from community gastroenterologists, Sandborn et al. [12] found that patients who continued on the same maintenance dose had better outcomes than patients who reduced the dose of oral 5-ASA once remission had been achieved. Hence, until controlled trials demonstrate otherwise, it has been my practice to continue the same dose of 5-ASA for maintenance therapy as was used to induce remission.

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As far as dosing is concerned in the setting of maintenance therapy, while there is minimal evidence of a dose–response between 800 mg and 1.6 g daily, it appears that higher doses (>2 g daily) are more effective than lower doses and, in particular, for patients who have required higher dose-induction therapy.

Finally, while sulfasalazine was administered in divided doses and with meals to avoid intolerant side effects (to the sulfapyridine component), a number of trials have compared once daily dosing of oral 5-ASA to divided dosing with a variety of different 5-ASA formulations in active disease [11, 13, 14] and a recent meta-analysis by Ford et al. [15] confirmed that once-daily dosing of oral 5-ASA is comparable to divided dosing for the maintenance of remission.

To summarize, in active UC, all available 5-ASAs induce remissions independent of release mechanisms. The combination of oral and rectal administration of 5-ASA is the most effective (while not necessarily the best tolerated) therapy for both extensive and distal colitis. There is dosing flexibility for mild-moderate disease activity between 2 and 4.8 g/daily and once daily administration is comparable to multiple daily doses. In the setting of quiescent UC, all oral 5-ASAs have demonstrated efficacy in maintaining clinical remissions. While additional controlled trials would be beneficial, observational studies have suggested that the maintenance dose may depend upon the dose required to induce remissions. Higher doses may also be required for patients who have required steroids to induce remission and, similar to the setting of active UC, once daily dosing is effective and may improve adherence.

Disclosure Statement

S.B.H. is a lecturer for Falk and a consultant for Ferring, Salix and Shire.

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