Optimizing clinical use of mesalazine (5-aminosalicylic acid) in inflammatory bowel disease

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***Abstract*:** Mesalazine [5-aminosalicylic acid (5-ASA)] has been used for over 30 years in the treatment of inflammatory bowel disease (IBD). It is a highly effective, safe, and well-tolerated drug for treatment of mild to moderate ulcerative colitis, which represents most patients with this disease. Recent studies of patient adherence to 5-ASA therapies in ulcerative colitis have highlighted the need for regimens that enable long-term compliance to significantly reduce the risk of troublesome and debilitating flares in the short term, and possibly colon cancer in the long term. Indeed, much of the recent innovation in clinical use of 5-ASA in colitis has come from studies of novel delivery mechanisms and simplified oral dosing schedules. These studies have provided much needed clarity on essential matters such as starting dose, dose escalation, and efficacy in terms of the ideal clinical endpoint - mucosal healing. Various manufacturers are re-evaluating their products to determine the safety and efficacy of such dosing regimens. Although once widely employed in the treatment of Crohn's disease (CD), the accumulated body of evidence now suggests that there is a much more limited role for 5-ASA in this particular form of inflammatory bowel disease. Recent 5-ASA randomized-controlled trials, comparative studies, and outcomes research have led to refined treatment strategies and awareness for practitioners to better inform, engage and facilitate patients in optimal use of 5-ASA in inflammatory bowel disease.

***Keywords*:** 5-aminosalicylic acid, Crohn's disease, delayed-action preparations, inflammatory bowel disease, mesalazine, ulcerative colitis

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Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are the two major forms of idiopathic inflammatory bowel disease (IBD). The pathogenesis of these diseases is incompletely understood and there are no medical cures available at this time. Several pharmacological therapies aimed at controlling intestinal inflammation have been developed. Corticosteroids and aminosalicylates have been at the cornerstone of IBD therapy for decades and, in general, act via multiple nonspecific systemic and local immunosuppressant effects, respectively. Biological therapies such as engineered antibodies against tumor necrosis factor-α have more potent and precise anti-inflammatory actions. Surgery has been viewed as curative in UC, since total colectomy removes the affected organ. By comparison, CD tends to recur following surgical resection of the affected bowel, but the once commonplace use of aminosalicylates for postoperative prevention of recurrent CD has more recently begun to fall out of favor.

Assessment of therapeutic efficacy in IBD has traditionally focused on physicians' overall clinical impression and formalized scoring tools based on clinical parameters. There is now a paradigm shift in the assessment and management of IBD. The importance and acceptance of a more objective measure of disease activity, endoscopic (mucosal) healing, is emerging [Lichtenstein and Rutgeerts, 2010], as various clinical criteria do not always correlate with actual mucosal disease. For instance, patients may have dramatic symptoms of IBD despite minimal or absent mucosal disease activity or only limited extent of involvement (e.g. proctitis). This is suggestive of irritable bowel syndrome that often follows in the wake of once active IBD [Keohane *et al.* 2011]. Alternatively, patients may feel fairly well

but have marked mucosal inflammation. In CD patients, mucosal healing has been associated with higher long-term steroid-free remission rates [Baert *et al.* 2010; Froslie *et al.* 2007]. Studies in UC have correlated mucosal healing with lower rates of relapse, and lower rates of surgery and colorectal cancer [Lichtenstein and Rutgeerts, 2010; Froslie *et al.* 2007].

Aminosalicylates are one of the oldest therapies currently used in the management of IBD. Salazopyrin is the prototype drug in this category, but mesalazine (5-aminosalicylic acid [5-ASA]) is the active moiety of this parent compound and is the main aminosalicylate used in IBD treatment today. These are very safe drugs that can be administered orally or rectally to manage inflammation localized to different regions of the gastrointestinal tract, with little systemic absorption. Oral formulations vary somewhat in their delivery mechanisms and the newer drugs allow for targeted release to specific regions of the gastrointestinal tract and a more convenient dosing form and schedule. 5-ASA is highly effective in mild to moderate UC, which accounts for approximately 90% of patients with UC at first presentation [Langholz *et al.* 1991]. Although 5-ASA was once used as a first-line treatment in various types of CD, contemporary views hold that 5-ASA agents have a much more limited role in CD therapy. Even so, many CD patients continue to be prescribed these medications and subsequently have ongoing inflammation, putting them at real risk of disease progression and the development of complications. There is also considerable monetary cost associated with the inappropriate or suboptimal use of 5-ASA products in IBD [Siegel, 2009; Gearry *et al.* 2007]. There is good evidence however to support 5-ASA for the induction and maintenance of both clinical and endoscopic remission in mild to moderate UC.

Pharmacology

It is worth briefly reviewing the pharmacokinetics of orally administered aminosalicylates in humans. Although still poorly understood, the proposed mechanisms of action of 5-ASA have recently been reviewed [Desreumaux and Ghosh, 2006] and will not be discussed in this article. 5-ASA is a hydrophilic small organic acid that is avidly absorbed in the small intestine and rapidly N-acetylated in the intestinal epithelium and liver to produce the therapeutically inactive molecule, N-acetyl-5-ASA [Allgayer, 1992]. Some of this inactive metabolite is secreted back into the lumen and excreted in feces. 5-ASA that escapes N-acetylation is metabolized by the liver and excreted by the kidneys [Zhou *et al.* 1999]. The clinical efficacy of 5-ASA is not dependent upon systemic absorption and redistribution to the target organ, but rather is due to its topical effects on the colon.

After oral ingestion, 5-ASA is effectively absorbed by the small bowel and much of the remaining drug is excreted unabsorbed drug in the feces [Zhou *et al.* 1999]. In order to maximize colonic luminal concentrations of 5-ASA, pharmaceutical manufacturers have formulated 5-ASA in various release vehicles to achieve controlled delayed dissolution or pH-dependent release of 5-ASA [Allgayer, 1992] and, more recently, engineered drug matrices to facilitate mucosal contact and penetration [Prantera *et al.* 2005]. Inert carrier molecules have also been employed to achieve targeted release in the colon dependent upon release from the parent prodrug by the enzymatic activity of bacteria that reside predominantly in the distal ileum and throughout the colon [Truelove, 1988]. Scintigraphic methods have been employed to study the kinetics of 5-ASA release from formulated coatings, but often these studies employ healthy individuals and it is uncertain whether such kinetics reliably predicts drug release in patients with active UC and associated abnormalities of intestinal motility, absorption, and secretion. Indeed, failure of optimal release of 5-ASA at the site of inflammation likely contributes to failed clinical response in some patients. Suppositories, enemas, and foam suspensions ensure direct topical delivery to the diseased mucosa in the case of distal colitis, avoiding the unpredictability of delayed release forms of oral 5-ASA [Allgayer, 1992]. A substantial proportion of UC patients have mild to moderate disease limited to the distal colon only and thus amenable to treatment by direct intrarectal administration of 5-ASA.

Oral delayed-release formulations deliver high concentrations of 5-ASA to the lumen of the distal gut in humans but it is hydrophilic, and tends to partition poorly into the intestinal mucosa and has no carrier process for facilitating intramucosal delivery [Zhou *et al.* 1999]. Therefore, the concentration of 5-ASA in the colonic lumen is estimated to be 10–100 mM and exceeds that achieved in the colonic mucosa by 100-fold [Rousseaux *et al.* 2005].

As already mentioned, 5-ASA that is absorbed by colonic epithelial cells is rapidly metabolized and rendered therapeutically inactive.

Mesalazine in Crohn's disease

Treatment of active Crohn's disease

5-ASA medications have long been used as first-line therapy in CD. The data evaluating the use of these drugs as induction and maintenance therapy in CD are conflicting, however. Definitions of response and remission are quite variable between studies. One trial in patients with active CD evaluated the effect of ethylcellulose-coated 5-ASA (Pentasa®) that provides both small bowel and colonic delivery [Singleton *et al.* 1993]. Over 300 patients were enrolled in this randomized, placebo-controlled trial. Patients given this form of 5-ASA did significantly better than those in the placebo group in terms of both response and remission as measured by the Crohn's Disease Activity Index (CDAI). The benefit seemed to be greatest in patients with small bowel disease. Two other placebo-controlled trials showed that patients with active CD fared no better than those on placebo [Mahida and Jewell, 1990; Rasmussen *et al.* 1987], and one of these negative trials assessed only patients with small bowel disease. A recent meta-analysis summarized the effects of ethylcellulose-coated 5-ASA as an induction agent in patients with mild to moderate CD [Hanauer and Stromberg, 2004]. A total of 615 patients were included in the meta-analysis, representing three randomized, placebo-controlled trials. Those in the treatment groups received 4 g of oral 5-ASA per day for 16 weeks. The primary efficacy endpoint was CDAI, but mucosal healing was not assessed in any of the included studies. A significant difference in CDAI was noted in the 5-ASA group, but the net difference in CDAI between the two groups was only 18 points. Although statistically significant, such a small change in CDAI score is unlikely to be clinically significant, especially considering the short-term nature of these trials. Based on these findings, the current European Crohn's and Colitis Organization (ECCO) discourages the use of 5-ASA drugs in both ileal and colonic disease, even if mild [Travis *et al.* 2006]. The relative inefficacy of 5-ASA in CD may be due to the fact that, as a 'topical' agent, it only addresses mucosal disease and may not have activity in deeper layers of the bowel where CD also occurs.

Maintenance of remission in Crohn's disease

The role of 5-ASA in maintaining remission in CD has also been investigated. This therapeutic approach is still commonly used. Once patients achieve remission with corticosteroids, they may be placed on a 5-ASA agent in an attempt to maintain the remission. Unfortunately the 5-ASA medications are no better at maintaining remission in CD than they are at inducing it. One group conducted a meta-analysis of 5-ASA therapy for maintenance of CD remission which included seven randomized, placebo-controlled trials and a total of 1500 patients [Akobeng and Gardener, 2005]. There was no significant difference in maintenance of remission between 5-ASA and placebo.

Prevention of postoperative recurrence in Crohn's disease

Ford and colleagues recently performed a definitive systematic review and meta-analysis of 11 eligible randomized-controlled trials of 5-ASA or sulfasalazine for maintenance of surgically induced remission in CD [Ford *et al.* 2010]. The included studies represented 1282 patients with postoperative follow up of at least 6 months and, overall, aminosalicylates significantly reduced the risk of relapse. This effect was largely driven by the six studies of 5-ASA ($n = 834$), in which an average oral dose of 3.0 g/day was associated with a relative risk of relapse was of 0.80 (95% CI = 0.70–0.92) for a number needed to treat of 10. All of the 5-ASA studies included in these analyses had duration of follow up of at least 48 weeks. In the remaining five studies ($n = 448$ patients), sulfasalazine showed no significant effect in preventing postoperative relapse of CD. However, it should be noted that the average dose of sulfasalazine in these trials was 3.0 g/day, which represents delivery of only about 1 g per day of the active 5-ASA moiety and makes suboptimal dosing a likely explanation for these discordant findings in sulfasalazine-treated patients. Clinical indices were used to assess relapse in all but one of the analyzed 5-ASA studies. In the only study in which the objective endpoint of endoscopic recurrence was assessed [Caprilli *et al.* 1994], 5-ASA significantly reduced CD recurrence at 6, 12, and 24 months postoperatively, suggesting that this drug can maintain mucosal healing. The modest magnitude of clinical efficacy of 5-ASA in postoperative prevention of CD demonstrated in the systematic review and meta-analysis by Ford and colleagues is largely in agreement with a

recent Cochrane Collaboration Review [Doherty *et al.* 2009].

Although the apparent clinical benefit of 5-ASA for the prevention of postoperative recurrence of CD is modest, a recent head-to-head comparison of 5-ASA and azathioprine sheds some light on the practical use of 5-ASA in this setting. Reinisch and colleagues recently reported a double blind, double dummy, randomized trial of oral 5-ASA 4.0 g/day Eudragit L enteric coated tablets (Salofalk®) *versus* azathioprine (2.0–2.5 mg/kg/day) for prevention of postoperative relapse of CD [Reinisch *et al.* 2010]. Seventy-eight patients that had undergone ileocolonic resection were followed for 1 year and assessed for the primary endpoint of therapeutic failure, defined by CDAI $\geq$200 and an increase of $\geq$60 points from baseline, or drug discontinuation due to ineffectiveness or adverse side effects. At the end of the study, there was no statistically significant difference in the primary endpoint (composite of clinical recurrence and drug toxicity) between the two groups (22% azathioprine *versus* 11% 5-ASA, $p = 0.19$), with treatment failure in the azathioprine group being driven entirely by discontinuation of drug due to adverse reactions. However, if the analysis focused on clinical recurrence alone, azathioprine was found to be superior to 5-ASA, with none of the 41 azathioprine-treated patients meeting this endpoint *versus* 11% (4/37) of those treated with 5-ASA, a statistically significant difference ($p = 0.031$).

It is important to note that patients in the study of Reinisch and colleagues were not enrolled immediately after surgery, but rather within 6 to 24 months of operation, and patients were included only if they actually had some degree of endoscopic recurrence (mean Rutgeerts score of 3, corresponding to diffuse aphthous ileitis). Intolerance aside, more patients in the azathioprine group (63%) achieved some degree of mucosal healing (at least a 1 point reduction in Rutgeerts score) than in the 5-ASA group (34%). Overall, this study demonstrated that oral delayed-release 5-ASA is very well tolerated in postoperative CD patients and was associated with a low risk of clinical relapse despite established endoscopic recurrence of the disease at study entry. Of those patients that underwent end-of-treatment ileocolonoscopy, one third had achieved some degree of downgrading of the baseline mucosal lesion, lending further support to the use of 5-ASA in selected postoperative patients with lower risk of clinical recurrence (e.g. first surgery, fibrostenotic disease, or nonsmokers).

Mesalazine in ulcerative colitis

Treatment of active ulcerative colitis

The use of 5-ASA in UC has been investigated extensively. These agents have been first-line therapy for the majority of UC patients for decades. Meta-analysis of high-quality studies comparing oral 5-ASA to placebo for induction of UC remission showed that 5-ASA was superior with a pooled odds ratio of 2, but was no better than the less expensive parent compound, salazopyrin [Sutherland *et al.* 1993]. An updated meta-analysis that included more studies confirmed this initial impression [Sutherland and MacDonald, 2003]. Biddle and Miner assessed the use of 5-ASA enemas for active left-sided UC in 90 patients who were previously unresponsive or intolerant to conventional therapy [Biddle and Miner, 1990]. After 12 weeks of 5-ASA enema therapy, nearly 90% had a favorable endoscopic response and over 50% achieved clinical and endoscopic remission.

There is also evidence to support the concurrent use of oral and rectal forms of 5-ASA. Safdi and colleagues performed a randomized-controlled trial that followed 60 patients with mild to moderate left-sided colitis over 6 weeks of therapy. The combination of a once daily 4.0 g 5-ASA enema with at least 2.4 g/d of oral mesalazine resulted in lower disease activity scores than either oral or rectal 5-ASA alone in patients whose disease was limited to the left colon [Safdi *et al.* 1997]. A more recent study assessed the use of this combined mode of 5-ASA delivery in more extensive UC (disease extending proximal to the splenic flexure) in 127 outpatients with mild to moderate UC [Marteau *et al.* 2005]. All patients received a total of 4 g of oral mesalazine daily for 8 weeks. They were randomized to receive 1 g of rectal mesalazine (100 mL enema) daily *versus* placebo for the initial 4 weeks. Disease activity scores and endoscopic scores were assessed at weeks 4 and 8. Patients who received combination 5-ASA therapy had greater improvement at both weeks 4 and 8 and they were significantly more likely to be in remission at week 8. The investigators also commented that combination therapy was well accepted by patients and that it should be considered as a

viable first-line therapeutic approach, even in patients with extensive disease.

Maintenance of remission in ulcerative colitis

The 5-ASA agents have been proven to be very effective maintenance therapies in UC. The Mesalamine Study Group examined 264 patients with UC in remission followed over 6 months [Hanauer *et al.* 1996]. They demonstrated that continued use of oral mesalazine significantly increased the likelihood of maintaining remission in UC patients in whom remission was originally induced by mesalazine. Remarkable in this study was the finding that as little as 0.8 g/day was effective in maintaining remission, but there was incremental benefit in those taking 1.6 g/day. A meta-analysis of over 2400 patients confirmed that 5-ASA was superior to placebo in maintaining remission in UC, with a number needed to treat of six [Sutherland *et al.* 2002].

Mesalazine dose, frequency, and adherence to therapy

While the evidence supporting the use of 5-ASA drugs for induction and maintenance of remission in UC is clear, drug compliance has been identified as a major obstacle to optimizing therapy. Patients who are nonadherent to 5-ASA maintenance therapy are about fivefold more likely to relapse in the subsequent 2 years than treatment-compliant patients [Kane *et al.* 2003]. Early practice with 5-ASA drugs was to administer them as split dosing of numerous tablets three or four times daily. The most recent research has focused on determining the optimal dosing of 5-ASA drugs, and on developing and testing formulations that allow for less frequent daily dosing and lower pill burden. Equally important is the development of an engaged and attentive physician–patient relationship in management of UC, where patient tendency is to discontinue maintenance medications when their disease comes under control.

Whereas previously the dose, schedule, and duration of 5-ASA therapies has been unclear and somewhat empirical, recent large clinical trials of 5-ASA in UC have provided a clearer basis for its use in clinical practice. Administration of 5-ASA in multiple daily doses is largely an extrapolation of how the parent compound, sulfasalazine, was given to avoid toxicities associated with the sulfapyridine moiety which is readily absorbed after oral dosing [Allgayer, 1992]. As discussed in the following paragraphs, once daily administration of various proprietary forms of 5-ASA has been proven safe and effective in contemporary clinical trials, and many clinicians have applied this more practical dosing scheme to other delayed and sustained release formulations of oral 5-ASA.

Initial treatment of active UC should be based on clinical severity [Hanauer, 1996]. For mild UC, defined as fewer than four bowel movements per day with only intermittent bleeding and no signs of systemic toxicity (fever, tachycardia, anemia, normal erythrocyte sedimentation rate), a starting oral dose of 2.4 g once daily has been shown to be as effective as higher doses. For moderate disease (4–6 bowel movements per day, frequent hematochezia, and minimal signs of systemic toxicity) there seems to be some incremental benefit of using higher doses. There is fair rationale for choosing to start high-dose 5-ASA in select patients with moderate UC flares who previously had experienced difficult to control disease, as evidenced by prior requirements for systemic corticosteroids or multiple medications including combined oral and rectal 5-ASA. There is probably no role for 5-ASA in the immediate management of severe UC (>6 bloody bowel movements per day with prominent systemic features).

Meta-analyses have suggested that there is a threshold of treatment effect at a minimum dose of 2.0 g/day 5-ASA for induction remission or response [Sutherland and MacDonald, 2006]. A study designed to directly assess dose dependency of response suggested a plateau in treatment effect around 3.0 g/day 5-ASA without further benefit at higher doses [Kruis *et al.* 2003]. The ASCEND trials were a series of dose-finding trials for 5-ASA in UC. The ASCEND I trial studied patients with mild-moderate UC treated for 6 weeks with either 4.8 or 2.4 g/day of an oral delayed release Eudragit S formulation of 5-ASA (Asacol®) administered as divided doses TID [Hanauer *et al.* 2007]. There was no significant difference between the 4.8 and 2.4 g/day doses of 5-ASA in achieving overall clinical improvement (i.e. remission or response), with 56% and 51% of patients achieving this primary endpoint, respectively. However, in the subgroup of patients in this study with moderately active disease, the higher dose of 5-ASA was better by an absolute difference of 15% in achieving therapeutic success (72% *vs.* 57%, $p < 0.05$). The ASCEND II trial went on to focus on patients with moderately active UC,

and confirmed a statistically superior effect of the 4.8 g/day over the 2.4 g/day dose (72% overall response *vs.* 59%, respectively) [Hanauer *et al.* 2005]. In ASCEND I and II, the absolute difference of 13–15% increase in clinical success at 6 weeks with the 4.8 g/day dose compared with the 2.4 g/day dose is small and probably of limited clinical significance and, moreover, conceivably the end response may have been the same between the two doses if a later time point for assessment were chosen (e.g. 8 weeks). The ASCEND III trial also called to question the added benefit of high-dose 5-ASA in management of moderate UC, as the overall treatment success at 6 weeks was equivalent between the 4.8 and 2.4 g/day groups (70% and 66%, respectively). In subgroup analyses of ASCEND III, there was a significant benefit of 4.8 g/day *vs.* 2.4 g/day dosing in those patients with a history of difficult to treat UC, specifically those who required steroids or more than two medications (steroids, oral 5-ASA, rectal 5-ASA, or immunomodulators) to gain control of their disease in the past. A final point about the ASCEND trials is that the 5-ASA was administered in divided doses given three times daily. The reported efficacy of this dosing schedule is likely to be less in actual clinical practice where TID dosing predicts poor patient adherence, underdosing, and diminished effectiveness of 5-ASA therapy.

Lichtenstein and colleagues performed a placebo-controlled study of 5-ASA dosing frequency using a novel targeted release formulation of 5-ASA comprised of a pH-dependent coating overlying hydrophilic and lipophilic matrices known as Multi Matrix System® (MMX) [Lichtenstein *et al.* 2007]. They compared 4.8 g/day given as a single daily oral dose and 2.4 g/day (given as 1.2 g PO BID) in patients with mild to moderate UC over 8 weeks. A significantly greater percentage of patients treated with either 2.4 or 4.8 g/day of MMX 5-ASA achieved combined clinical and endoscopic remission (34.1% and 29.2%, respectively) compared with placebo-treated patients (12.9%, $p < 0.01$), but this study was not powered to assess relative differences between the two 5-ASA dosing regimens. Kamm and colleagues performed a dose-finding study that compared two different doses of MMX 5-ASA given once daily and 2.4 g/day divided three times daily of Eudragit S delayed release 5-ASA (Asacol®) in patients with mild to moderate UC [Kamm *et al.* 2007]. The primary endpoint of clinical and endoscopic remission at 8 weeks was achieved in 40.5% and 41.2% of patients receiving 2.4 and 4.8 g/day MMX, respectively, which was significantly better than placebo (22.1%). The 2.4 g/day (TID divided dosing) Eudragit S formulation of 5-ASA tested in this study was not significantly better than placebo, meeting endpoint in only 32.6% of patients ($p = 0.124$). Sandborn and colleagues pooled the data from the two MMX phase III induction studies to enable a more accurate measure of efficacy *versus* placebo and a more robust assessment of some of the secondary outcomes measures common to both trials [Sandborn *et al.* 2007]. At 8 weeks of therapy, both MMX groups (2.4 and 4.8 g/day) showed significantly higher clinical remission and mucosal healing rates (37.2% and 35.1%, respectively) than placebo (17.5%, $p < 0.001$). There was also no apparent dose–response relationship with any secondary outcomes such as stool frequency, rectal bleeding scores, endoscopic appearance, or other composite measures of UC activity. Kamm and colleagues then reported an extension of the two MMX phase III studies in which patients who failed to achieve remission after 8 weeks were continued or started on 4.8 g/day 5-ASA for an additional 8 weeks [Kamm *et al.* 2009]. These were patients that in the parent studies had received MMX 2.4 or 4.8 g/day, Asacol 2.4 g/day, or placebo. Regardless of prior treatment, about 60% of patients achieved remission after an additional 8 weeks on 5-ASA provided as MMX 4.8 g/day. Interestingly, of those patients that had failed to achieve remission with MMX 4.8 g/day in the parent trials, 60% achieved remission by simply continuing treatment with the same dose of MMX for another 8 weeks. These findings suggest persistence with 5-ASA treatment up to 16 weeks before declaring therapeutic failure. Considering the essentially equivalent therapeutic success in UC patients after the initial 8 weeks of treatment with 2.4 and 4.8 g/day 5-ASA, there is fair rationale for a step-up approach (i.e. start 4.8 g/day 5-ASA in those patients that do not achieve treatment success after 8 weeks on 2.4 g/day).

In light of the MMX studies demonstrating safety, efficacy, and practical advantage of once daily 5-ASA dosing, other proprietary formulations have been tested in this dosing schedule. Kruis and colleagues performed a noninferiority study comparing once daily dosing (3.0 g/day) to three times daily dosing (1.0 g three times daily)

of Salofalk® granules in patients with mild to moderate active UC [Kruis *et al.* 2009]. This was a positive trial, showing noninferiority of the 3.0 g once daily dosing, with 79.1% and 75.7% achieving clinical remission after 8 weeks of once or thrice daily dosing, respectively. The only significant difference between the groups was that more proctosigmoiditis patients in the once daily dosage group achieved remission, suggesting that a once daily bolus dose may achieve higher peak intraluminal concentrations of the drug to better affect inflammation in the distal colon.

Rather than for induction of remission in UC, other manufacturers have tested proprietary 5-ASA formulations in once daily *versus* multidose format in the context of maintenance of remission in UC. Sandborn and colleagues showed that 1.6–2.4 g once daily Asacol® was equivalent in efficacy to twice daily dosing of this product for prevention of UC relapse over a 1 year observation period [Sandborn *et al.* 2010]. By comparison, others showed that a 2.0 g once daily dosage of oral ethylcellulose-coated 5-ASA (Pentasa®) was statistically superior to the 1.0 g twice daily format in maintenance of clinical remission in UC [Dignass *et al.* 2009]. Approximately three quarters of the patients in the study of Dignass and colleagues had left-sided colitis. Long-term safety and tolerability of 2.4 g/day of MMX 5-ASA has been demonstrated [Kamm *et al.* 2008], and this study also proved that single or divided dose MMX regimens have equivalent efficacy in maintenance of clinical and endoscopic remission in UC at 12 months. For maintenance of clinical remission and mucosal healing in left-sided UC over 1 year, 2.4 g/day MMX 5-ASA once daily was therapeutically equal to 2.4 g/day Asacol® twice daily [Prantera *et al.* 2009]. The above studies all support both efficacy and safety of a variety of once daily dosage formulations of 5-ASA used in the management of UC. Clinical trials aside, the new simplified once daily 5-ASA regimens are likely to be superior in actual clinical practice to former 5-ASA multidose schedules due to increased patient compliance, and by possibly achieving higher intraluminal 5-ASA concentrations after bolus dosing.

Safety

Aminosalicylates have the best safety profile of all medical therapies currently used in IBD. Minor but common side effects of 5-ASA include headache, nausea, dyspepsia, flatulence, and diarrhea. Rare but serious side effects include pleuritis, pericarditis, myocarditis, pancreatitis, and cholestatic hepatitis. Mesalazine-induced nephritis and renal dysfunction have been described and forms the basis for suggested monitoring of renal function in IBD patients on continuous oral 5-ASA maintenance therapy [Patel *et al.* 2009]. Patients may experience worsening symptoms of colitis due to the osmotic effects of the drug or, far less commonly, the development eosinophilic colitis with peripheral eosinophilia characterizing this phenomenon as a drug hypersensitivity reaction.

Mesalazine and colon cancer chemoprevention

Individuals with colitis are at significantly increased risk of developing colorectal cancer, perhaps twofold to threefold compared with the general population. This excess risk is of similar magnitude in both UC and colonic CD patients [Bernstein *et al.* 2001]. Therefore, recommendations for colonoscopy with mucosal biopsy have been devised to screen for dysplasia and cancer, and treatments to prevent colorectal cancer in this patient group have been investigated. Chan and Lichtenstein identified the ideal chemopreventive therapy as one that is 'efficacious in the prevention of cancer, easily administered, affordable, safe and well-tolerated, with minimal side-effects' [Chan and Lichtenstein, 2006]. 5-ASA agents have been evaluated for chemoprophylactic properties although, to date, there have been no randomized, placebo-controlled trials. The bulk of the current literature is retrospective and focuses generally on patients with UC.

There is indirect evidence of the cancer chemopreventive action of 5-ASA from studies examining patient adherence to prescribed 5-ASA therapy and subsequent development of colorectal cancer. For example, Eaden and colleagues performed a case–control study of 102 patients with UC and a diagnosis of colorectal cancer compared with matched controls. Patients who were regular users of 5-ASA were 75% less likely to develop colorectal cancer and this was highly statistically significant [Eaden *et al.* 2000]. Another study assessed the risk of development of colorectal cancer in UC patients taking sulfasalazine. Patients who were compliant with sulfasalazine treatment were significantly less likely to develop colon cancer, with an absolute risk reduction of 27% [Moody *et al.* 1996]. A large, nested case–control study compared rates of

colorectal cancer between regular users (compliant) and noncompliant users of 5-ASA. Both UC and CD patients were included. Regular users of 5-ASA were less likely to develop colorectal cancer with an adjusted odds ratio of 0.6 [van Staa *et al.* 2005]. There appears to be both a threshold and dose dependency of the chemoprophylactic effects of 5-ASA. In a case-control study Rubin and colleagues showed through logistic regression that a daily dose of 1.2 g or more of 5-ASA reduced the odds of developing colorectal cancer or dysplasia by 72% and the degree of protection correlated with dose [Rubin *et al.* 2006].

Velayos and colleagues recently published a meta-analysis of 9 studies comprising 1932 patients examining the relationship between use of aminosalicylates and subsequent development of colorectal cancer in patients with longstanding UC [Velayos *et al.* 2005]. Their analysis showed an adjusted summary odds ratio of 0.51 (0.37–0.69) for development of dysplasia or colorectal cancer in patients with UC who took aminosalicylates. A similar magnitude of protection was seen if the harder endpoint of colorectal cancer was used. Each study included in the meta-analysis was retrospective in design; all studies individually reached the same conclusions but each was subject to unique biases and limitations. A major issue that may confound interpretation of such retrospective studies is whether 5-ASA use by UC patients is simply a marker of attentiveness of those patients or their physicians to other factors that may reduce risk of colorectal cancer.

Although meta-analyses tend to consolidate limited, biased data as fact, the burden of evidence suggests that 5-ASA has significant colon cancer chemoprophylactic effects and mechanistically this is believable. Although prospective, randomized, placebo-controlled studies would answer this question, due to the relatively rare occurrence of colorectal cancer in UC and long latency to its development, such large and lengthy studies are unlikely to be undertaken. However, additional support of the chemprophylactic effects of 5-ASA comes from numerous experimental studies with cell culture or animal models of colonic epithelial carcinogenesis that confirm mechanistically that 5-ASA inhibits carcinogenesis, adding weight to clinical observations in IBD.

Colon cancer in the IBD population is believed to develop differently than sporadic cancers in patients without IBD. Instead of progressing through the adenomatous polyp phase, colon cancer in IBD patients may develop from nonpolypoid, dysplastic mucosal changes. Active colonic inflammation predisposes to dysplasia and is therefore a risk factor for colon cancer in patients with IBD. Logically, controlling colonic inflammation should reduce this risk, and part of the chemopreventive effect of 5-ASA agents is certainly due to anti-inflammatory action. Indeed these agents are structurally similar to aspirin, an anti-inflammatory drug that has been shown to reduce rates of sporadic colorectal cancer in individuals without IBD [Asano and McLeod, 2004]. Proposed mechanisms include modulation of cyclooxygenase-2, NFκB activity and scavenging of reactive oxygen species. In particular PPAR-gamma, a nuclear receptor that is involved in mediating colonic inflammation, in part through modulation of NFκB, has been shown *in vitro* to play a pivotal role in cell cycle progression and apoptosis independent of its anti-inflammatory effect [Jiang *et al.* 1998].

Although the anti-inflammatory effects of 5-ASA likely contribute colon cancer prevention, there seems to be some distinct and specific antineoplastic effects. For example, 5-ASA reduces activity of the Wnt/beta-catenin pathway [Jiang *et al.* 1998]. Increased activity of this pathway has been well established to be present in the majority of early colorectal cancers.

There are currently no firm guidelines on the use of 5-ASA agents as chemoprevention for colorectal cancer. There is not enough evidence currently to commit all individuals with IBD to 5-ASA therapy in an effort to reduce their risk of malignancy. More consideration may be given to patients with IBD that are at higher risk for colon cancer, including those with extensive disease, primary sclerosing cholangitis, or family history of colorectal cancer. Rather than a questionable reduction in relatively small and remote risks of colorectal cancer attributable to chronic colitis, patients may be more willing to make a longstanding commitment to 5-ASA therapy based on clear proof that it is highly effective in reducing annual risk of disease exacerbations.

Summary

Recent advances in pharmaceutical formulation and clinical application of 5-ASA, as well as

improved knowledge of its mechanisms of action and colon cancer chemoprophylactic effects, has led to renewed interest in this foundational drug in IBD therapy [Iacucci *et al.* 2010]. 5-ASA medications act through incompletely understood topical anti-inflammatory effects in the small bowel and colonic mucosa. Various targeted release mechanisms have been developed to facilitate gut mucosal delivery of 5-ASA with limited systemic absorption and, as such, 5-ASA drugs have very few systemic toxicities. Although 5-ASA is very safe and well tolerated, patients should still be informed of rare but serious adverse effects (e.g. pancreatitis, pleuritis, myocarditis, etc.), paradoxical worsening of symptoms at treatment outset, and long-term need to monitor renal function.

5-ASA products are most useful in the setting of UC where they have well-proven efficacy in both the induction and maintenance of clinical and endoscopic remission. The recent demonstration that these agents promote and sustain mucosal healing is important since mounting evidence supports a correlation between mucosal healing and highly relevant clinical outcomes such as decreased risk of UC recurrence and need for surgery [Lichtenstein and Rutgeerts, 2010]. New evidence supports simplified once daily regimens and lower starting doses without loss of benefit. This is important because frequent dosing schedules have been associated with poorer compliance to therapy, which in turn is associated with higher risks of disease recurrence. The optimized dosing strategies demonstrated in recent UC trials are an excellent example of comparative effectiveness research [Siegel, 2009], and have provided guidance in the clinical use of 5-ASA agents that likely extends across proprietary labels. As evidence-based and optimized application of 5-ASA is widely adopted by practitioners, substantial cost savings are likely to be found.

There is strong evidence to support the use of 5-ASA at a dose of 2.4 g once daily for induction of remission in most patients with mild to moderate UC. If remission is not achieved after 6–8 weeks, dose escalation from 2.4 to 4.8 g/day should be considered before proceeding to corticosteroids, as a substantial proportion of patients can capture remission at the higher dose. Higher doses (i.e. 4.8 g once daily) should be considered upfront in patients who have had difficulty in managing UC in the past. In general, the oral dose that achieves remission should be the dose chosen for continued maintenance therapy. The simultaneous use of oral and rectal formulations of 5-ASA is also a proven strategy to accelerate and maximize treatment success in UC.

5-ASA has a much more limited role in the management of CD and, in particular, is not effective in treating active CD. Such practice is not the standard of care and is potentially detrimental, delaying more appropriate therapies and allowing inflammation to continue with the potential for perforating or obstructive complications. Postoperative recurrence is statistically significantly decreased in patients with CD taking 5-ASA. Although the magnitude of this effect is small and its durability in the longer term is unknown, current evidence suggest it be considered as an option for postoperative CD patients at lower risk of recurrence or those patients concerned about the safety or tolerability of immunomodulators.

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