REVIEW ARTICLE

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Improving Delivery of Aminosalicylates in Ulcerative Colitis

Effect on Patient Outcomes

Nielsen Q. Fernandez-Becker and *Alan C. Moss*

Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

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Abstract

Developments in drug delivery technology have expanded the formulations of 5-aminosalicylic acid (5-ASA) available to clinicians over the last 50 years. Delivery of adequate doses of 5-ASA to the colon can be achieved by pH-dependent, delayed-release or pro-drug formulations. Despite some variations in the pharmacokinetics between individual preparations, the clinical effects in induction of response and maintenance of remission in ulcerative colitis appear to be consistent. Direct comparison studies between different preparations have yielded similar results in primary endpoints, although differences in secondary endpoints or *post hoc* analyses have been noted. The development of delivery methods that allow once-daily administration represents a potential means to improve the low medication adherence rates reported in patients with ulcerative colitis.

The development of 5-aminosalicylic acid (5-ASA) as a therapy for ulcerative colitis was a major milestone in the treatment of this disease. The last 50 years has seen an evolution of technological methods for successful delivery of 5-ASAs to areas of active disease. This review examines the pharmacological and clinical aspects of 5-ASAs with a particular focus on drug delivery methods. Relevant studies were identified using PubMed. Relevant references from identified studies were reviewed to ensure pertinent papers were included in the review.

For many years, sulfasalazine was the mainstay of treatment for ulcerative colitis and remains so in some parts of the world. It was initially developed as a drug for the treatment of rheumatoid arthritis and later applied to the treatment of colitis. Sulfasalazine was designed by Svartz and Willsteadt to combine the anti-inflammatory properties of 5-ASA with the antibacterial properties of sulfapyridine at a time when the pathogenesis of rheumatoid arthritis was thought to be a result of a combination of infectious and inflammatory causes.[1,2] A randomized controlled trial demonstrated its efficacy in ulcerative colitis in 1962.[3] Subsequent experiments led to the identification of the active component of sulfasalazine; 5-ASA enemas, but not sulfapyridine enemas, led to clinical improvement of patients with active ulcerative colitis.[4] This experiment suggested that the therapeutically active moiety in sulfasalazine was 5-ASA. Further confirmation came from studies demonstrating that 5-ASA suppositories were superior to placebo or sulfapyridine suppositories in the treatment of proctitis,[5] and that oral sulfasalazine and 5-ASA suppositories had similar efficacy in ulcerative colitis.[6] From these studies, the hypothesis emerged that 5-ASA acts topically on the inflamed mucosa and that its delivery to the colon intact requires the sulfapyridine component.

Sulfasalazine is a pro-drug that consists of a molecule of sulfapyridine linked by an azo bond to 5-ASA.[2] Approximately 30% of the drug is absorbed in the small intestine and the remainder reaches the colon intact.[7] Once there, resident bacteria split the drug into its components by cleaving the azo bond.[8] Sulfapyridine is more readily absorbed by colonic epithelia than 5-ASA.[2,9] The 5-ASA component makes up the largest component of drug in the faeces and, to a lesser extent, sulfasalazine and sulfapyridine are also eliminated via this route.[1] Although sulfasalazine is efficacious in the treatment of ulcerative colitis, its use is limited by adverse reactions in approximately 20–30% of patients.[10,11] The sulfapyridine element undergoes conjugation and acetylation in the liver. Many of the adverse effects have been attributed to genetic differences in individuals at the level of the acetylation step.[10] Minor adverse effects include nausea, vomiting, fever and rash.[11] More serious adverse reactions include haemolytic anaemia, reticulocytosis, cyanosis, leukopenia and agranulocytosis.[10] Toxic epidermal necrolysis, pancreatitis and neurological manifestations have also been reported.[1]

Given the adverse effects of sulfasalazine, there was an impetus to investigate sulfapyridine-free alternatives. This led to the development of several oral formulations of 5-ASA, including pH-dependent forms and a delayed-release formulation, as well as rectal formulations. There are also pro-drugs, agents that are similar to sulfasalazine in the way they deliver the active moiety (5-ASA) to the colon. These include olsalazine and balsalazide.

While it is clear that 5-ASAs are effective in treating ulcerative colitis, their exact mechanism of action is still unclear. In the colon, 5-ASA is thought to interact with the damaged epithelium, where it is converted to the inactive acetylated form.[12] This metabolite is either absorbed into the blood and then excreted in the urine or secreted into the colonic lumen where it is eliminated in the faeces.[12] Free 5-ASA is also absorbed into the blood stream and is excreted in the urine.[12] The exact interaction that occurs between 5-ASA and the colonic epithelium is poorly understood. However, 5-ASA agents have been shown to have varied effects, both in cell-mediated immune processes and inflammation (table I).[13] 5-ASA has been shown to inhibit T-cell proliferation by blocking interleukin (IL)-2 production in peripheral mononuclear cells.[14] Furthermore, sulfasalazine was found to alter the expres-

Table I. Proposed therapeutic effects of 5-aminosalicylic acids

Immune processes
Inhibit T-cell proliferation by blocking IL-2 production in peripheral mononuclear cells[14]
Alteration of cell adhesion expression pattern[15]
Inhibition of antibody production by B cells[17]
Interference with macrophage and neutrophil functions[15,16,18]
Inflammation
Decrease production of IL-1 and TNF[20-22]
TNF receptor blockade[23]
Inhibition of cyclo-oxygenase[24,25]
Decreased production of leukotriene B4 and prostaglandin E2[21,26-28]
Activation of PPARγ[29]
Inhibition of lipoxygenase and 5-lipooxygnase-activating protein[13,19]
NF-κB regulation[30]
Oxygen derived free radicals
Decreased superoxide anion production[31]
Decrease in membrane lipid peroxidation[32]

IL = interleukin; **NF-κB** = nuclear factor-κB; **PPARγ** = peroxisome proliferator-activated receptor-γ; **TNF** = tumour necrosis factor.

sion of cell adhesion molecules, which is thought to cause decreased leukocyte mobility in the inflamed mucosa.[15] Other effects of 5-ASA and sulfasalazine include inhibition of antibody production by B cells, and interference with macrophage and neutrophil function.[16-19]

Many *in vitro* studies confirmed a wide range of anti-inflammatory properties. Not only has 5-ASA been implicated in decreasing the production of IL-1 and tumour necrosis factor (TNF)-α, but sulfasalazine blocked binding of TNF to its receptor.[13,19-23] Other inflammation-related effects of sulfasalazine and 5-ASA are the inhibition of cyclo-oxygenase and decreased production of leukotriene B4.[13,19,24-28] In addition, both sulfasalazine and 5-ASA have been implicated in blocking the production and chemotactic activities of leukotrienes via inhibition of both 5-lipoxygenase and 5-lipooxigenase-activating protein.[13,19] 5-ASA is also thought to play a role as a free radical scavenger and antioxidant.[13,19,31,32] The pleiotropic effect of 5-ASA on pro-inflammatory factors raised the possibility that perhaps the effects occur through a regulation of a central mediator of inflammatory and immune responses.[13] Indeed, recent *in vitro* studies suggest the involvement of the transcription factor nuclear factor-κB, which is known to have a role in chronic inflammatory disease.[13,30] The peroxisome proliferator-activated receptor-γ (PPARγ) has emerged as a key receptor mediating the anti-inflammatory effects of aminosalicylates. Recent studies have shown that aminosalicylates are synthetic ligands for PPARγ in colonic epithelial cells. 5-ASA is able to induce PPARγ expression, bind PPARγ and induce translocation and conformational change, and recruit vitamin D_3 receptor-interacting protein, a coactivator molecule.[29] Activation of PPARγ results in the regulation of inflammatory signalling pathways and impairs mucosal production of inflammatory cytokines, proliferation of inflammatory cells and expression of adhesion molecules.

1. Drug Delivery Systems

1.1 Oral pH-Dependent Systems

Given that 5-ASA exerts its anti-inflammatory effect by direct contact with the inflamed mucosa, the key to effective drug delivery is getting sufficient doses of 5-ASA to the area of intestinal inflammation.[4-6] Since oral 5-ASA is readily absorbed in the small intestine,[3] protecting the active agent from uptake on its journey to the colon has required the development of specific delivery systems. These can be divided into pH-dependent and pH-independent methods (table II).

Eudragit-S® [1] is a pH-sensitive polymer that dissolves at a pH >7, allowing the release of the drug in the terminal ileum and colon.[19,33,34] This mechanism allows for a rapid release of 5-ASA in the colon upon dissolution of the capsule. Asacol® and Ipocol® are two examples using this technology, the latter having a thinner Eudragit-S® coating.[35] Eudragit-L® is a variation of the Eudragit-S® polymer that dissolves at a lower pH (>6), leading to release of active 5-ASA through the jejunum, terminal ileum and colon.[19,33,34] Both tablet and micro-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Table II. Different 5-aminosalicylic acid (5-ASA) delivery systems, formulation and site of 5-ASA release

Generic name	Trade name	Formulation	Delivery method	Site of 5-ASA release
5-ASA (mesalazine)	Mesalamine®, Asacol® and Ipocol®	5-ASA coated with Eudragit-S® resin	pH dependent soluble pH ≥7	Terminal ileum, colon
	Claversal® Salofalk®	5-ASA coated with Eudragit-L® resin	pH dependent soluble pH ≥6	Jejunum, ileum, colon
	Pentasa®	5-ASA microgranules coated in semi-permeable ethylcellulose	Delayed release through ethylcellulose coat	Duodenum, jejunum, ileum, colon
	Lialda™	5-ASA coated with Multi Matrix system technology with lipophilic and hydrophilic matrices	pH dependent soluble at pH >7 Delayed release through matrix	Terminal ileum, colon
Balsalazide	Colazal® and Colazide®	5-ASA dimerized to inert carrier molecule via an azo bond	pH independent bacterial cleavage of azo bond	Colon
Olsalazine	Dipentum®	Two 5-ASA molecules dimerized via an azo bond	pH independent bacterial cleavage of azo bond	Colon

pellet forms of Eudragit-L® have been tested in ulcerative colitits, with similar efficacy.[36] Claversal® and Salofalk® are encapsulated by Eudragit-L®. Studies comparing the bioavailability of Eudragit-S® and -L® coated formulations of mesalazine (mesalamine) in ileostomy and healthy controls demonstrated that the Eudragit-L® has a distribution of release that occurs more proximally than Eudragit-S®.[37]

There was initial speculation that pH variations in different individuals may translate to different absorption patterns and differences in efficacy in patients with inflammatory bowel disease.[12,34,38] This has been the subject of five small studies.[39-43] In two of the studies, measured pH levels in the terminal ileum and colon were found to be lower in patients with active ulcerative colitis.[41,42] In contrast, in 1998, Press et al.[43] reported higher pH levels in these areas in patients with active ulcerative colitis and another study found no pH differences in patients with and without active colitis.[39] Given the relative consistency of therapeutic effects of 5-ASA in the colon in clinical practice, it is unlikely that intestinal pH in patients with ulcerative colitis significantly influences global clinical responses, but may influence results in individual patients.

Recently, a novel pH-dependent 5-ASA delivery system was introduced, Multi Matrix (MMX) 5-ASA (Lialda™). In this formulation, MMX System technology is utilized, which contains lipophilic and hydrophilic matrices.[44,45] The coating is pH-dependent, allowing for release of the drug at pH >7 in the terminal ileum and colon. The hydrophilic parts interact with aqueous components of intestinal fluid, making the tablet swell in to a viscous gel state. Theoretically, this allows for slow diffusion of the drug out of the tablet. In addition, pieces of the tablet break off, allowing for release of 5-ASA from the tablet core.[44,45] The role of the lipophilic core is to repel water from entering the core of the tablet, therefore prolonging the half-life of the drug.[44,45]

1.2 Oral pH-Independent Systems

Oral pH-independent mechanisms of 5-ASA delivery involve either semi-permeable membrane coatings or the use of azo bonds that are sensitive to colonic bacteria. Ethylcellulose is a semi-permeable membrane that allows for sustained slow release of mesalazine in the duodenum, jejunum, ileum and colon. This process is pH independent. Approximately 20% of the drug is released in the small intestine, the rest of the drug being delivered to the colon.[46] In theory, this makes this delivery system suitable for patients with more proximal inflammatory disease, such as in patients with Crohn's disease.[47]

Pro-drugs incorporate a different delivery system by exploiting the enzymatic-sensitivity of diazo bonds. In addition to sulfasalazine, two pro-drugs

are currently on the market for use in ulcerative colitis, balsalazide and olsalazine. Balsalazide is a pro-drug with the components 5-ASA and an inert carrier molecule (4-aminobenzoyl-β-alanine [4-ABA]) that is held together by an azo-bond. Like sulfasalazine, this drug is metabolized by azo-reductase produced by colonic bacteria.[48] The drug is generally well tolerated by patients with active and inactive colitis. Approximately 25% of the drug is absorbed in the form of N-acetyl-5-ASA, 5-ASA, 4-ABA or N-acetyl-4-ABA.[48] 4-ABA accounts for 10–15% of the absorbed drug.[48] Olsalazine is a pro-drug in which two 5-ASA molecules are dimerized via an azo bond. The pharmacokinetics are thought to be similar to sulfasalazine. After an oral load, relatively high concentrations of 5-ASA are found in the stool.[33,49-52] Given that these drugs rely on colonic bacteria for their activity, it is interesting to speculate whether concomitant antibacterial treatment or individual colonic flora would affect their efficacy. Consistent with this, there are reports of decreased azo reduction in the setting of profuse diarrhoea.[53] Furthermore, a one-third reduction in the cleavage of sulfasalazine was reported after a course of ampicillin.[54]

1.3 Rectal Delivery Systems

Rectal delivery offers the advantage of direct application of the active drug to the inflamed mucosa and, thus, has been used to treat distal ulcerative colitis. Different formulations of 5-ASA have been packaged into suppositories, liquid enemas, foam enemas and, most recently, gel enemas to treat distal ulcerative colitis. These differ in their capacity to spread retrograde along the colon. Scintigraphical studies using radiolabelled 5-ASA have shown that suppositories can consistently deliver active drug only to the rectum.[55] Foams reliably coat the proximal sigmoid colon,[55] while liquid enemas, partly because of their larger volume, consistently deliver the drug as far as the splenic flexure.[55] Viscosity and volume of the enema appear to be the most important factors for proximal distribution. Newer gel formulations are able to reach as far as the splenic flexure.[56] Some studies have suggested that patients seem to prefer foam or gel formulations over liquid enemas, reporting ease of application and higher degree of retention.[55] This may influence medication adherence.

2. Clinical Efficacy

2.1 Oral Mesalazine

2.1.1 Eudragit-Coated

Early studies demonstrated that Eudragit®-coated mesalazine was more effective than placebo in treating mild to moderately active ulcerative colitis.[57,58] Schroeder et al.,[57] compared Eudragit®-coated mesalazine with placebo in a randomized, double-blind, placebo-controlled trial. The patients had mildly to moderately active colitis. Eighty-seven patients were randomly assigned to either placebo or one of two doses of Eudragit®-coated mesalazine (1.6 or 4.8 g/day). Clinical assessment included patient daily records that catalogued symptoms, such as rectal bleeding and number of stools, as well as a subjective sense of well-being. A physicians global assessment score was calculated at each visit. This included the patient's records in addition to objective measures such as results of flexible sigmoidoscopy. After 6 weeks, 24% of patients treated with 4.8 g/day of Eudragit®-coated mesalazine achieved complete remission and 50% achieved partial response.[57] In the placebo group, only 5% achieved complete remission and 13% partial remission ($p < 0.0001$).[57] Patients treated with Eudragit®-coated mesalazine 1.6 g/day showed a trend towards improvement when compared with placebo, but the difference was not significant ($p = 0.51$).[57]

Additional evidence of the efficacy of Eudragit®-coated mesalazine came from a multicentre, double-blind, placebo-controlled trial. Sninsky and colleagues[58] demonstrated that 5-ASA, in the form of Eudragit®-coated mesalazine in a dose of 2.4 g/day, was effective in the treatment of mild to moderate colitis. Patients that were treated with 2.4 g/day improved by 32% compared with 9% ($p = 0.003$) of those given placebo 3 weeks into treatment.[58]

When compared with sulfasalazine at equimolar doses of 5-ASA, rectal bleeding subsided in 75% of the patients on Eudragit-coated mesalazine, compared with 47% in the sulfasalazine group ($p < 0.05$).[59] However, this did not translate to endoscopic improvement.

The Eudragit®-coated formulations have also been shown to be efficacious for maintenance of remission of ulcerative disease. Dew et al.,[60] noted that 5-ASA and sulfasalazine were comparable at maintaining remission. These authors later reported that at 24 weeks there was no difference between an average daily dose of 2.7 g of 5-ASA and 2.3 g of sulfasalazine in the maintenance of remission.[61] Riley et al.[62] also failed to find a statistical difference between sulfasalazine and 5-ASA. In 1996, the 5-ASA study group addressed whether there is a dose response for maintenance of remission. They reported a randomized, multicentre, double-blind, placebo-controlled clinical trial that studied the efficacy of 5-ASA as long-term maintenance therapy. A total of 264 patients with ulcerative colitis who had been in remission for at least 1 month, while receiving sulfasalazine or any form of 5-ASA, were enrolled in the study.[63] The patients were randomized to receive placebo, or 0.8 or 1.6 g/day of Eudragit®-coated mesalazine. In total, 39% of patients treated with placebo maintained remission, compared with 58.8% of patients receiving Eudragit®-coated mesalazine 0.8 g/day ($p = 0.036$) and 65.5% of patients treated with Eudragit®-coated mesalazine 1.6 g/day ($p = 0.006$).[63] Paoluzi et al.[64] also studied Eudragit®-coated mesalazine at doses of 1.2 or 2.4 g/day in maintaining remission in patients with inactive ulcerative colitis and found no statistically significant differences between the two dosages.

2.1.2 Ethylcellulose-Coated

Release of 5-ASA from an ethylcellulose coating (Pentasa®), unlike Eudragit®-coated mesalazine, is not dependent on pH. Instead, ethylcellulose allows the release of the therapeutic drug continuously over several hours.[37,46,65] Studies in ileostomy patients and healthy volunteers, involving analysis of blood for N-acetyl-5-ASA and the excretion of 5-ASA in the faeces, showed that approximately 50% of the drug was released in the small bowel and the rest in the colon.[37,46,65]

Randomized clinical trials have demonstrated that ethylcellulose-coated mesalazine is efficacious in treating ulcerative colitis. Ethylcellulose-coated mesalazine was compared with placebo in a randomized, multicentre, double-blind trial of 1, 2 or 4 g/day in mild to moderate ulcerative colitis.[66] Clinical improvement was assessed using the physicians assessment and sigmoidoscopy. Ethylcellulose-coated mesalazine was found to be significantly superior to placebo in all the parameters tested. In a multicentre double-blind study, Munakata et al.[67] compared ethylcellulose-coated mesalazine (1.5 g/day) to sulfasalazine (3 g/day) in the treatment of mild to moderately active ulcerative colitis and found that both drugs had similar efficacies regarding clinical improvement. The safety profile of ethylcellulose-coated mesalazine was found to be better than that of sulfasalazine.[67]

In the maintenance of remission, Miner and colleagues[68] performed a 12-month placebo-controlled study with 4 g/day of ethylcellulose-coated mesalazine for this indication. Patients were stratified to either pancolitis or left-sided colitis based on history and endoscopic examination. The ethylcellulose-coated mesalazine group fared better than placebo, 64% versus 38% ($p = 0.0004$) for maintenance of remission. In a double-blind comparison of sulfasalazine and ethylcellulose-coated mesalazine, both drugs were equally effective at maintaining remission.[69] When two dosages of ethylcellulose-coated mesalazine were compared in patients with ulcerative colitis in remission, the higher dose (3 g/day) resulted in fewer relapses (33%) compared with 44% with the lower dose (1.5 g/day) [$p = 0.057$].[70]

2.1.3 Multi Matrix System

In two controlled clinical trials, the efficacy of MMX 5-ASA in induction of remission was reported recently.[44,45] Lichtenstein et al.[45] performed a randomized, double-blind, parallel-group, multicentre, phase III study in patients with mild to moderate colitis. A total of 280 patients were randomized to either placebo or MMX 5-ASA 2.4 g/day (given as

1.2 g twice daily) or 4.8 g/day. The primary endpoint of the study was the percentage of patients in clinical and endoscopic remission. They reported that 34.1% of patients treated with MMX 5-ASA 2.4 g/day and 29.2% of patients treated with 4.8 g/day went into remission compared with 12.9% receiving placebo. Kamm et al.[44] compared MMX 5-ASA with Eudragit®-coated mesalazine and placebo. The authors performed a randomized, phase III, double-blind, double-dummy, parallel-group, placebo-controlled study. A total of 343 subjects were randomized to either MMX 5-ASA 2.4 or 4.8 g/day, or Eudragit®-coated mesalazine 2.4 g/day given in divided doses for 8 weeks. These authors found no advantage of Eudragit®-coated mesalazine over placebo in the treatment of ulcerative colitis. The MMX formulation was found to induce clinical and endoscopic remission in 40.5% and 41.2% in patients treated with MMX 5-ASA 2.4 and 4.8 g/day, respectively. The lack of superiority of Eudragit®-coated mesalazine to placebo in this study was surprising given prior studies of this drug.

2.2 Oral Diazo-Bonded Formulations

2.2.1 Balsalazide

The efficacy of balsalazide in clinical trials has been inconsistent. Initially, placebo-controlled studies failed to demonstrate improved efficacy of balsalazide at doses of 4.75 and 6.75 g/day over placebo. At the end of a 4-week phase III study, patients receiving balsalazide were no better than those receiving placebo with respect to physicians global assessment, stool frequency, rectal bleeding and overall assessment.[71] In contrast, a study comparing balsalazide with mesalazine concluded similar efficacy in treating ulcerative colitis, with a better adverse effect profile.[72] The study by Green et al.[72] was the only one that showed the superiority of equimolar doses of balsalazide over mesalazine. In this study, the authors performed a double-blind study comparing balsalazide 6.75 g/day and mesalazine 2.4 g/day on the treatment of active ulcerative colitis (mild to severe). The histological grade and severity of the disease was determined before starting therapy. The results indicated that a greater percentage of patients achieved remission at intervals of 4, 8 and 12 weeks in the balsalazide group than in the mesalazine group. At 12 weeks, 62% of the balsalazide-treated patients were in remission compared with 37% of those treated with mesalazine ($p = 0.0159$).[72]

Subsequent studies reported equivalence of balsalazide to mesalazine. Levine et al.[71] compared two different doses of balsalazide (6.75 and 2.25 g/day) with mesalazine 2.4 g/day. The primary endpoint was statistically significant between treatment groups with respect to rectal bleeding and at least one other symptom or sign. While a statistical difference was seen between the two balsalazide administration groups with respect to primary and secondary outcomes, there was no statistical difference when compared with mesalazine.[71] This study confirmed the dose response effect previously noted in prior 5-ASA studies and demonstrated equivalence of balsalazide to mesalazine.[71] Pruitt et al.[73] also failed to show a difference between balsalazide (6.75 g/day) and mesalazine (2.4 g/day). Balsalazide therapy achieved improvement sooner than mesalazine therapy, with a median time to remission of 25 days compared with 37 days.[73] The authors speculated that perhaps 5-ASA delayed-release formulations may be released prematurely in the small intestine. In support of this notion, the authors cited data that at the 2-week mark, the concentrations of 5-ASA and N-acetyl-5-ASA were higher in the mesalazine-treated group than in the balsalazide-treated group. Arguing against this is an ileostomy study that shows the majority of intact 5-ASA is present in the small bowel effluent ileostomy patients.[65] Furthermore, in healthy patients, 5-ASA and N-acetyl-5-ASA from balsalazide and mesalazine were found to be comparable.[12] Although the studies do show quicker response in left-sided disease, sometimes, depending on the severity of disease, doses as high as 4.8 g/day of Eudragit®-coated mesalazine were required to induce remission. A noted difference between the studies was that the Eudragit®-coated mesalazine used was produced by two different companies. It has been sug-

gested that differences in formulation may influence efficacy and safety.[74]

2.2.2 Olsalazine

In 1985, Selby et al.[75] compared olsalazine as enema and oral formulations with placebo for 2 weeks. Sixty patients with mild left-sided colitis were randomized to receive an enema nightly for 2 weeks, containing olsalazine 2 g or placebo. Clinical and sigmoidoscopic status was monitored. A total of 19 of 29 patients (66%) improved clinically, while 17 of 19 (89%) improved sigmoidoscopically. These findings were not significantly different from those in the placebo group. With respect to the oral trial, the authors randomized 40 patients with mild, distal ulcerative colitis with olsalazine 0.5 g or placebo four times daily. Again, response was measured by clinical improvement and histology. In contrast to results with the enema, the patients treated with oral olsalazine fared better than the placebo arm. A total of 13 of 20 patients improved compared with 8 of 20 receiving placebo ($p < 0.02$).[75] Nine patients worsened while receiving placebo, compared with only one who was being treated with olsalazine. The adverse effects associated with oral olsalazine in this study were headache, light headedness and diarrhoea.[75]

Feurle et al.[49] compared olsalazine 2 g/day with placebo in a study group that consisted of their first attack of ulcerative colitis or patients who had discontinued treatment and had relapsed. In a total of 105 patients, 52 received olsalazine, while 53 received placebo. There was only modest advantage to olsalazine in induction of remission and improvement. The following parameters were significantly better after treatment with olsalazine: (i) general well-being; (ii) abdominal pain; (iii) blood and mucus in stool; and (iv) endoscopic improvement.[49] In the placebo arm, the only parameter that improved was rectal bleeding.[49] Unfortunately, five patients in the olsalazine group experienced severe diarrhoea, two patients withdrew from the study because of this problem. By detecting metabolites in the plasma and urine, a compliance level of 82.6% was estimated.[49]

In a third study, the effect of olsalazine was modest compared with placebo and diarrhoea was noted to be a problem.[76]

In subsequent studies comparing mesalazine and olsalazine, the available data suggests similar efficacies. Kruis et al.[51] compared olsalazine and Eudragit®-coated mesalazine in a randomized, multicentre, double-blind trial in patients with mild to moderate active ulcerative colitis. A total of 88 patients were treated with olsalazine 3 g/day, while 80 patients were treated with Eudragit®-coated mesalazine 3 g/day. The endpoints were endoscopic remission, clinical improvement as measured by a clinical activity index. At the end of 12 weeks, the authors found that both drugs were equally efficacious with respect to endoscopic and clinical remission. Diarrhoea was an undesirable effect in 12% of patients treated with olsalazine and 7% of those treated with Eudragit-L®-coated mesalazine.[51] The diarrhoea adverse effect appeared in numerous studies, which has limited its use in active ulcerative colitis.[33,49-52]

The olsalazine data is perplexing; while some studies found it to be no better or modestly better than placebo, other studies report similar efficacy to other forms of 5-ASA. Olsalazine was noted to be the only 5-ASA drug that was not better than placebo and sulfasalazine in a meta-analysis that pooled data from four placebo controlled trials.[77,78]

While olsalazine was inconsistent in treating active ulcerative colitis, the data supports its use for maintenance purposes.[52,79] Travis et al.[52] randomly assigned 198 patients to olsalazine 0.5, 1 or 2 g/day of for 12 weeks. These patients had a history of ulcerative colitis, diagnosed by standard criteria and were in remission for 3 months prior to the study. The higher dose was the best for maintaining remission patients with proctitis but there was no advantage of the higher dose for maintenance in patients with pancolitis. In a different study, olsalazine was found to be superior to mesalazine in prevention of relapses.[79] 100 patients with ulcerative colitis, who were currently in remission, were randomized to treatment with olsalazine 1 g/day or mesalazine 1.2 g/day. They were followed-up for 12 months.

Overall, the rate of treatment failure was lower in the olsalazine group (24%) than in the mesalazine group (46%). This difference was significant with a p-value of 0.025. The rate of disease relapse was reduced for the olsalazine group, where only 12% relapsed compared with 33% in the mesalazine group ($p = 0.024$).[79] Patients with pancolitis were more likely to relapse than those with left-sided disease. It is possible that the superiority of olsalazine in maintenance of remission in left-sided disease is because more drug is delivered to the left colon than the pH-dependent delivery with Eudragit®-coated mesalazine, although this has not been confirmed.[79]

2.3 Rectal Therapy

Rectal 5-ASA therapy is effective in treating distal ulcerative colitis. Placebo-controlled trials have determined that 5-ASA enemas are effective in inducing remission in patients with mild to moderately active left-sided colitis.[80-84] The doses used in these studies were 1–4 g/day. There does not appear to be a dose response and Campieri et al.[81] concluded that 1 g/day was sufficient for the treatment of mild to moderate distal disease. In a 30-day study comparing 5-ASA enemas 2 g/100 mL/day and 1 g/day suppositories, no difference was found in terms of efficacy, although patients reported a preference for suppositories.[80] When mesalazine gelatin suppositories were compared with mesalazine microgranule suppositories, they had comparable efficacies in induction of remission in patients with active ulcerative proctitis.[85]

Similarly, there does not appear to be a difference in efficacy between 5-ASA foams and enemas, but patients do report better quality of life with the foam.[86] Rectal forms of 5-ASA are often used in conjunction with oral formulations. This combination has been shown to be superior to rectal therapy or oral therapy alone. Safdi et al.[87] studied the effect of oral therapy (mesalazine 2.4 g/day), rectal therapy (mesalazine 4 g/day suspension enema) and combination therapy (oral and rectal therapy) on distal colitis with a disease activity index between 4 and 10. The patients had confirmed ulcerative colitis, with the most proximal limit at 50 cm.[87] At 6 weeks, the patients treated with combination therapy reported greater improvement than the groups treated with oral or rectal therapy alone, but the difference was not significant.[87] Combination therapy was superior to either oral or rectal therapy alone with respect to rectal bleeding cessation. A total of 88.9% of patients achieved cessation of rectal bleeding compared with 45% treated with oral mesalazine and 11% treated with rectal mesalazine ($p = 0.013$).[87] The days to cessation of rectal bleeding were significantly less in the combination therapy group (11.89%) versus 25.50% in the oral mesalazine group and 24.9% in the rectal mesalazine group.[87] It is not clear whether the superiority of combined therapy is due to the effectively higher dose of 5-ASA used.

In addition to inducing remission, rectal therapy has been shown to maintain remission in patients with left-sided distal colitis and proctitis with doses of 1–4 g/day enemas or 0.5–1 g/day suppositories.[88-91] There is no consensus as to the optimum dose, and a dose response has not been confirmed. Recent data reported that adding weekend 5-ASA enema to oral 5-ASA therapy produced a significant reduction in relapse rates (18% vs 76%).[92]

2.4 Optimal Dose of 5-Aminosalicylic Acid for Induction and Maintenance of Remission

The studies that have established the role of 5-ASA in the treatment of ulcerative colitis were conducted using an array of different doses and agents. The optimal dose for remission induction remains somewhat of a contentious issue. Most will agree that there is a dose response, favouring higher doses of 5-ASA. Theoretically, increasing the dose of 5-ASA may increase efficacy by saturating the enzymatic acetylating capacity of the epithelium.[93] Free 5-ASA can then exert its anti-inflammatory effects on the affected epithelium.

Schroeder et al.,[57] in their placebo-controlled study on mesalazine, did note a dose response. In a meta-analysis, Sutherland and Macdonald[94] found that, for active disease, 5-ASA 1.6 g/day was not sufficient, even though it was the equivalent dose of

sulfasalazine 2.5 g/day. The pooled data suggested that at least 2 g/day of 5-ASA was necessary for treatment of active colitis. There was a trend towards better efficacy with higher doses, but none of the new formulations of 5-ASA were found to be superior to sulfasalazine.[94] Their meta-analysis showed a superiority trend for 5-ASA; however, this advantage was not statistically significant. This dose response was corroborated by the ASCEND (Assessing the Safety and Clinical Efficacy of a New Dose of 5-ASA) I and ASCEND II trials, which suggest that 5-ASA 4.8 g/day is superior to a 2.4 g daily dose for patients with moderately active colitis.[95]

Placebo-controlled studies demonstrated the superiority of ethylcellulose-coated mesalazine 4 g/day to placebo for maintenance of remission.[68-70] Studies with mesalazine suggest that doses ranging from 800 mg to 1.6 g/day are effective as are equimolar doses of olsalazine and balsalazide.[50,60,61,66,68,69,96] In a meta-analysis, Sutherland and Macdonald[94] reported that the pooled data showed that there was no dose response when it came to maintenance therapy as there was in active disease.

2.5 Adverse Reactions

5-ASA formulations were initially marketed as a safer alternative to sulfasalazine. It is still not completely clear whether these drugs are indeed safer than sulfasalazine. These drugs are generally very well tolerated, but they are not devoid of adverse effects and these have been extensively reviewed elsewhere.[97] The most common adverse effects in clinical trials were headache, nausea and vomiting, which appear to be equally related to all the 5-ASA drugs. Less common but more serious reactions include interstitial nephritis, pancreatitis and exacerbation of colitis.[97] The utility of olsalazine was hampered by problems with secretory type diarrhoea that have not been common with mesalazine compounds. This has been attributed, at least in part, to the presence of the azo bond, which has prosecretory effects on rabbit mucosa *in vitro*.[98] It is not clear why this is manifested clinically only with olsalazine. The pancreatitis and interstitial nephritis appear to be idiosyncratic reactions.[99] In summary, these drugs are a good alternative in patients who are intolerant to sulfasalazine therapy, but practitioners should be aware of the potential adverse effects and inform their patients well.

3. Compliance

In many of the studies discussed in this review, compliance with the prescribed medication was monitored by pill count and patient enquiry to assess adherence. Compliance in these studies was thought to be in the range of 70% and >95%.[100] Studies on medication adherence in many chronic diseases is reported to be as low as 40–50%.[100] Non-adherence rates in patients with inflammatory bowel disease can be as high as 60% and mesalazine is the medication with the lowest adherence rates in these patients.[100] Kane et al.[100] found that non-adherence to maintenance therapy is highest in individuals taking multiple medications, of male sex and unmarried status.

In addition, non-adherence increases the risk of disease relapses significantly. Kane et al.[101] showed that patients who were non-adherent were less likely to maintain a remission (39%) than those that adhered to treatment (89%) [p = 0.001]. The main reason for non-adherence was forgetfulness; however, patients also reported too many pills as a reason.[101] Another study found that disease activity is also a factor and that patients with inactive disease tended to not take their medications regularly.[102] On the other hand, patients with active colitis were more compliant. In addition, number of pills and three times daily administration also contributed to 5-ASA non-adherence.[102] It will be interesting to see whether the once-daily formulation of MMX 5-ASA improves adherence. Clearly, more research in this area is necessary to shed some light on why patients are non-adherent and if any interventions can improve compliance rates.

4. Future Directions and Conclusion

The data described here from both clinical trials and meta-analyses provides evidence of similar effi-

cacies between most 5-ASA delivery methods in the induction and maintenance of clinical response in ulcerative colitis. Minor variations in clinical outcomes between delivery methods, for example depending on location of disease or time to response, have been identified in some trials based on *post hoc* analyses or secondary endpoints. The fact that switching between 5-ASAs can produce improved response rates in individual patients should be an important consideration in practice. The cumulative clinical experience is of 5-ASA agents being predictable and effective in their anti-inflammatory properties, regardless of which delivery method is chosen. There appears to be some evidence that the risk of adverse effects is higher with sulfasalazine than other 5-ASAs and that diarrhoea can be an issue with olsalazine.

For topical agents, the development of well tolerated agents and patient adherence remain priorities. Despite evidence for the beneficial effects of topical 5-ASAs, discomfort and difficulty with administration can lead to medication non-adherence in some patients.[56] Availability of well tolerated and effective topical agents for left-sided disease is important. There are ongoing studies of new ways to deliver rectal 5-ASA. For example, a rectal gel version of MMX-mesalazine is currently in development. Such a product may prove to be very useful in proctitis and proctosigmoiditis. It is proposed that the product will have a sustained release of medication that may require less frequent application. In the UK, 5-ASA foams have been shown to adequately distribute 5-ASA to the level of the sigmoid colon, and are thought to improve tolerance and compliance with medication.[55,56] Preliminary experiments with a gel formulation of 5-ASA demonstrated good retrograde spread in the colon to the level of the splenic flexure.[56] The study compared the gel with 5-ASA foam and found that it was easier to retain and less uncomfortable. In addition, the 5-ASA gel was as efficacious as the foam formulation.[56]

With so many choices amongst oral 5-ASAs, the natural dilemma becomes which drug to use for treatment of patients with active mild to moderate colitis. The clinical trials have established the efficacy of 5-ASAs; a meta-analysis of 19 trials involving 2032 patients has confirmed that 5-ASA therapy is superior to placebo at all dosage groups in active colitis.[78] Only one 5-ASA, olsalazine, failed to induce improvement or endoscopic remission in four clinical trials.[76,103-105] It is not clear whether olsalazine efficacy was reduced secondary to patient withdrawal due to adverse effects.[78] Compared with sulfasalazine, the pooled data suggested a slight, non-significant advantage of 5-ASA.[78] With regards to maintenance of remission, the role of these drugs is clearly established with a statistically significant advantage for sulfasalazine over newer 5-ASA for this indication.[77]

If one accepts that the 5-ASA formulations have similar efficacies, then the choice of medication should be tailored to the patient's needs, taking into consideration factors such as cost, administration regimens and disease geography. For example, in a patient with colitis that is most active in the cecum, oral pH-dependent formulations or delayed-release formulations are a better choice than rectal therapy and possibly pro-drug formulations. Patients with mostly distal colitis may benefit more from the azo-bonded formulations, such as balsalazide, and/or rectal therapy. Some patients may respond to and tolerate certain formulations of 5-ASA better than others. Yang[106] prospectively followed-up 17 patients with mild to moderately active ulcerative colitis who had not responded to or were intolerant to other forms of mesalazine to determine if they would respond to balsalazide. A total of 24% of the patients achieved complete remission with balsalazide therapy, while 6% of patients reported more than 50% improvement of symptoms. Interestingly, two patients who had developed alopecia on mesalazine had an improvement in symptoms after institution of balsalazide therapy.[106]

As discussed, some factors predict the likelihood of patients showing poor compliance rates with oral 5-ASAs; male sex, multiple pills, non-marital status.[100] These patients may do better with once-daily administration, although this has not been formally confirmed. Whether interventions, such as patient

education or support, would improve compliance is unclear. Compliance is important not only for induction and remission, but also for long-term colorectal cancer prophylaxis in patients with ulcerative colitis.[107,108]

In conclusion, 5-ASA agents remain the first agents of choice for patients to induce and maintain remission in active ulcerative colitis. The drug delivery system used does not seem to be important for clinical response, but therapy should be tailored primarily based on disease geography, patient tolerance and medication adherence. Secondary considerations, such as compliance, may be influenced by dose administration schedules, but this remains to be confirmed in clinical trials.

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Correspondence: Dr *Alan C. Moss*, Center for Inflammatory Bowel Disease, Division of Gastroenterology, Rabb/Rose 1, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, MA 02215, USA.
E-mail: amoss@bidmc.harvard.edu