

Faculty

Russell D. Cohen, MD, FACP, AGAF

Associate Professor of Medicine
Department of Medicine/Section
of Gastroenterology
University of Chicago
Chicago, Illinois

Gary R. Lichtenstein, MD

Director, Inflammatory Bowel
Disease Center
Hospital of the University of
Pennsylvania
Professor of Medicine,
Gastrointestinal Division
Department of Medicine
University of Pennsylvania
School of Medicine
Philadelphia, Pennsylvania

Alan V. Safdi, MD

Chairman, Section of Gastroenterology
Deaconess Hospital System
President, Ohio Gastroenterology
and Liver Institute
President, Consultants for
Clinical Research
Cincinnati, Ohio

Contributing Editor

William J. Sandborn, MD

Professor of Medicine
Division of Gastroenterology
and Hepatology
Mayo Clinic
Rochester, Minnesota

5-ASA Treatment for Ulcerative Colitis: What's on the Horizon?

Proceedings From an Expert Panel Discussion
Convened May 18, 2008
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Target Audience

This publication is specifically designed for practicing gastroenterologists and other medical professionals involved in the diagnosis and treatment of gastrointestinal (GI) disorders who wish to update their knowledge of newly released safety and efficacy data of various treatment options shown to be effective in the management of patients with mild to moderate ulcerative colitis (UC).

Statement of Need/Program Overview

The clinical monograph *5-ASA Treatment for Ulcerative Colitis: What's on the Horizon?* will highlight clinically relevant issues regarding the use of 5-aminosalicylate (5-ASA) therapies in the treatment of UC and Crohn's disease. With ongoing exploration and advancements in 5-ASA formulations, there is a distinct educational need to educate gastroenterologists on newly released safety and efficacy data. A thorough understanding of treatment option differences will help facilitate incremental improvements in patient care.

Educational Objectives

Upon completion of the CME activity, participants should be able to:

- Discuss the most recent data regarding existing and newer oral 5-ASA therapies for treatment of mild to moderate UC.
- Evaluate the potential role of newer oral 5-ASA agents relative to existing therapies in the management of UC.
- Describe optimal induction dosing of newer and existing oral 5-ASA therapies for mild to moderate UC.
- Describe optimal oral 5-ASA maintenance dosing strategies for patients with quiescent UC.
- Evaluate the factors involved in determining adherence in patients with quiescent disease.

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5-ASA Treatment for Ulcerative Colitis: What's on the Horizon?

Proceedings From an Expert Panel Discussion
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Introduction

This supplement summarizes an expert panel discussion held on May 18, 2008 during Digestive Disease Week in San Diego, California, which was convened to review clinically relevant issues regarding the oral 5-aminosalicylates (5-ASA) agents in ulcerative colitis (UC) and to share the latest opinions and data regarding new 5-ASA agents in development.

Oral 5-Aminosalicylates: The Current Landscape

The 5-ASA agents have been, and continue to be, the mainstay of therapy for induction and maintenance of remission of mild to moderate UC.^{1,2} All of the oral

5-ASA agents available in the United States, except olsalazine, are approved for use in active UC, while sulfasalazine, olsalazine, and delayed-release mesalamine are approved for maintenance of remission of UC. The major differences of the currently available agents are summarized in Table 1.

Because these agents act topically, an important clinical goal is to maximize delivery of the active drug (5-ASA, or mesalamine) to the site of inflammation in the colonic mucosa while minimizing systemic absorption from the small intestine.^{1,4} Although rectal 5-ASA formulations (ie, gels, liquids, and foam enemas) fulfill these criteria, patients often find these therapies impractical and associated with undesirable side effects such as leakage and abdominal bloating, leading to poor adherence.^{4,5} The oral 5-ASA formulations target 5-ASA

Table 1. Oral 5-ASA Formulations*

Agent	Formulation	Availability	FDA-approved Indication	
			Acute UC	Maintenance of Remission of UC
Azo-bonded Formulations				
Sulfasalazine (Azulfidine®)	5-ASA linked to sulfapyridine by azo-bond	Tablet: 500 mg (200 mg 5-ASA)	✓	✓
Olsalazine (Dipentum®)	5-ASA dimer linked by azo-bond	Capsule: 250 mg (225 mg 5-ASA)		✓
Balsalazide (Colazal®)	5-ASA linked to inert carrier by azo-bond	Capsule: 750 mg (262 mg 5-ASA)	✓	
Mesalamine Formulations				
Mesalamine (Asacol®)	Eudragit® S-coated tablets (delayed-release)	Tablet: 400 mg	✓	✓
Mesalamine (Lialda™)	Advanced, multimatrix system (delayed-release)	Tablet: 1200 mg	✓	
Mesalamine (Pentasa®)	Ethylcellulose-coated microgranules (controlled-release)	Capsules: 250, 500 mg	✓	

*Only agents currently available in the United States are listed.

Adapted from Baumgart et al.³

delivery to the colon by various delivery systems and are generally considered to be more practical and patient-friendly than rectal preparations.

The oral 5-ASA preparations can be broadly viewed in two categories: (1) azo-bonded prodrugs (sulfasalazine, olsalazine, balsalazide); and (2) mesalamine formulations using delayed- or controlled-release mechanisms to deliver 5-ASA to the colon.⁶ Sulfasalazine, the original azo-bonded 5-ASA prodrug, undergoes metabolism by bacterial azoreductase enzymes in the colonic lumen to release the active 5-ASA moiety and the therapeutically inactive sulfapyridine.⁷ Absorbed systemically from the colon, sulfapyridine is believed to be responsible for the hypersensitivity and many of the dose-related adverse effects associated with sulfasalazine (eg, headache, nausea, dyspepsia).^{1,7} In contrast, olsalazine and balsalazide are prodrugs that deliver 5-ASA to the colon without using a sulfapyridine carrier. Olsalazine is a 5-ASA dimer linked by a diazo bond, whereas balsalazide links 5-ASA via a diazo bond to an inactive carrier molecule, 4-aminobenzoic acid.⁸

In contrast to the azo-bonded drugs, several mesalamine formulations deliver 5-ASA to the colonic mucosa through various pH-dependent or sustained-release mechanisms. Asacol[®] is a delayed-release formulation that delivers 5-ASA coated with an acrylic-based resin (Eudragit[®] S) that dissolves at pH of 7 or greater.^{7,9} Approved in January 2007, Lialda[™] is a newer formulation that consists of a core of lipophilic and hydrophilic matrices (ie, multimatrix core, MMX[®]) enclosed within a pH-dependent coating. Like Asacol[®], the pH-dependent coating delays release of mesalamine until the tablet is exposed to a pH of 7 or greater.¹⁰⁻¹² Pentasa[®] is a controlled-release, pH-independent formulation containing microspheres of 5-ASA enclosed within a moisture-sensitive, methylcellulose, semipermeable membrane.^{4,9}

Clinical Differences Among 5-ASA Formulations

Site of Delivery/Pharmacokinetics. Differences in delivery mechanisms of the 5-ASA formulations impact the site of delivery of active drug as well as the pharmacokinetics of the preparations. Whereas the azo-bonded drugs release 5-ASA only in the colon, the pH-dependent mesalamine formulations release active drug in the terminal ileum and colon.^{6,7} Unlike the other formulations, controlled-release mesalamine begins releasing 5-ASA in the duodenum and continues throughout the jejunum, ileum, and colon (ie, entire gastrointestinal tract).^{4,7}

Although disease activity may affect colonic pH in patients with UC, the clinical impact on the pharmacokinetics of 5-ASA formulations remains unclear. In a small

study examining colonic pH, 3 of 6 (50%) patients with active UC had very low pH, ranging from 2.3 to 3.4, in the proximal parts of the colon.¹³ Such observations have prompted speculation that reduced colonic pH in active disease could reduce the bioavailability of pH-dependent mesalamine formulations.¹⁴ Indeed, a scintigraphic study documented extremely variable GI transit times and disintegration sites of a pH-dependent, Eudragit[®] S coated mesalamine preparation available in Europe (Pentacol[®]) among 12 patients with inflammatory bowel disease (IBD) or irritable bowel syndrome.¹⁵ Although these findings were attributed to variations in intraluminal pH, the clinical relevance of these data has not been confirmed in controlled trials.

It is postulated that an "ideal" 5-ASA preparation would yield low plasma concentrations and urinary recovery but high fecal concentrations. However, fecal concentrations provide only an indirect measure of the drug available to local colonic tissue.¹⁶ Studies have demonstrated that different 5-ASA delivery systems result in variable serum, mucosal, and fecal 5-ASA levels. A meta-analysis of 40 studies, however, concluded that the systemic exposure to 5-ASA, as measured by urinary and fecal excretion of total 5-ASA (5-ASA plus N-acetyl-5-ASA), was comparable for all oral mesalamine formulations and prodrugs.⁷

A number of clinical trials have demonstrated significant differences in mucosal 5-ASA concentrations achieved with various 5-ASA formulations. De Vos et al reported significant differences in mucosal 5-ASA concentrations as determined from ileocolonic biopsy specimens from 61 patients treated with near-equimolar concentrations of various 5-ASA formulations for one week.¹⁶ The highest mucosal 5-ASA levels were associated with delayed-release mesalamine (Asacol[®]) therapy (298.5 ± 37.3 ng/mg), with much lower 5-ASA concentrations noted after treatment with controlled-release mesalamine (25.7 ± 2.2 ng/mg) and olsalazine (11.0 ± 3.2 ng/mg). Similarly, Naganuma et al documented significantly higher mucosal concentrations of 5-ASA from biopsies of the rectum and sigmoid colon of 13 patients with distal UC taking sulfasalazine compared with 11 patients taking oral controlled-release mesalamine (Pentasa[®]) ($P < .01$ for rectal concentrations, $P < .05$ for colonic concentrations).¹⁷ Moreover, total mucosal 5-ASA concentrations were much higher among 5 patients treated with both oral and rectal mesalamine compared with those receiving oral mesalamine alone (110.4 ± 77.0 $\mu\text{g/g}$ vs 6.6 ± 3.6 $\mu\text{g/g}$ in the rectum, $P < .05$; 73 ± 26.7 $\mu\text{g/g}$ vs 22.2 ± 10.3 $\mu\text{g/g}$ in the sigmoid colon, $P < .05$).

The clinical relevance of these findings is supported by observations that mucosal 5-ASA concentrations may correlate inversely with endoscopic and histologic

improvements as well as with clinical improvement as demonstrated by the Disease Activity Index (DAI) ($r=0.712$, $P<.001$).^{17,18} Additionally, Naganuma et al demonstrated significantly higher rectal 5-ASA concentrations in patients without blood in stool compared to those with blood in stool ($P<.01$). These observations are underscored by the results of several randomized controlled trials demonstrating superior clinical efficacy of combination therapy with oral and rectal mesalamine agents compared with oral mesalamine alone.^{19,20} However, it is not clear from these studies if the superior efficacy is due to larger doses of mesalamine or to the combination of oral and rectal routes of administration.

Clinical Efficacy. Comparing the relative efficacy of the 5-ASAs across clinical trials has been difficult, largely owing to differences in study design. Unlike Crohn's disease trials, where the Crohn's Disease Activity Index (CDAI) is considered the gold standard for measuring disease activity, there are no standardized indices of disease activity in UC.^{4,9,21,22} Additionally, the US Food and Drug Administration (FDA) has not defined standard endpoints or outcomes for assessing the efficacy of therapies in UC clinical trials. Although clinical remission rates or symptomatic improvement have traditionally been used as primary endpoints, endoscopic remission has recently been recognized as a prognostic factor and treatment goal in UC.²³⁻²⁵ Lastly, conclusions from UC studies may be influenced by reliance on secondary endpoints or post-hoc analyses rather than clearly defined primary trial endpoints.⁹ Thus, comparing results across UC studies is considered to be extremely complex, if not inappropriate.⁴

Bearing in mind these limitations, clinical trials conducted with the 5-ASA formulations suggest that the clinical efficacy of these agents is broadly similar in UC patients with mild to moderate disease.^{9,26,27} A possible exception may be olsalazine, whose efficacy in acute disease has not been confirmed because of high drop-out rates due to dose-related diarrhea.^{2,28} The 5-ASA agents usually act within 2 to 4 weeks, and placebo-controlled trials in active UC generally demonstrate clinical response rates ranging from 40% and approaching 80%.^{2,24-26,29,30} These agents have also demonstrated efficacy in maintenance of remission of mild to moderate UC.^{2,31,32}

Relatively few clinical trials have directly compared the oral 5-ASA agents in UC patients. A number of trials have found sulfasalazine to be at least as effective as newer 5-ASA agents in treating both active and quiescent disease.^{26,31} Indeed, 2 meta-analyses failed to demonstrate that any of the newer agents have superior efficacy to sulfasalazine, either for induction or maintenance of remission.^{26,31} However, the ability to reach effective doses

of sulfasalazine (2-6 g/day) is often precluded by the development of intolerable adverse effects.^{2,33,34}

Three randomized, controlled trials have compared balsalazide 6.75 g/day to delayed-release mesalamine 2.4 g/day in patients with active mild to moderate UC.^{6,8,24} The overall efficacy (primary endpoint) was similar in the balsalazide and delayed-release mesalamine groups in 2 of these trials, although balsalazide was superior to mesalamine at achieving symptomatic and complete remission in the other study.^{6,8,24} Subgroup analyses suggested that balsalazide provided relief significantly faster than mesalamine in all 3 studies.^{6,8,24}

Despite a number of trials examining various dosages of the 5-ASAs, a dose-response relationship for these agents has not been consistently demonstrated. Over 20 years ago, Sutherland et al observed a slight trend for a dose-response effect for the 5-ASA agents in a meta-analysis of 16 trials in active UC.²⁶ Other evidence in favor of a dose-response included early studies with delayed-release mesalamine (Asacol®) indicating superior efficacy of 4.8 g/day or 2.4 g/day to 1.6 g/day, data demonstrating significant efficacy of 4 g/day controlled-release mesalamine compared with 2 g/day, and a randomized, controlled trial indicating that balsalazide 6.75 g/day is significantly more effective than 2.25 g/day.^{6,25,30,35}

These findings have not been consistent in subsequent studies, particularly with the various mesalamine formulations. A higher dose of controlled-release mesalamine (4 g/day) has not been consistently superior to a lower dose (2 g/day), and large, randomized, controlled trials of delayed-release mesalamine (Lialda™) did not suggest a greater clinical benefit for patients receiving 4.8 g/day compared with 2.4 g/day.^{11,29,35,36} Similarly, 3 randomized, controlled trials (ASCEND I, II, and III) failed to find a significant difference in efficacy between delayed-release mesalamine (Asacol®) 4.8 g/day and 2.4 g/day in patients with mild to moderate active disease or in a subset of patients with mild disease.³⁷⁻³⁹ However, subanalyses conducted in the ASCEND I and II trials indicated a treatment benefit of the higher dose among patients with moderate disease, and subanalyses in the ASCEND I, II, and III trials indicated a treatment benefit for the higher dose among patients who had previously received oral or rectal mesalamine, steroids, and/or multiple medications.

Tolerability. Intolerance to the sulfapyridine component of sulfasalazine is common, accounting for the nausea, vomiting, dyspepsia, anorexia, and headache frequently encountered with the drug in up to one third of patients.^{2,40} Less commonly, severe adverse effects such as pancreatitis, hepatitis, drug-induced connective tissue disease, bone marrow suppression, nephrotoxicity

and interstitial nephritis, and abnormal sperm counts or morphology have been observed.² The other azo-bonded drugs and the mesalamine formulations are generally well tolerated, and approximately 80% of patients who are intolerant to sulfasalazine can tolerate these agents.² The most common adverse effects reported with the 5-ASA agents include headaches and GI symptoms such as diarrhea, gas, and nausea.⁴¹ Olsalazine is associated with dose-related diarrhea due to ileal secretion.^{2,4} Although well tolerated by most patients, serious adverse effects such as nephritis, interstitial pneumonitis, worsening of colitis, and pancreatitis have been reported with the 5-ASA formulations.⁴²

Adherence With 5-ASA Therapies

Although the 5-ASA agents have proven efficacy and are generally well tolerated, nonadherence with these therapies is a significant problem in UC patients. Many of the existing formulations are limited in the amount of 5-ASA delivered per tablet or capsule, resulting in the need for patients to take large numbers of tablets in multiple daily dosing regimens.⁴ Such complicated regimens can negatively impact medication adherence, which has been particularly noted with maintenance therapies in UC patients.^{5,43} Although adherence may be a problem in active disease as well, studies have documented nonadherence rates of up to 60% in patients with quiescent UC.⁵ Nonadherence can impair clinical outcomes in this population, with one study in 99 UC patients in remission demonstrating a 61% chance of maintaining remission among adherent patients compared with 39% in those who were nonadherent with their maintenance mesalamine regimens ($P=.001$; Figure 1).⁴³

Nonadherence with medication is complex, and many factors contributing to this behavior have been identified in the UC population. Complicated dosage regimens, large numbers of tablets, three-times-daily dosing, and impact of inconvenient dosing schedules on daily life have been associated with and/or cited by patients as reasons for nonadherence in UC.^{5,43,44} Other factors associated with poor adherence noted in the IBD population include medication cost, fear of side effects, age (<40 years), disease duration and extent (left-sided disease), disease remission, recent diagnosis, gender (male), single status, depression, and full-time employment.^{5,44-46} The patient's relationship with the physician and personal belief system are also important in determining adherence with UC regimens.^{5,47}

Given the many factors that may contribute to nonadherence in UC patients, a "one size fits all" intervention approach is unlikely to be effective for improving adherence. Effective physician-patient communication is

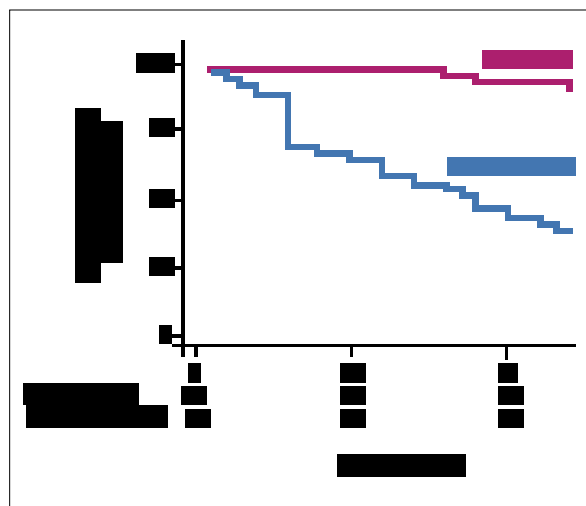


Figure 1. Nonadherence rates and clinical recurrence at 24 months.

Adapted from Kane et al.⁴³

essential in identifying reasons for poor adherence, understanding patients' lifestyles and treatment preference, and tailoring strategies for improvement in individual patients.⁴⁶ Simplifying dosing regimens may address barriers to adherence in some patients, particularly those in whom multiple daily dosing regimens are inconvenient and/or disruptive to their working lives.⁵ Because patients in remission may not perceive the value of maintenance medication, education regarding the potential benefits of adherence with 5-ASAs, such as reduced risk of clinical relapse and possible reduction in colorectal cancer incidence, may be helpful.^{5,43,48}

Newer 5-ASA Formulations

Given the problem of nonadherence and its potentially negative impact on clinical outcomes in UC patients, several new 5-ASA formulations are currently under development with the intent of effectively delivering 5-ASA to the colonic mucosa in more convenient dosing regimens than is possible with many of the existing formulations.⁴³ These formulations include new dosage strengths of existing products as well as a novel mesalamine micropellet formulation (Table 2).

Azo-Bonded Formulations

Balsalazide 1.1 g tablets are a new balsalazide formulation under investigation for use in active mild to moderate UC. In contrast to existing balsalazide 750 mg capsules, which deliver 262 mg 5-ASA per capsule, each

Table 2. New Oral 5-ASA Formulations Under Development for UC

Product	Dose of 5-ASA	Dosage Regimen*	Delivery System
Balsalazide (Colazal®) tablet	1.1 g/day	Active UC: 3.3 g BID ⁴⁹	5-ASA linked to inert carrier by azo-bond
Delayed-release mesalamine (Asacol®) tablets, 800 mg	800 mg/tablet	Active UC: 4.8 g/day divided TID ^{38,39}	pH dependent (pH of 7) Eudragit® S-coated tablets ^{37,38}
Mesalamine granules (currently marketed as Salofalk Granu-Stix®, Dr. Falk Pharma, Germany)†	375 mg/capsule	Active UC: 1.5–3.0 g/day once daily or divided TID ⁵⁰ Remission maintenance: 1.5 g (4 × 375 mg capsules) once daily ^{51,52,55}	pH dependent (pH of 6) Eudragit® L-coated pellets with a retarding polymer in the pellet core (delayed and sustained release)

*Dosage regimens currently under investigation.

†FDA approved for remission maintenance.

BID=twice daily; TID=three times daily.

Adapted from Sandborn et al.⁴

1.1 g tablet delivers 400 mg 5-ASA to the colon.⁵³ This higher-potency balsalazide allows for twice-daily dosing (3.3 g twice daily) as compared with the three-times-daily dosing regimen approved for balsalazide capsules. Further, this difference translates into a lower pill burden for patients, with the newer formulation requiring a total of 6 tablets per day compared with 9 capsules daily with currently available balsalazide capsules.

In a large, multicenter, double-blind, phase 3 trial, 249 patients with mildly to moderately active UC were randomized to balsalazide tablets 3.3 g/day (three 1.1 g tablets twice daily) (n=166) or placebo for 8 weeks (n=83).⁴⁹ At the end of the treatment period, 92/166 (55%) patients who received balsalazide achieved the primary endpoint—clinical improvement and improvement in rectal bleeding—compared with 33/83 (40%) of placebo-treated patients. Compared with placebo, balsalazide was also associated with significantly greater clinical remission ($P=.01$) and mucosal healing rates ($P=.004$), as well as improvements in bowel frequency, rectal bleeding ($P\leq.01$), and physician's global assessment ($P\leq.01$). In addition, significant improvements in patient-reported quality of life, as measured by the Inflammatory Bowel Disease Questionnaire (IBDQ), were noted as early as 2 weeks (IBDQ scores 27.9 for balsalazide vs 20.1 for placebo, $P=.01$) and were sustained through 8 weeks (32.7 vs 29.7, $P=.03$).⁵³ The vast majority (73%) of patients reported that they were satisfied or very satisfied with their study treatment compared with 56% of those receiving placebo ($P=.02$).

Balsalazide tablets were well tolerated, with fewer balsalazide-treated patients reporting adverse events than placebo-treated patients.⁵⁴

Mesalamine Formulations

Mesalamine Granules. Various micropellet formulations of 5-ASA have been studied for use in UC.⁴ Uncapsulated mesalamine pellets (Salofalk Granu-Stix®) are currently available in Europe where they are indicated for acute UC at a dosage of 1.5–3 g/day divided in 3 daily doses. They are also indicated for maintenance of remission at a dose of 3 g/day, divided in three daily doses. In the United States, FDA approval was recently granted for encapsulated mesalamine granules (APRISO™), which are mesalamine pellets with an enteric, pH-dependent coating (Eudragit® L) combined with an additional retarding polymer matrix core.^{4,55} Through the use of microsphere technology (Intellicor™), this mesalamine formulation provides delayed, yet extended and continuous, release of mesalamine for 6–7 hours. Unlike other pH-dependent mesalamine formulations, which release 5-ASA at pH of 7.0 or greater, mesalamine granules are designed to release 5-ASA at a pH of 6.0 or above, the approximate pH of the ileum and colon.^{31,55} Thus, this formulation is designed to begin releasing mesalamine in the ileum after the Eudragit® L coating dissolves, but because of the matrix polymer within the core, more mesalamine is released in the distal intestine and continued throughout the colon.⁵⁶

Scintigraphic and pharmacokinetic data have demonstrated that mesalamine granules provide prolonged release of 5-ASA relative to tablet formulations.^{57,58} Brunner et al used gamma-scintigraphy to follow the GI transit of 14 healthy male volunteers who received a single dose of ¹⁵³Sm-labeled mesalamine granules 500 mg or 500 mg tablets (Salofalk®).⁵⁷ Gastrointestinal transit was comparable for both formulations, with both releasing 5-ASA in the same target region (the ileocecal region) and at nearly the same time (3.3 ± 1 hours for mesalamine granules and 3.8 ± 1 hours for mesalamine tablets, *P* = .08). Comparison of the mean plasma concentration versus time profiles, however, revealed lower AUC_t values for mesalamine granules than tablets (968 ± 629 ng.h/mL vs 2206 ± 1767 ng.h/mL, *P* = .02), suggesting a more prolonged release of 5-ASA from mesalamine granules.⁵⁷

Subsequent pharmacokinetic studies in healthy volunteers have demonstrated that once-daily dosing of mesalamine granules is consistent with an extended release of mesalamine and unaltered by ingestion of a high-fat meal.⁵⁹ In addition, the systemic absorption of 5-ASA from mesalamine granules was found to be low and comparable whether administered in doses of 1.6 g once daily (5-ASA C_{max} 3.0 ± 1.7 µg/mL, N-Ac-5-ASA C_{max} 4.5 ± 1.8 µg/mL) or 0.8 g twice daily (5-ASA C_{max} 1.8 ± 0.7 µg/mL, N-Ac-5-ASA C_{max} 3.6 ± 1.2 µg/mL).⁵⁸

The efficacy of mesalamine granules in patients with active UC has been demonstrated in 3 randomized, controlled trials.^{50,56,60} As with other mesalamine formulations, however, a consistent dose-response relationship has not been demonstrated with mesalamine granules.

In a randomized, double-blind, multicenter, dose-finding trial, 321 patients with mildly to moderately active UC received mesalamine pellets in doses of 0.5 g 3 times daily (n=103), 1.0 g 3 times daily (n=107), or 1.5 g 3 times daily (n=106).⁵⁶ Clinical remission, defined as Clinical Activity Index (CAI) of 4 or less, was achieved by 66%, 50%, and 55% of patients receiving 1.0 g 3 times daily, 0.5 g 3 times daily, and 1.5 g 3 times daily, respectively. The majority (84%) of patients receiving 1.0 g 3 times daily had endoscopic improvement, compared with 53% of those receiving 0.5 g 3 times daily (*P* ≤ .0001 vs 1.0 g 3 times daily) and 70% receiving 1.5 g 3 times daily.⁵⁶ Patient quality of life, measured with the life quality index (LQI), improved to a similar degree across all 3 treatment groups. The formulation was well tolerated, with up to 82% of patients rating the global tolerability as very good or good. Although these results failed to reveal a dose response, they did suggest that mesalamine granules have promising efficacy, high patient acceptability, and a favorable safety profile in mild to moderate active UC.

In a subsequent double-blind, dose-escalating trial, 223 patients with mildly to moderately active UC were randomized to Eudragit® L coated mesalamine pellets (n=115) or tablets (n=118) (Röhm, Germany) in doses of 1.5 g 3 times daily for 8 weeks.⁶⁰ Dosage increase to 3 g/day was allowed in patients with inadequate response to the initial dose, starting from the first follow-up visit at 2 weeks. After nearly 3 weeks of treatment, clinical remission (defined as CAI ≤ 4) was comparable between treatment groups (47% for pellets, 42% for tablets). Escalating the dose to 3.0 g/day increased total remission rates to 67% for pellets and 68% for tablets after 8 weeks. The higher dose was significantly more effective than the initial dose (*P* < .0001), as determined by absolute and relative mean decreases in CAI compared with mean CAI values before dose escalation. Endoscopic (80% for pellets, 83% for tablets) and histologic (48% for pellets, 52% for tablets) improvement was also comparable between treatment groups. Thus, mesalamine pellets were as effective as tablets in this study, and contrary to the results reported by Kruis et al, dose escalation to 3.0 g/day was effective in those patients not responding to an initial dose of 1.5 g/day.⁵⁶

More recently, Kruis et al demonstrated efficacy of once-daily dosing of mesalamine granules in active UC. In this randomized, double-blind, multicenter, phase 3 study, 380 patients with active UC received mesalamine granules (Salofalk® granules) in doses of 3 g once daily (n=191) or 1 g three-times-daily (n=189) for 8 weeks.⁵⁰ The once-daily regimen was found to be at least as effective as three times daily dosing, with nearly 80% of patients in each group entering clinical remission (defined as CAI ≤ 4) at the final visit (Figure 2). Secondary efficacy endpoints (Figure 3) and safety were comparable between treatment groups as well.

As in active disease, several dosages of mesalamine granules have been found effective in maintaining remission of UC.^{51,52} Kruis et al examined the 1-year remission rates of patients with quiescent UC who were randomized to receive three different doses of mesalamine granules (Salofalk® granules).⁵¹ In this double-blind, double-dummy, multicenter trial, a total of 647 patients with mildly to moderately active disease, who had achieved clinical (CAI ≤ 4) or endoscopic (Endoscopic Index [EI] ≤ 3) remission within the previous 12 weeks, were randomized to mesalamine granules 3 g once daily (n=217), 1.5 g once daily (n=212), or 0.5 g 3 times daily (n=218). All three dosages were effective at maintaining remission, with 74.7%, 60.8%, and 68.8% of patients receiving 3 g once daily, 1.5 g once daily, and 0.5 g 3 times daily, respectively, in clinical remission at 1 year. The drug was well tolerated in all dosage groups, and there was no increased risk of adverse effects associated with once-daily

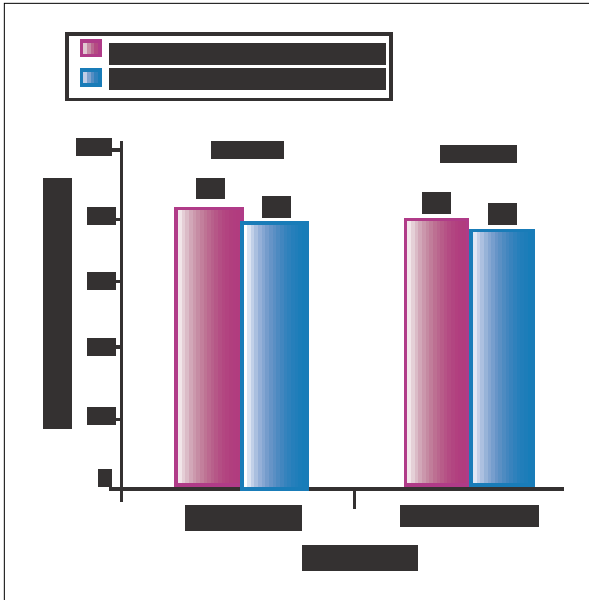


Figure 2. Granulated mesalamine 3 g daily vs 1 g three times daily: primary efficacy endpoint.

Adapted from Kruis et al.⁵⁰

treatment or with a higher dose compared to the 0.5 g three-times-daily regimen.

Once-daily dosing of mesalamine granules has been found effective in maintaining remission of UC in patients previously maintained on a wide range of 5-ASA formulations. Lichtenstein et al reported the results of a large clinical trial involving 487 patients with documented UC remission.⁵² Remission was defined as revised Sutherland Disease Activity Index subscores or rectal bleeding of 0 and mucosal appearance of less than 2. Patients received four 375-mg mesalamine granules capsules (1.5 g/day) (n=322) or placebo (n=165) once daily for 6 months. Before switching to mesalamine granules, over half (51%) of patients had received delayed-release mesalamine, followed by sulfasalazine (30%), balsalazide (11%), suppositories/enemas (7%), and olsalazine (1%) for a median duration of 3 months (range, 0 to 14 months). More patients who received mesalamine granules maintained remission after 6 months than those receiving placebo (78% vs 59%, $P<.001$). This translated into a 77% probability of remaining relapse-free at 6 months among patients who switched to mesalamine granules compared to 50% of those on placebo ($P<.001$).

Delayed-Release Mesalamine 800 mg. An 800-mg tablet of delayed-release mesalamine formulated with a pH-dependent Eudragit® S coating, which is approved for use in Canada and the United Kingdom, is currently under investigation in the United States for use

in patients with mildly to moderately active UC.³⁷⁻³⁹ At the approved dosage for active UC of 2.4 g/day, this formulation would reduce pill burden to 3 tablets per day compared to 6 tablets per day with the existing 400-mg tablets.⁶¹ Although therapy is usually initiated at a dose of 2.4 g/day, the dosage is often increased to 4.8 g/day in patients who do not respond to the lower dose.³⁹ In this setting, the new 800-mg formulation would reduce the number of tablets patients take daily from 12 to 6.

The efficacy of the delayed-release mesalamine 800-mg tablet has been studied in 3 large randomized, double-blind trials (ASCEND I, II, and III).³⁷⁻³⁹ All 3 trials included patients with mildly to moderately active UC (ASCEND I and II) or moderately active UC (ASCEND III) who were randomized to 6 weeks of treatment with either delayed-release mesalamine 2.4 g/day (2 × 3 400 mg Asacol® tablets 3 times daily) or 4.8 g/day (800 mg investigational tablet 3 times daily). A total of 301 patients were randomized in ASCEND I, 386 were randomized in ASCEND II, and 772 patients were randomized in ASCEND III.³⁷⁻³⁹ The primary endpoint was treatment success, defined as complete remission or response to therapy from baseline to week 6.

In the ASCEND I trial (n=301), both dosages of delayed-release mesalamine achieved similar rates of treatment success at week 6 (51% in the 2.4 g/day vs 56% in the 4.8 g/day). Both treatment groups experienced significant improvements in quality of life as measured by IBDQ scores ($P\leq.05$). As previously discussed, both ASCEND I and II demonstrated superiority of the 4.8 g/day dose among patients with moderate disease compared with the 2.4 g/day dose.^{38,39} Although not statistically significant, the median time for patients to achieve normal stool frequency and have resolution of rectal bleeding was shorter for patients who received the higher dose compared with 2.4 g/day dose in both studies (20 days for 4.8 g/day vs 28 days for 2.4 g/day in ASCEND I; 21 days for 4.8 g/day vs 32 days for 2.4 g/day in ASCEND II).³⁸ In the ASCEND III trial, the primary objective was to demonstrate that 4.8 g/day was non-inferior (equivalent) to 2.4 g/day. Non-inferiority for the 4.8 g/day dose was demonstrated, with treatment success achieved in 70% (273/389) and 66% (251/383) of patients receiving 4.8 g/day and 2.4 g/day, respectively (95% CI for 2.4–4.8 success rates, -11.2, 1.9).³⁷ The 4.8 g/day dose was not superior to 2.4 g/day. Evidence of a therapeutic advantage of 4.8 g/day was seen in patients with a clinical history of more difficult to treat disease (previous oral or rectal mesalamine, steroids, or multiple medications). Both dosages were well tolerated, with no significant differences in the rates of adverse events between treatment groups.³⁷⁻³⁹

Figure 3. Granulated mesalamine 3 g once daily vs 1 g 3 times daily: secondary efficacy endpoints.

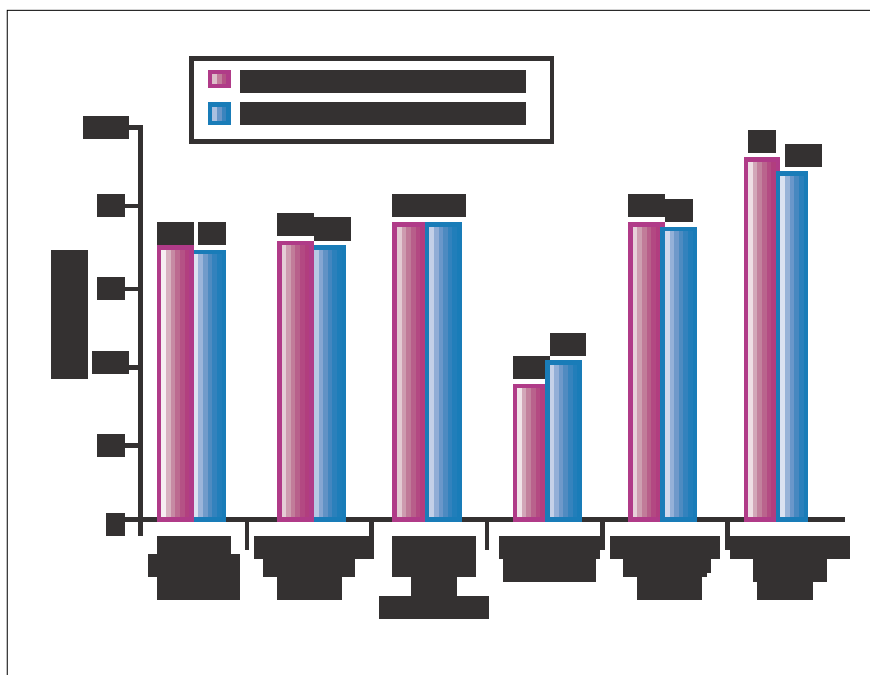
*Patients at baseline DAI ≥ 2 .

†At least marked improvement.

‡At least slight improvement.

DAI=Disease Activity Index; EI=Endoscopic Index; PGA=Physician's Global Assessment.

Adapted from Kruijs et al.⁵⁰



Clinical Advantages of New 5-ASA Formulations

The key clinical advantage of the new 5-ASA formulations is the ability to deliver therapeutic concentrations of 5-ASA to the colon with a smaller number of tablets than existing formulations. This translates into more convenient dosing regimens for patients, which in turn may enhance treatment adherence and clinical outcomes. If it receives approval, balsalazide 1.1 g tablets will become the only azo-bonded 5-ASA for active UC in a twice-daily regimen, while the delayed-release mesalamine 800-mg tablets cut the required pill burden in half compared to the existing formulation. Mesalamine granules appear to be effective for both induction and maintenance of remission of UC in a once-daily regimen. This represents a significant gain for this medication class as only 1 agent (delayed-release mesalamine [Lialda™]) is currently indicated for once-daily dosing.¹²

Mesalamine granules for maintenance of UC remission in a 1.5 g/day dose is among the lowest 5-ASA doses with proven efficacy in UC maintenance. Although relying on low-dose therapy for maintenance of remission may be a paradigm shift for some clinicians, this 1.5 g/day extended-delivery formulation is similar to the 1.6 g/day delayed-release mesalamine (Asacol®) with demonstrated efficacy in preventing relapse.³² Moreover, given data indicating 1.2 g/day 5-ASA may be the minimal effective dose for possibly reducing colorectal cancer risk in IBD

patients, 1.5 g/day mesalamine granules may be an effective dose for chemoprevention.⁶²

The clinical utility of the new 5-ASA formulations for use in Crohn's disease has not yet been explored. The efficacy of the 5-ASA agents in Crohn's disease remains controversial. Furthermore, there may be an emphasis on small bowel release, in addition to colonic release, in different Crohn's disease patients, depending on the disease location.⁶³ Controlled clinical trials may be helpful in determining whether these new mesalamine formulations are effective in Crohn's disease.

Conclusions

The oral 5-ASA agents are effective, well tolerated, and remain first-line therapy for mild to moderate UC. Because these agents act topically, an essential feature is to deliver 5-ASA effectively to the site of inflammation in the colon while minimizing systemic absorption from the small intestine. Although the currently available agents accomplish these goals, many formulations require large numbers of tablets taken in multiple daily doses, which can impair patient adherence and increase the risk of clinical recurrence. Along with the recently approved delayed-release mesalamine 1200-mg tablets, balsalazide 1.1 g tablets, delayed-release mesalamine 800-mg tablets, and mesalamine granules are new 5-ASA formulations in development that aim to deliver therapeutic concentrations

of 5-ASA to the colonic mucosa in a smaller number of tablets and more convenient dosing regimens than existing formulations. It is hoped that the convenience and efficacy offered by these new formulations will improve patients' abilities to comply with their regimens, ultimately improving overall treatment success.

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