Once-daily MMX mesalamine for the treatment of mild-to-moderate ulcerative colitis

Prashant Kedia[1]
Russell D Cohen[2]

[1]Pritzker Medical School, The University of Chicago, Chicago, IL, USA; [2]Clinical Inflammatory Bowel Disease, Department of Medicine, Section of Gastroenterology, The University of Chicago Medical Center, Chicago, IL, USA

Abstract: First-line therapies in the treatment of patients with mild-to-moderate ulcerative colitis are sulfasalazine or one of the mesalamine derivatives. Mesalamine is popular given its safety profile and reasonable efficacy in many patients. However, compliance is poor with regimens demanding large number of pills dosed multiple times a day and non-compliance has been correlated with disease relapse. Mesalamine requires direct contact with the inflamed colonic mucosa. To avoid proximal absorption, a variety of delivery systems has been utilized to time the release of active mesalamine to the areas affected by colitis. The most common mesalamine release mechanisms include azo-bond prodrug carriers, pH-dependent dissolution, and moisture-sensitive product dispersion. Novel technology has resulted in the development and FDA-approval of a multi-matrix release (MMX) mesalamine. Pharmacodynamic studies suggest a reliable drug delivery system with homogenous release throughout the entire colon. By incorporating the largest amount of mesalamine (1.2 g) per pill, this new product dramatically decreases the number of pills needed to attain a therapeutic daily dosage, and is the first agent approved at once-daily dosing. These factors are expected to increase patient compliance with prescribed mesalamine dosing, and in turn decrease relapse rates of active ulcerative colitis.

Keywords: mesalamine, sulfasalazine, balsalazide, olsalazine, ulcerative colitis, inflammatory bowel disease

Introduction

Ulcerative colitis (UC) is a chronic disease characterized by periods of active disease and remission that result in inflammation of the colonic mucosa. Patients often experience symptoms of abdominal pain, diarrhea, rectal bleeding, fatigue, weight loss, and loss of appetite. UC has various extraintestinal manifestations such as arthritis, inflammation of the eye, liver and biliary disease, rashes, anemia, and osteoporosis, which can all worsen patients' quality of life (QoL) during active episodes.

The pathologic mechanism of UC is unknown. However it is hypothesized that an overly active immune system may cause colonic inflammation in response to a variety of triggers including dietary substances, unknown infectious agents, and/or common colonic bacteria (Wen and Fiocchi 2004; Kovvali et al 2005). The genetic predisposition to developing ulcerative colitis is also a complex matter, with multiple genes likely responsible, varying in different populations (Yang et al 1993; Mansfield et al 1994).

Although UC can manifest symptoms at any age, patients are usually diagnosed between the ages of 15 to 30 years. In the Western world, the prevalence of UC has been shown to be over 200 cases per 100,000 people, with an incidence rate of 7 new cases in 100,000 per year (Ghosh et al 2000; Loftus et al 2000).

Ulcerative colitis (UC) almost always involves the rectum and a continuous portion of the colon. Inflammation is most often limited to the left side of the colon in the majority of UC patients. Approximately 33%–55% of patients fall into the category

Correspondence: Russell D Cohen
5841 S. Maryland Avenue, MC 4076, Chicago, IL 60637, USA
Tel +1 773 702 0719
Fax +1 773 702 2182
Email rcohen@medicine.bsd.uchicago.edu

of proctitis, which is disease limited to the rectum or the rectosigmoid, while about 30% exhibit colitis extending to the splenic flexure (~60 cm from the anal verge), and 15%–30% with extensive colitis, extending proximally beyond the splenic flexure. Approximately 15% of patients have extensive colitis, which is disease extending beyond the splenic flexure (Farmer et al 1993; Langholz et al 1996; Ghosh et al 2000).

Most patients will experience at least one relapse during the course of their disease. A population-based study showed that while 50% of UC patients are asymptomatic at any given time, about 97% experience at least one relapse of symptoms in a 10-year time-span (Hendriksen et al 1985). The progression and manifestation of UC varies greatly between patients on a yearly basis and symptomatic relapses can range from insignificant to incapacitating. Current disease trends show that patients are less likely to suffer relapses if they have less active disease and longer remission periods. Also patients who experience frequent relapses are more likely to have shorter remission periods (Riley et al 1988a). Therefore, the goals of current therapy for UC are to reduce symptoms during periods of active disease and prolong the duration of symptom-free remission periods.

Rationale for use of mesalamine in UC

Aminosalicylates are at present the treatment of choice for first line therapy of mild-to-moderate ulcerative colitis, with demonstrated efficacy and safety in patients with UC (Sutherland et al 2002). The exact mechanisms of aminosalicylates' actions are unknown. Studies suggest that there is a multifactorial basis for their anti-inflammatory and immunosuppressive efficacy. Due to its negative effect on the cyclooxygenase and lypoxygenase pathways, mesalamine (5-aminosalicylic acid) prevents the formation of inflammatory agents like prostaglandins and leukotrienes (Ligumsky et al 1981; Hawkey et al 1985). Studies have also shown that because of their negative effects on free-radical scavenging in the intestinal mucosa, mesalamine's anti-oxidant properties may help mitigate tissue injury (Ahnfelt-Ronne et al 1990). Mesalamine is also suspected to have immunosuppressive activity via inhibiting T-cell activation and proliferation in addition to down-regulating cytokine activity (Burress et al 1997; Santucci et al 2005).

Although the exact mechanism is uncertain, mesalamine is thought to have topical anti-inflammatory activity in the colon. Therefore, the clinical goal is to deliver as much active drug to the affected portions of the colonic mucosa while minimizing systemic absorption in efforts to reduce adverse effects. The efficacy of mesalamine-based compounds is associated with the local concentration of the drug and by the amount of active substance that reaches the diseased site (Ardizzone et al 1999; Pokrotnieks et al 2000).

The usefulness of sulfasalazine, along with oral mesalamine compounds, for inducing remission in patients with active ulcerative colitis has been shown in various studies. (Sutherland et al 2000; Sninsky et al 1991; Singleton et al 1993; Hanauer et al 1993; Green et al 1998) A recent meta-analysis encompassing studies from 1981–2005 demonstrated that mesalamine was superior to placebo in regards to measured outcomes, which were induction of clinical remission, clinical improvement, endoscopic remission, and endoscopic improvement (Sutherland and Macdonald 2006a).

There have also been various studies looking at the efficacy of mesalamine compounds in maintaining remission in UC patients (Miner et al 1995; Modigliani et al 1996; The Mesalamine Study Group 1996; Sutherland et al 1997; Green et al 1998; Hanauer et al 2000). A recent meta-analysis review looked at a large number of similar studies and concluded that mesalamine compounds were superior to placebo as a maintenance therapy (Sutherland and Macdonald 2006b). The statistical analyses demonstrated that the Peto odds ratio for the failure to maintain clinical or endoscopic remission (withdrawals and relapses) for mesalamine versus placebo was 0.47 (95% CI, 0.36–0.62) with a number-needed-to-treat (NNT) of 6.

These data have direct clinical application as several studies have shown that the health-related quality of life (HRQoL) of patients with UC is related to the severity of their symptoms, and that patients experiencing a disease flare reported significantly poorer overall HRQoL than those in symptomatic remission. Among 160 UC patients with active disease, all aspects of HRQoL, as measured by the Inflammatory Bowel Disease Questionnaire (IBDQ), were significantly lower than for those in symptomatic remission (Casellas et al 2001). A further, large-scale, multi-center study involving 528 patients with UC found that patients with active disease of any severity experienced impairment in their HRQoL across all domains of the IBDQ and patients with moderate to severe disease reported the greatest impairment across all domains (Casellas et al 2005). Therefore the induction and maintenance of remission may be the primary means for improving UC patients' lives on a day-to-day basis.

Review of existing formulations of mesalamine

Mesalamine is available in a number of oral and rectal (topical) formulations including tablets, micropellets (granules),

suppositories, and enemas. Several oral formulations have been developed, most of which have been designed with various mechanisms to postpone the release of the active mesalamine compound until reaching the terminal ileum/colon in order to prevent proximal absorption in the small intestines.

Azo-bonded prodrugs

One group of mesalamine formulations, the azo-bonded prodrugs, comprise a mesalamine molecule bound by an azo-bond to either a transporter molecule or another mesalamine molecule. The azo-bond is cleaved by colonic bacteria containing azoreductase enzyme, freeing up the active mesalamine. This system helps to maximize delivery of mesalamine to the colon by resisting proximal intestinal absorption and gastric breakdown.

Sulfasalazine

Sulfasalazine (Azulfidine®; Pharmacia and Upjohn; Pfizer; New York, NY, USA) was the first oral formulation of mesalamine shown to be effective in the therapy of UC. It consists of a sulfapyridine molecule bonded to a mesalamine molecule. Sulfasalazine has been show to be effective therapy for UC in various studies, which demonstrate that a dose of 2–6 g/day can induce remission in about 50%–80% of patients (Baron et al 1962; Dick et al 1964). A meta-analysis of all oral mesalamine formulations concluded that sulfasalazine was associated with a slightly but significantly higher rate of maintenance of UC remission compared with other mesalamine formulations at 6 months, but that maintenance with sulfasalazine was similar to other mesalamine-agents at 12 months (Sutherland and Macdonald 2006b). Because of its cost-effectiveness and efficacy, sulfasalazine had been the mainstay of treatment for UC for almost 40 years. With the advent of the non-sulfa-containing mesalamine agents, its use has become limited due to a number of demonstrated dose-dependent adverse events (including headache, nausea, dyspepsia, and allergy) related to the sulfur in the sulfapyridine moiety (Nielsen 1982; Myers et al 1987).

Other azo-bonded drugs have been developed using various carrier-molecules other than sulfapyridine in order to avoid related side-effects.

Olsalazine sodium

Olsalazine sodium (Dipentum®; UCB Inc., Smyrna, GA, USA) consists of two mesalamine molecules linked together by an azo-bond. A randomized controlled study with 198 patients showed that olsalazine was effective in maintaining remission in UC patients after 12 months in a dose-dependent manner (Travis et al 1994). Results from the trial demonstrated that at 12 months maintenance of remission was achieved in 60% of patients receiving 0.5 g/day, 70% of patients receiving 1.0 g/day, and 78% of patients receiving 2.0 g/day. Due to treatment-related side-effects (primarily diarrhea), 12% of patients discontinued their treatment. Another study also demonstrated that diarrhea is a significant treatment-related side-effect of olsalazine, affecting 16% of patients in the olsalazine-arm of the trial (Wright et al 1993; Kruis et al 1995). In another study of maintenance of remission in UC, treatment failure rates were lower with olsalazine (1.0 g/day) than with pH-release mesalamine (1.2 g/day) (24% vs 46%; p = 0.025) (Courtney et al 1992).

Balsalazide disodium

Balsalazide disodium (Colazal®; Salix Pharmaceuticals Inc., Morrisville, NC, USA) is an azo-bonded drug containing a mesalamine molecule bonded to 4-aminobenzoyl-β-alanine (4-ABA). Balsalazide has been shown to maintain remission of UC in a dose-dependent manner, while minimizing many of the treatment-limiting side-effects associated with sulfasalazine and olsalazine. One randomized controlled study showed the balsalazide maintained remission after 12 months in 64% of patients taking 4 g/day and 45% of patients taking 2 g/day (p < 0.01) (Giaffer et al 1992). Both doses of the drug were well-tolerated with about 9% and 12% of patients on the 2 g/day and 4 g/day dosages withdrawing due to gastrointestinal intolerance. Balsalazide has also been shown to stabilize the fluctuations in symptom severity by maintaining symptom control over the long term in patients with stable remission and those with newly attained remission (Green et al 2004). One study showed superior clinical remission rates at 1, 2, and 3 months with balsalazide 6.75 g/day than with equimolar doses of pH-release mesalamine 2.4 g/day (3-month rates: 62% vs 37%, p = 0.02) (Green et al 1998).

Delayed-release mesalamine

Mesalamine has also been compounded into formulations that control the release of the active agent by a variety of mechanisms. One example is pH-release mesalamine (Asacol®; Procter & Gamble Pharmaceuticals, Cincinnati, OH, USA), which utilizes a gastro-resistant resin film (eg, Eudragrit-S®) that dissolves at a pH of 7 or greater, releasing the active mesalamine. pH-release mesalamine exhibits similar remission rates after 48 weeks of treatment compared with sulfasalazine (62% vs 61%, p > 0.90) (Riley et al 1988b). However, pH-release mesalamine had lower 12-month remission maintenance rates

than olsalazine in a separate study (Courtney et al 1992). While data extrapolated from previous clinical trials have suggested superior clinical response rates with higher doses of pH-release mesalamine, the recent large ASCEND-1 trial found no clear dose-related benefit between daily doses of 2.4 g vs 4.8 g in the treatment of mild-to-moderate UC, although the ASCEND-2 trial showed a benefit in response, but not remission, with the 4.8 g dose in patients with moderately severe disease (Hanauer et al 2005). The most common side-effects associated with pH-dependent release mesalamine in a 6-month study were headache, flu symptoms, diarrhea, rhinitis, and abdominal pain (The Mesalamine Study Group 1996).

Moisture-release mesalamine

Moisture-release mesalamine (Pentasa®; Shire US Inc., Wayne, PA, USA) consists of microspheres containing mesalamine enclosed within an ethylcellulose semi-permeable membrane, which allows time- and moisture-sensitive release of the active drug. The mesalamine is released throughout the small and large intestines from the duodenum to the rectum, which also makes it a useful treatment for small bowel Crohn's disease. A randomized controlled UC trial showed that moisture-release mesalamine maintained remission in 64% of patients after 12 months when receiving 4 g/day vs 38% of patients receiving placebo (p = 0.0004) (Miner et al 1995). The mesalamine was well tolerated; abdominal pain, nausea, and hepatitis were the most common treatment-related adverse events leading to treatment withdrawal.

All of the sulfur-free mesalamine formulations have acceptable and similar safety profiles. Moreover, a recent meta-analysis found no significant difference in systemic absorption between various oral mesalamine compounds or pro-drug treatments (Sandborn and Hanauer 2003). However, a previous study showed that mucosal biopsies taken 1-week after cessation of treatment with various oral formulations produced an almost 1000-fold variation in mesalamine concentration in similar locations throughout patients' distal gastrointestinal tracts, depending upon the agent (De Vos et al 1992). More recently it has been demonstrated that mesalamine concentration is inversely associated with endoscopic and histological activity scores in UC (Frieri et al 2000). Thus it is possible that the variance in mucosal concentrations of mesalamine between different oral formulations may account, in part, for their different efficacies.

Mesalamine enemas and suppositories

Mesalamine enemas and suppositories are extremely effective in the treatment of left-sided ulcerative colitis, ulcerative proctosigmoiditis, and ulcerative proctitis (Cohen et al 2000). Since these agents do not need to protect the mesalamine from digestion, there is no need for a pro-drug or controlled-release. These formulations deliver therapeutic concentrations of mesalamine to the distal regions of the colon, which are sometimes not adequately dosed using current oral formulation (Frieri et al 1999). Rectal formulations require patients to retain the formulation for as long as possible, which may be difficult during times when they are suffering from diarrhea. However, such delivery methods are associated with leakage as well as problems with retention, burning sensation and bloating (Gionchetti et al 1999; Lim et al 2004). Combination therapies with oral and topical mesalamine are superior to oral therapy alone in the treatment of active left-sided colitis, and maintenance of remission (d'Albasio et al 1997; Safdi et al 1997)

Rationale for once-daily formulations

UC is a chronic, relapsing disease that often requires medications to maintain a successfully induced response or remission. Most UC patients will experience at least one relapse after their initial diagnosis (Hendriksen et al 1985) and the severity of symptoms can intimately affect their HRQoL (Casellas et al 2001, 2005) The efficacy of a successful maintenance regimen depends in part upon patient compliance with the treatment.

Various studies have shown the correlation between compliance and maintenance of remission. In one observational study of 94 patients with quiescent UC, only 40% were adherent (defined as refilling less than 80% of prescribed dose) with their prescribed mesalamine dose (Kane et al 2001). Logistic regression identified male gender and a taking more than 4 prescription medications as predictors for non-adherence. A second study of 99 consecutive UC patients in remission on mesalamine therapy revealed that 89% of patients who were compliant with their mesalamine remained symptom-free at 12 months versus 39% of patients who were non-compliant (p < 0.001) (Kane et al 2003). Patients who were not adherent with their prescribed mesalamine had a greater than a 5-fold greater risk of recurrence than adherent patients (p < 0.001).

Another study aimed at determining compliance of patients on sulfasalazine maintenance therapy measured the serum sulfapyridine levels in patients during hospitalization and at 6 month follow-up (van Hees and van Tongeren 1982). Despite instructions to maintain the same dosages as outpatients, serum sulfapyridine levels were substantially lower in 41% of the patients at the 6-month follow up visit, suggesting non-compliance. Furthermore, 21 out of 175 patients had *no*

detectable level of sulfapyridine in their serum after repeat follow-ups up to 4 years, although many still claimed to be taking their medication.

The reasons for non-compliance with mesalamine therapy are complex and various independent risk factors have been identified, including male gender, single status, full-time employment, and 3-times daily dosing (Kane et al 2001; Shale and Riley 2003). Also, in patients who are in periods of disease remission, the lack of symptomatic reminders may affect their ability or interest in complying with complex dosing schedules. The inconvenience of frequent multiple-times-a-day dosing, together with the number of tablets/capsules required per day, have been identified as key factors in reducing patient compliance with therapy in UC (Kane et al 2003a; Shale and Riley 2003). A recent cross-sectional assessed patient compliance with mesalamine maintenance-dosage therapy via urine mesalamine levels and direct inquiry (consisting of a structured interview and standardized questionnaires) (Shale and Riley 2003). Results of the study showed that 43% of patients took less than 80% of their prescribed medication and 12% of patients had no detectable mesalamine in their urine at all. When the group patients with disease quiescence were questioned about their non-compliance, 70% claimed that they had "just forgot", 30% complained that there were "too many pills" to take, and 20% were unconvinced that they needed the amount of medicine prescribed (Kane et al 2003a; Shale and Riley 2003). These studies imply that many of the existing oral formulations of mesalamine require multiple doses per day with numerous tablets, and from the information above these complicated dosing schedules may conflict with the activities of daily living of patients and lead to non-compliance.

In an attempt to determine whether once-daily dosing would improve patient outcomes, a small pilot study consisting of 22 subjects compared once-daily pH-release mesalamine therapy with the conventional 2 or 3 times daily dosing in maintaining symptomatic UC remission (Kane et al 2003b). After 3 months, 100% (12 of 12) of the once-daily dosed patients were compliant with their medication regimen as opposed to 70% (7 of 10) on the conventional dosing regimen (p = 0.04). However by the 6-month follow-up, 1 patient in each group had experienced symptomatic relapse and the compliance rates between groups were comparable. Sample size limitations prevented a true assessment of the impact of one-daily dosing upon efficacy.

Another potential benefit of compliance with mesalamine therapy has been elucidated by a number of epidemiologic studies that have suggested that the regular use of mesalamine is associated with about a 2-fold reduction in the probability of developing colorectal cancer in UC patients. A meta-analysis of 116 studies concluded that the risk of patients with UC for developing colorectal cancer is 2%, 8%, and 18% at 10, 20, and 30 years (Eaden et al 2001). Given this information, improving patient compliance with mesalamine therapy is an important means to improving QoL and long-term health outcomes in people suffering from UC.

The limitations of current oral mesalamine formulations have forced the research and development of new agents and regimens that are favorable in ensuring compliance, while still maintaining adequate delivery of the drug to the affected regions of the colon. Recent developments include high-dose tablet formulations to limit the number of pills required, once-daily regimens of existing formulations to limit the intrusiveness of therapy on daily activities, and novel formulations offering more convenient dosing in addition to improved drug delivery to the whole colon (Cohen 2006).

Overview of pharmacology of MMX

A novel formulation of oral mesalamine, MMX (SPD476, Shire Pharmaceuticals Inc., Wayne PA, USA), is a high strength (1.2 g mesalamine/tablet) medication that utilizes a Multi-Matrix System™ (MMX) to deliver active aminosalicylates throughout the colon, thus making it a potentially very useful treatment in UC.

MMX mesalamine uses a patented polymeric matrix model designed with a lipophilic matrix embedded within a hydrophilic matrix (Prantera et al 2005). The drug's core holds a lipophilic matrix consisting of mesalamine microparticles dispersed throughout a hydrophilic matrix, which is then surrounded by a pH-dependent (pH 7.0) gastro-resistant film. This design allows the tablet to resist breakdown until the terminal ileum where intra-luminal pH levels reach a sufficiently high level. As the outer coating dissolves, the hydrophilic matrix draws in intestinal fluid, thus making the tablet swell and form a gel-like mass (D'Haens et al 2006). This viscous mass tempers the diffusion and breakdown of the tablet, thus allowing dissemination of the mesalamine molecules in a slow linear kinetics profile throughout the colon. In addition, studies indicate that the hydrophilic matrix may also adhere to the colonic mucosa. This form of delivery allows for a more homogenous release of the active drug at the ascending, transverse, and descending colon, along with the sigmoid and rectum (Prantera et al 2005).

Results of clinical studies

One of the first trials published to investigate the clinical efficacy of MMX mesalamine was the Prantera study

(Prantera et al 2005). The goal of this randomized, double-blind, double-dummy trial was to judge the therapeutic response to MMX in UC patients with left-sided disease and assess how this novel formulation would compare with topical mesalamine therapy. Seventy-nine patients were randomized to receive either oral MMX mesalamine 3.6 g/day (1.2 g tablets dosed 3 times/day) with a bedtime placebo enema or similarly dosed oral placebo tablets with a bedtime mesalamine 4 g/100 mL enema for 8 weeks. Both sets of tablets and enemas were visually identical. The primary endpoint was the rates of induction of remission at 8 weeks between the two groups. Clinical remission was defined as a Rachmilewitz (Rachmilewitz 1989) clinical activity index (CAI) ≤4 at 8 weeks. Secondary endpoints were: 1) duration of symptoms until improvement as measured per patient journals and 2) endoscopic/histological improvement, defined by the endoscopic index (EI) developed by Rachmilewitz and the score from Floren and colleagues (Floren et al 1987). At 8 weeks, clinical remission rates were 60% for the MMX arm vs 50% in the mesalamine enema arm; endoscopic and histological remission rates were 45% and 15% vs 37% and 8%, respectively. Compliance rates for the MMX group were 97% overall (97% for patients in remission and 93% for patients with active symptoms), compared with rates of 88% and 66% in the mesalamine enema group, respectively.

The SPD476-202 study was a phase II, multi-center, double-blinded, randomized dose-ranging induction study in mild-moderate UC (D'Haens et al 2006). The 38 patients were randomized to once-daily dosing of MMX mesalamine at doses of either 1.2, 2.4, or 4.8 g for 8 weeks. The primary endpoint for the study was remission at 8 weeks, defined as a UC-DAI score ≤1 with a score of 0 for rectal bleeding and stool frequency, and at least a 1-point reduction from baseline in sigmoidoscopy score. The secondary endpoints of the trial were: 1) change in UC-DAI score, 2) change in sigmoidoscopic appearance and histology after 8 weeks, and 3) change in symptoms from baseline to 2, 4, and 8 weeks. A total of 6 patients achieved complete remission: 4 (30.8%) in the 2.4 g/day dose group and 2 (18.2%) in the 4.8 g/day dose group, and 0 (0%) in the 1.2 g/day dose group. The difference in remission rates between groups was not statistically significant. In terms of secondary endpoints, patients receiving 4.8 g/day exhibited the greatest reduction in average UC-DAI score along with histological improvements after 8 weeks. In general, MMX was well-tolerated among the three groups. Although the population size was limited (36), the data suggested that MMX mesalamine given

at 2.4 g/day or 4.8 g/day is an effective once-daily treatment for mild-to-moderate UC.

Two large phase III studies (SPD476-301; SPD476-302) have now been completed and published, showing MMX mesalamine to be efficacious for the induction of remission, sigmoidoscopic improvement and improvement of symptoms in patients with mild-to-moderate UC following 8 weeks' once- or twice-daily dosing of 2.4 g/day or once-daily dosing of 4.8 g/day MMX mesalamine.

SPD476-301 was a randomized, double-blind, placebo-controlled multi-center trial in 280 patients with mild-moderate UC (Lichtenstein et al 2007). Patients were randomly assigned to receive either MMX mesalamine 2.4 g/day (1.2 g tablets twice daily) or 4.8 g/day (once daily), or placebo for 8 weeks. The primary endpoint of the study was clinical and endoscopic remission at week 8, defined as 1) a modified UC-DAI score of ≤1 with 2) rectal bleeding and stool frequency scores of 0, and 3) at least a one-point reduction in the more stringent sigmoidoscopy score from baseline. Clinical and endoscopic remission rates at week 8 were higher in both the 2.4 g twice daily MMX (34.1%, $p < 0.001$) and the 4.8 g once daily MMX (29.2%; $p = 0.009$) than in placebo (12.9%). Clinical improvement rates were 55.7% and 59.6%, vs 25.9%, respectively ($p < 0.001$ for either MMX vs placebo). Sigmoidoscopic improvement rates were 61.4% and 69.7% vs 35.5%, respectively ($p < 0.01$ for 4.8 g once daily vs placebo).

SPD476-302 was a randomized, double-blind, double-dummy, placebo-controlled multi-center trial in 343 patients with mild-moderate UC (Kamm et al 2007). Patients were randomized to receive either MMX mesalamine 2.4 g/day (once daily), MMX mesalamine 4.8 g/day (once daily), pH-release mesalamine (Asacol®) 2.4 g/day (800 mg 3 times daily), or placebo for 8 weeks. The primary endpoint and clinical and endoscopic remission at 8 weeks, as previously described in the SPD476-301 study, were higher in patients receiving either MMX 2.4 g/day (40.5%, $p = 0.01$ vs placebo) or MMX 4.8 g/day (41.2%, $p = 0.007$), but not the pH-release mesalamine (32.6%, $p = $ ns), than for placebo (22.1%) ($p = 0.033$). Clinical remission rates were higher in the 2.4 g MMX (41.7%, $p = 0.006$ vs placebo) and the 4.8 g MMX group (41.2%, $p = 0.007$), but not the pH-release mesalamine group (33.7%, $p = 0.089$), than in placebo (22.1%). Endoscopic remission rates were higher in the 2.4 g MMX (69.0%, $p = 0.003$ vs placebo), the 4.8 g MMX (77.6%, $p < 0.001$), and the pH-release mesalamine (61.6%, $p = 0.047$) than for placebo (46.5%). Clinical improvement rates were also higher in the 2.4 g MMX (60.7%, $p = 0.006$

vs placebo), the 4.8 g MMX (64.7%, p < 0.001), and the pH-release mesalamine (55.8%, p = 0.033) than for placebo (39.5%).

Potential for use in clinical practice

The MMX formulation of mesalamine was FDA-approved for use in mild to moderate ulcerative colitis in early 2007, and will be sold under the brand name Lialda™ in the US and Mezavant™ in Europe (Shire Pharmaceuticals Inc., Wayne, PA, USA). Dosing will be once or twice daily, at 2.4–4.8 g (2–4 pills). Being the first once-a-day dosed mesalamine, as well as one that provides over 4 g of drug with one-half to one-third fewer pills than the current moisture-release or pH-dependent release products available in the US, there has been much speculation as to the impact that this new formulation may have upon physician prescribing habits, and patient demand. The results from the clinical trials reviewed above show that MMX dosed once daily is superior to placebo. The study also included a comparison of a pH-release mesalamine with placebo, but not MMX with pH-release mesalamine, so it is not possible to determine if one agent is more effective than the other (Kamm et al 2007).

Previous studies have suggested that the azo-bond release mechanism may be more effective than the pH-dependent release in some UC patients, based in part on the presumed failure of the initial pH-dependent coating to dissolve in individuals who do not attain such a high pH in their colon, which may be the problem especially in patients with active colitis (Fallingborg et al 1989, 1993; Green et al 1998). As the MMX compound also employs a similar pH-sensitive coating for its initial release, it too could theoretically be subject to this same failure.

The answers to these perplexing questions may come in the setting of formalized controlled comparison trials in the years to come. Meanwhile, the true test will occur in the physician's office, with the temptation to use only 2–4 mesalamine pills with once-daily dosing, and in the patients themselves, as this new formulation is used outside the confines of controlled clinical trials. Whether physicians will immediately use this new agent, use it solely for patients newly prescribed with mesalamine or for those failing therapy with one of the other mesalamine agents, or switch patients currently responding to their current therapy will depend upon a few issues. One is the agent's performance in the "real world"; another is patient preference, which may be swayed by commercial product marketing. A less glamorous, but perhaps more realistic view, is that the decision may be made by cost-conscious pharmacy benefits managers at the major health insurers and state and federal prescription programs, who may look solely at drug cost and ignore the potential cost savings of improved patient compliance and decreased patient relapse rates. Given the safety of mesalamine products, it is not unreasonable to afford the patient the opportunity to simplify their medication regimen, freeing themselves from repeated medication dosing and the constant reminder that they have a disease. The move to once-daily dosing with fewer pills will hopefully be reflected in other novel agents and reformulations in the future.

Disclosures

RC has served on the speaker's bureau of and/or as a consultant for the following companies whose products are mentioned in this manuscript: Axcan-Scandipharm, Proctor and Gamble, Salix Pharmaceuticals, Shire Pharmaceuticals, Solvay Pharmaceuticals, UCB Pharma.

References

Ahnfelt-Ronne I, Nielsen OH, Christensen A, et al. 1990. Clinical evidence supporting the radical scavenger mechanism of 5-aminosalicylic acid. *Gastroenterology*, 98:1162–9.

Ardizzone S, Doldo P, Ranzi T, et al. 1999. Mesalazine foam (Salofalk foam) in the treatment of active distal ulcerative colitis. A comparative trial vs Salofalk enema. The SAF-3 study group. *Ital J Gastroenterol Hepatol*, 31:677–84.

Baron JH, Connell AM, Lennard-Jones JE, et al. 1962. Sulphasalazine and salicylazosulphadimidine in ulcerative colitis. *Lancet*, 1:1094–6.

Burress GC, Musch MW, Jurivich DA, et al. 1997. Effects of mesalamine on the hsp72 stress response in rat IEC-18 intestinal epithelial cells. *Gastroenterology*, 113:1474–9.

Casellas F, Arenas JI, Baudet JS, et al. 2005. Impairment of health-related quality of life in patients with inflammatory bowel disease: a Spanish multicenter study. *Inflamm Bowel Dis*, 11:488–96.

Casellas F, Lopez-Vivancos J, Badia X, et al. 2001. Influence of inflammatory bowel disease on different dimensions of quality of life. *Eur J Gastroenterol Hepatol*, 13:567–72.

Cohen RD. 2006. Review article: evolutionary advances in the delivery of aminosalicylates for the treatment of ulcerative colitis. *Aliment Pharmacol Ther*, 24:465–74.

Cohen RD, Woseth DM, Thisted RA, et al. 2000. A meta-analysis and overview of the literature on treatment options for left-sided ulcerative colitis and ulcerative proctitis. *Am J Gastroenterol*, 95:1263–76.

Courtney MG, Nunes DP, Bergin CF, et al.1992. Randomised comparison of olsalazine and mesalazine in prevention of relapses in ulcerative colitis. *Lancet*, 339:1279–81.

d'Albasio G, Pacini F, Camarri E, et al. 1997. Combined therapy with 5-aminosalicylic acid tablets and enemas for maintaining remission in ulcerative colitis: a randomized double-blind study. *Am J Gastroenterol*, 92:1143–7.

D'Haens G, Hommes D, Engels L, et al. 2006. Once daily MMX mesalazine for the treatment of mild-to-moderate ulcerative colitis: a phase II, dose-ranging study. *Aliment Pharmacol Ther*, 24:1087–97.

De Vos M, Verdievel H, Schoonjans R, et al. 1992. Concentrations of 5-ASA and Ac-5-ASA in human ileocolonic biopsy homogenates after oral 5-ASA preparations. *Gut*, 33:1338–42.

Dick AP, Grayson MJ, Carpenter RG, et al. 1964. Controlled trial of sulphasalazine in the treatment of ulcerative colitis. *Gut*, 5:437–42.

Eaden JA, Abrams KR, Mayberry JF. 2001. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut*, 48:526–35.

Fallingborg J, Christensen LA, Ingeman-Nielsen M, et al. 1989. pH-profile and regional transit times of the normal gut measured by a radiotelemetry device. *Aliment Pharmacol Ther*, 3:605–13.

Fallingborg J, Christensen LA, Jacobsen BA, et al. 1993. Very low intraluminal colonic pH in patients with active ulcerative colitis. *Dig Dis Sci*, 38:1989–93.

Farmer RG, Easley KA, Rankin GB. 1993. Clinical patterns, natural history, and progression of ulcerative colitis. A long-term follow-up of 1116 patients. *Dig Dis Sci*, 38:1137–46.

Floren CH, Benoni C, Willen R. 1987. Histologic and colonoscopic assessment of disease extension in ulcerative colitis. *Scand J Gastroenterol*, 22:459–62.

Frieri G, Giacomelli R, Pimpo M, et al. 2000. Mucosal 5-aminosalicylic acid concentration inversely correlates with severity of colonic inflammation in patients with ulcerative colitis. *Gut*, 47:410–4.

Frieri G, Pimpo MT, Palumbo GC, et al. 1999. Rectal and colonic mesalazine concentration in ulcerative colitis: oral vs. oral plus topical treatment. *Aliment Pharmacol Ther*, 13:1413–7.

Gendre JP, Mary JY, Florent C, et al. 1993. Oral mesalamine (Pentasa) as maintenance treatment in Crohn's disease: a multicenter placebo-controlled study. The Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives (GETAID). *Gastroenterology*, 104:435–9.

Ghosh S, Shand A, Ferguson A. 2000. Ulcerative colitis. *BMJ*, 320:1119–23.

Giaffer MH, Holdsworth CD, Lennard-Jones JE, et al. 1992. Improved maintenance of remission in ulcerative colitis by balsalazide 4 g/day compared with 2 g/day. *Aliment Pharmacol Ther*, 6:479–85.

Gionchetti P, Ardizzone S, Benvenuti ME, et al. 1999. A new mesalazine gel enema in the treatment of left-sided ulcerative colitis: a randomized controlled multicentre trial. *Aliment Pharmacol Ther*, 13:381–8.

Green JR, Gibson JA, Kerr GD, et al. 1998. Maintenance of remission of ulcerative colitis: a comparison between balsalazide 3 g daily and mesalazine 1.2 g daily over 12 months. ABACUS Investigator group. *Aliment Pharmacol Ther*, 12:1207–16.

Green JR, Lobo AJ, Holdsworth CD, et al. 1998. Balsalazide is more effective and better tolerated than mesalamine in the treatment of acute ulcerative colitis. The Abacus Investigator Group. *Gastroenterology*, 114:15–22.

Green JR, Swan CH, Gibson JA, et al. 2004. Patient-led variable dosing with balsalazide as long-term therapy for maintenance in ulcerative colitis: a 3-year prospective observational study. *Aliment Pharmacol Ther*, 19:435–42.

Hanauer S, Good LI, Goodman MW, et al. 2000. Long-term use of mesalamine (Rowasa) suppositories in remission maintenance of ulcerative proctitis. *Am J Gastroenterol*, 95:1749–54.

Hanauer SB, Sandborn WJ, Kornbluth A, et al. Delayed-release oral mesalamine at 4.8 g/day (800 mg tablet) for the treatment of moderately active ulcerative colitis: the ASCEND II trial. *Am J Gastroenterol*, Nov 2005; 100(11):2478–85.

Hanauer S, Schwartz J, Robinson M, et al. 1993. Mesalamine capsules for treatment of active ulcerative colitis: results of a controlled trial. Pentasa Study Group. *Am J Gastroenterol*, 88:1188–97.

Hawkey CJ, Boughton-Smith NK, Whittle BJ. 1985. Modulation of human colonic arachidonic acid metabolism by sulfasalazine. *Dig Dis Sci*, 30:1161–5.

Hendriksen C, Kreiner S, Binder V. 1985. Long term prognosis in ulcerative colitis – based on results from a regional patient group from the county of Copenhagen. *Gut*, 26:158–63.

Kamm MA, Sandborn WJ, Gassull M, et al. 2007. Once-daily, high-concentration MMX mesalamine in active ulcerative colitis. *Gastroenterology*, 132:66–75.

Kane S, Huo D, Aikens J, et al. 2003. Medication nonadherence and the outcomes of patients with quiescent ulcerative colitis. *Am J Med*, 114:39–43.

Kane S, Huo D, Magnanti K. 2003. A pilot feasibility study of once daily versus conventional dosing mesalamine for maintenance of ulcerative colitis. *Clin Gastroenterol Hepatol*, 1:170–3.

Kane SV, Cohen RD, Aikens JE, et al. 2001. Prevalence of nonadherence with maintenance mesalamine in quiescent ulcerative colitis. *Am J Gastroenterol*, 96:2929–33.

Kovvali G, Das KM. 2005. Molecular mimicry may contribute to pathogenesis of ulcerative colitis. *FEBS Lett*, 579:2261–6.

Kruis W, Judmaier G, Kayasseh L, et al. 1995. Double-blind dose-finding study of olsalazine versus sulphasalazine as maintenance therapy for ulcerative colitis. *Eur J Gastroenterol Hepatol*, 7:391–6.

Langholz E, Munkholm P, Davidsen M, et al. 1996. Changes in extent of ulcerative colitis: a study on the course and prognostic factors. *Scand J Gastroenterol*, 31:260–6.

Lichtenstein GR, Kamm MA, Boddu P, et al. 2007. Effect of once- or twice-daily MMX mesalamine (SPD476) for the induction of remission of mild to moderately active ulcerative colitis. *Clin Gastroenterol Hepatol*, 5:95–102.

Ligumsky M, Karmeli F, Sharon P, et al. 1981. Enhanced thromboxane A2 and prostacyclin production by cultured rectal mucosa in ulcerative colitis and its inhibition by steroids and sulfasalazine. *Gastroenterology*, 81:444–9.

Lim WC, Hanauer SB. 2004. Controversies with aminosalicylates in inflammatory bowel disease. *Rev Gastroenterol Disord*, 4:104–17.

Loftus EV, Jr. Silverstein MD, Sandborn WJ, et al. 2000. Ulcerative colitis in Olmsted County, Minnesota, 1940–1993: incidence, prevalence, and survival. *Gut*, 46:336–43.

Mansfield JC, Holden H, Tarlow JK, et al. 1994. Novel genetic association between ulcerative colitis and the anti-inflammatory cytokine interleukin-1 receptor antagonist. *Gastroenterology*, 106:637–42.

Miner P, Hanauer S, Robinson M, et al. 1995. Safety and efficacy of controlled-release mesalamine for maintenance of remission in ulcerative colitis. Pentasa UC Maintenance Study Group. *Dig Dis Sci*, 40:296–304.

Modigliani R, Colombel JF, Dupas JL, et al. 1996. Mesalamine in Crohn's disease with steroid-induced remission: effect on steroid withdrawal and remission maintenance, Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives. *Gastroenterology*, 110:688–93.

Myers B, Evans DN, Rhodes J, et al. 1987. Metabolism and urinary excretion of 5-amino salicylic acid in healthy volunteers when given intravenously or released for absorption at different sites in the gastrointestinal tract. *Gut*, 28:196–200.

Nielsen OH. 1982. Sulfasalazine intolerance. A retrospective survey of the reasons for discontinuing treatment with sulfasalazine in patients with chronic inflammatory bowel disease. *Scand J Gastroenterol*, 17:389–93.

Pokrotnieks J, Marlicz K, Paradowski L, et al. 2004. Efficacy and tolerability of mesalazine foam enema (Salofalk foam) for distal ulcerative colitis: a double-blind, randomized, placebo-controlled study. *Aliment Pharmacol Ther*, 14:1191–8.

Prantera C, Viscido A, Biancone L, et al. 2005. A new oral delivery system for 5-ASA: preliminary clinical findings for MMx. *Inflamm Bowel Dis*, 11:421–27.

Rachmilewitz D. 1989. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. *BMJ*, 298:82–6.

Riley SA, Mani V, Goodman MJ, et al. 1988a. Comparison of delayed-release 5-aminosalicylic acid (mesalazine) and sulfasalazine as maintenance treatment for patients with ulcerative colitis. *Gastroenterology*, 94:1383–9.

Riley SA, Mani V, Goodman MJ, et al. 1988b. Comparison of delayed release 5 aminosalicylic acid (mesalazine) and sulphasalazine in the treatment of mild to moderate ulcerative colitis relapse. *Gut*, 29:669–74.

Safdi M, DeMicco M, Sninsky C, et al. 1997. A double-blind comparison of oral versus rectal mesalamine versus combination therapy in the treatment of distal ulcerative colitis. *Am J Gastroenterol*, 92:1867–71.

Sandborn WJ, Hanauer SB. 2003. Systematic review: the pharmacokinetic profiles of oral mesalazine formulations and mesalazine pro-drugs used in the management of ulcerative colitis. *Aliment Pharmacol Ther*, 17:29–42.

Santucci L, Wallace J, Mencarelli A, et al. 2005. Different sensitivity of lamina propria T-cell subsets to nitric oxide-induced apoptosis explains immunomodulatory activity of a nitric oxide-releasing derivative of mesalamine in rodent colitis. *Gastroenterology*, 128:1243–57.

Shale MJ, Riley SA. 2003. Studies of compliance with delayed-release mesalazine therapy in patients with inflammatory bowel disease. *Aliment Pharmacol Ther*, 18:191–8.

Singleton JW, Hanauer SB, Gitnick GL, et al. 1993. Mesalamine capsules for the treatment of active Crohn's disease: results of a 16-week trial. Pentasa Crohn's Disease Study Group. *Gastroenterology*, 104:1293–301.

Sninsky CA, Cort DH, Shanahan F, et al. 1991. Oral mesalamine (Asacol) for mildly to moderately active ulcerative colitis. A multicenter study. *Ann Intern Med*, 115:350–5.

Sutherland L, Macdonald JK. 2006a. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev*, (2):CD000543.

Sutherland L, Macdonald JK. 2006b. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev*, (2):CD000544.

Sutherland L, Roth D, Beck P, et al. 2000. Oral 5-aminosalicylic acid for inducing remission in ulcerative colitis. *Cochrane Database Syst Rev*, 2.

Sutherland L, Roth D, Beck P, et al. 2002. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev*, (4):CD000544.

Sutherland LR, Martin F, Bailey RJ, et al. 1997. A randomized, placebo-controlled, double-blind trial of mesalamine in the maintenance of remission of Crohn's disease. The Canadian Mesalamine for Remission of Crohn's Disease Study Group. *Gastroenterology*, 112:1069–77.

The Mesalamine Study Group.1996. An oral preparation of mesalamine as long-term maintenance therapy for ulcerative colitis. A randomized, placebo-controlled trial. The Mesalamine Study Group. *Ann Intern Med*, 124:204–11.

Travis SP, Tysk C, de Silva HJ, et al. 1994. Optimum dose of olsalazine for maintaining remission in ulcerative colitis. *Gut*, 35:1282–6.

van Hees PA, van Tongeren JH. 1982. Compliance to therapy in patients on a maintenance dose of sulfasalazine. *J Clin Gastroenterol*, 4:333–6.

Wen Z, Fiocchi C. 2004. Inflammatory bowel disease: autoimmune or immune-mediated pathogenesis? *Clin Dev Immunol*, 11:195–204.

Wright JP, O'Keefe EA, Cuming L, et al. 1993. Olsalazine in maintenance of clinical remission in patients with ulcerative colitis. *Dig Dis Sci*, 38:1837–42.

Yang H, Rotter JI, Toyoda H, et al. 1993. Ulcerative colitis: a genetically heterogeneous disorder defined by genetic (HLA class II) and subclinical (antineutrophil cytoplasmic antibodies) markers. *J Clin Invest*, 92:1080–4.