

## Mesalazine in inflammatory bowel disease: A trendy topic once again?

Marietta Iacucci MD<sup>1</sup>, Shanika de Silva MRCP<sup>2</sup>, Subrata Ghosh MD FRCPC FRCP FRCPE<sup>2</sup>

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5-aminosalicylic acid (5-ASA) preparations (eg, mesalazine, mesalamine) are well-established preparations used in the management of inflammatory bowel disease. These drugs are most useful for the treatment of mild to moderate flares of ulcerative colitis and, especially, for maintenance of remission. Although most gastroenterologists are very familiar with these drugs, the interest in these drugs has undergone a resurgence, with new preparations offering convenience and high dosage, while preserving their customary safety. New dosage regimens are likely to become standard practice in the near future. There is also considerable interest in chemoprevention of colorectal cancer in the context of inflammatory bowel disease, and the role of long-term maintenance therapy with 5-ASAs in achieving such chemoprevention. A mechanism of action for such chemoprevention has been provided by the agonism of the peroxisome proliferator-activated receptor-gamma by 5-ASA, which unifies its efficacy as an anti-inflammatory and chemopreventive agent. In the future, even more effective agents based on 5-ASA are expected, based on more powerful agonism of peroxisome proliferator-activated receptor-gamma; 5-ASA preparations have become 'trendy' again.

**Key Words:** 5-ASA; Adherence; Colorectal cancer; Delayed release; Inflammatory bowel disease; Mesalamine; Multimatrix system

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic relapsing conditions generally characterized by repetitive cycles of active and quiescent disease. Intestinal inflammation can result in bleeding and anemia, perforation with abscess or fistula formation, or subsequent fibrosis with intestinal obstruction (1). The natural history of inflammatory bowel disease (IBD) is dependent on the anatomical extent of involvement and activity of disease. The anatomical location and behaviour of CD, according to the Vienna (2) (or the more recent Montreal) classification, changes over time. At diagnosis, CD is located in the terminal ileum in 47%, the colon in 28%, the ileocolon in 21% and the upper gastrointestinal tract in 3% of patients. Disease behaviour is classified as nonstricturing and nonpenetrating in 70% of patients, stricturing in 17% and penetrating (fistulas or abscesses or both) in 13% of all patients at diagnosis. In clinical practice, disease activity is typically described as mild to moderate (ambulatory patients able to tolerate oral alimentation without manifestations of dehydration, toxicity, abdominal tenderness, painful mass, obstruction or more than 10% weight loss), moderate to severe disease (failure to respond to treatment for mild disease, more prominent symptoms of fever, weight loss, abdominal pain or tenderness, intermittent nausea, and vomiting without

### La mésalazine dans la maladie inflammatoire de l'intestin : De nouveau à la mode?

Les préparations d'acide 5-aminosalicylique (5 ASA) (p. ex., mésalazine, mesalamine) sont couramment utilisées dans la prise en charge des maladies inflammatoires de l'intestin. Ces médicaments sont surtout utiles pour le traitement des poussées de légères à modérées de la colite ulcéreuse et notamment pour le maintien de la rémission. Bien que la plupart des gastro-entérologues connaissent bien ces agents, l'intérêt à leur endroit renaît actuellement, puisque de nouvelles préparations offrent la même commodité en doses plus fortes, tout en préservant le profil d'innocuité habituel. Les nouveaux schémas posologiques risquent de devenir la norme dans un avenir rapproché. On s'intéresse également beaucoup à la chimioprévention du cancer colorectal dans le contexte de la maladie inflammatoire de l'intestin et au rôle du traitement d'entretien prolongé par 5-ASA pour parvenir à cette chimioprévention. On a proposé comme mode d'action de cette chimioprévention l'agonisme des récepteurs gamma activé par les proliférateurs du peroxyssome au moyen du 5-ASA, qui allie efficacité anti-inflammatoire et propriétés chimioprotectrices. On s'attend à ce que des agents à base de 5-ASA plus efficaces fassent leur apparition, en raison d'un effet agoniste plus puissant du récepteur gamma activé par les proliférateurs du peroxyssome. Les préparations de 5-ASA sont revenues à la mode.

obstruction or significant anemia) and severe to fulminant disease (persisting symptoms on corticosteroids, high fevers, persistent vomiting or evidence of intestinal obstruction) (2-4). In UC, 55% of patients have proctitis, approximately 30% of patients present with left-sided or distal colitis and only approximately 15% of patients present with extensive colitis. However, subsequent proximal extension occurs in approximately 35% of patients with initial proctitis or left-sided colitis. Similar to CD, the severity of UC is classified as mild, moderate, severe or fulminant. It is estimated that approximately 71% of patients present with moderately active UC, whereas 20% present with mildly active disease (5). Initial therapy for patients with mild to moderate IBD depends on the location and extent of disease, with oral or rectal therapies being used individually or in combination. Severe or fulminant disease requires hospitalization and intensive parenteral therapy.

The goals of drug treatment in IBD are the induction and maintenance of remission, achieving mucosal healing, the avoidance of surgical intervention and decreasing the likelihood of cancer developing as a result of chronic inflammation.

Mesalazine is useful in controlling active inflammation, maintaining remission and for chemoprevention. It has the advantage of being generally well-tolerated and safe for long-term use with

<sup>1</sup>Gastrointestinal Unit, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom; <sup>2</sup>Division of Gastroenterology, University of Calgary, Calgary, Alberta

Correspondence: Dr Subrata Ghosh, Division of Gastroenterology, University of Calgary, Teaching Research and Wellness Centre,

6th Floor, 3280 Hospital Drive Northwest, Calgary, Alberta T2N 4N1. Telephone 403-592-5010, fax 403-592-5080, e-mail ghosh@ucalgary.ca  
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**TABLE 1**  
**Different dose and delivery system of 5-aminosalicylic acid (ASA) formulations**

Generic 5-ASA name	Commercial name	Dose per tablet, capsule or sachet, mg	Formulation	Site(s) of delivery
Mesalazine	Pentasa*	500, 1000, 2000	Ethylcellulose-coated microgranules (slow, continuous release)	Duodenum to rectum
Mesalamine	Asacol†	400, 800	Eudragit S-coated tablets (release at pH >7)	Terminal ileum, colon
Mesalamine	Mezavant/Lialda‡	1200	Eudragit S-coated multimatrix system	Terminal ileum, colon
Mesalazine	Salofalk§	250	Eudragit L-coated tablets	Mid to distal ileum, colon
Mesalazine	Ipocol¶	400	Enteric coated with Eudragit S	Terminal ileum, colon
Sulfasalazine	Salazopyrin**	500	5-ASA linked to sulfapyridine by azo bond	Colon
Balsalazide	Colazal††	750	5-ASA linked to 4-aminobenzoyl-L-alanine by azo bond	Colon
Olsalazine	Dipentum‡‡	250	5-ASA dimer linked by azo bond	Colon

\*Shire Inc, USA; †Procter & Gamble Pharmaceuticals, USA; ‡Shire Inc, USA §Axcan Pharma Inc; ¶Sandoz Ltd, United Kingdom; \*\*Pharmacia Ltd, United Kingdom; ††Salix Pharmaceuticals, USA; ‡‡Celltech Pharmaceuticals Inc, USA

flexible dosing. Mesalazine, also known as mesalamine or 5-aminosalicylic acid (5-ASA), is the first-line treatment for IBD and remains the mainstay of treatment for mild to moderate UC; however, its use in CD is controversial (6). Indeed, the European Crohn's and Colitis Organization Consensus recently stated that oral aminosalicylates are not recommended for the treatment of mild to moderate CD (7). However, both the American and British National Gastroenterology Associations recommend the use of high-dose 5-ASA for the first-line treatment of mild ileal, ileocolonic or colonic CD (1,8). Clearly, there is conflicting evidence regarding the efficacy of oral aminosalicylates in active CD and their use in mild to moderate CD has been debated.

The action of mesalazine is believed to be predominantly topical at the site of inflammation, especially within the colon. The clinical aim, therefore, is to maximize delivery of the active drug – 5-ASA – to the colonic mucosa, while minimizing systemic absorption.

#### DIFFERENT 5-ASA FORMULATIONS AND MECHANISMS OF ACTION

5-ASAs are available in several oral and rectal (topical) formulations including tablets, micropellets (granules), suppositories and enemas, the latter may be aerosols, liquids or gels (Table 1).

Sulfasalazine was the first 5-ASA to be used for the treatment of symptoms and maintenance of remission in UC. It is composed of 5-ASA linked to sulfapyridine via a diazo bond that is cleaved by bacterial azoreductases in the colon to release the two components (9). Its use as a maintenance agent in UC is well documented, and in a meta-analysis of 11 trials involving 1598 patients (10), sulfasalazine had a slight therapeutic advantage over 5-ASA (OR 1.29; 95% CI 1.05 to 1.57). Compared with olsalazine for the maintenance of remission, sulfasalazine was found to be significantly more effective when the ORs from five trials were pooled (OR 1.4; 95% CI 1.07 to 1.84) (10). A meta-analysis investigating the failure to induce remission in active UC involving eight trials and 687 patients (6) demonstrated no significant differences between 5-ASA and sulfasalazine at induction of remission (OR 0.83; 95% CI 0.6 to 1.13).

It is recognized that a subgroup of patients with IBD suffer from enteropathic arthropathy – a condition that can be divided into a pauciarticular, large joint arthropathy or a bilateral

symmetrical polyarthropathy with or without axial involvement (11). Sulfasalazine has been shown to be beneficial in treating the synovitis associated with gut inflammation in UC rather than CD, if used in early disease (less than five years) and in the presence of peripheral involvement (12). The efficacy of sulfasalazine in the treatment of spondyloarthropathy has been demonstrated in a multicentre, placebo-controlled trial involving more than 350 patients (13), showing greater efficacy over placebo with respect to laboratory markers of inflammation and patients' own assessment of disease. It was suggested in some treatment guidelines (1) that selected patients with UC and reactive arthropathy would benefit from treatment with sulfasalazine. Therefore, sulfasalazine continues to retain a place in management.

The use of sulfasalazine, however, is mainly limited by side effects associated with allergic reactions and high rates of intolerance (up to 20%) to the sulfapyridine component. As a result, formulations based on the active moiety (ie, 5-ASA) have been evaluated and two main methods of 5-ASA delivery have been used. The first class is azobonded compounds that are controlled-release and pH dependent (pH 6 to 7). These molecules are nonabsorbable prodrugs that are cleaved in the colon by the bacterial enzyme azoreductase and released. Drugs that use this delivery strategy include balsalazide (Colazal, Salix Pharmaceuticals, USA) and olsalazine (Dipentum, Celltech Pharmaceuticals Inc, USA). The second class is a composite (pH-dependent combined with controlled release), in which the formulation contains a gastroresistant coating and a pH/transit-dependent controlled-release that prevents 5-ASA release until the drug reaches the distal ileum. Agents that use this strategy are delayed-release mesalazine tablets (Asacol, Procter & Gamble Pharmaceuticals, USA), Salofalk tablets and Salofalk Granustix (Axcan Pharma Inc). Pentasa (Shire Inc, USA), in contrast to the formulations described above, releases 5-ASA from the duodenum to the rectum, and is often used 'off-label' to treat CD in addition to its indicated use for UC (14,15).

The mechanism of action of mesalazine as an anti-inflammatory drug is diverse. It appears to act locally on colonic mucosa and reduces inflammation through a variety of anti-inflammatory processes. Several potential targets of 5-ASA action have been proposed. The current hypothesis is that 5-ASA activates a synthetic class of nuclear receptor. Peroxisome proliferator-activated receptor (PPAR)-gamma is a

key receptor that mediates the effect of 5-ASA therapy in IBD by transrepressing several key target genes such as nuclear factor B, signal transducers and activators of transcription. It has a role in the regulation of intestinal inflammation and is highly expressed in the colon, where epithelial cells and macrophages are the main cellular sources of this nuclear receptor. PPAR-gamma is also involved in cell proliferation, apoptosis, and modulation of cytokine production and antitumorigenic effects. Therefore, PPAR-gamma may form the basis for chemopreventive strategies against colorectal cancer (CRC).

However, additional mechanisms of action of mesalazine have been described. These include the inhibition of mediators of lipoxygenase and cyclooxygenase, interleukin-1, interleukin-2 and tumour necrosis factor-alpha. 5-ASA has also been recognized as a potent antioxidant and free-radical scavenger (16-22).

### CLINICAL IMPLICATIONS OF MEDICATION NONADHERENCE IN IBD PATIENTS

The reasons for noncompliance with 5-ASA therapy are complex. Male sex, single marital status, full-time employment and three-times daily dosing have all been identified as independent predictors of noncompliance (23).

Oral formulations that deliver 5-ASA topically to the disease activity site require multiple daily dosing, which is inconvenient. This multiple daily dosing can interfere with patient quality of life and can have a negative impact on drug adherence (24).

Moreover, several studies have demonstrated that mucosal concentrations of azobonded or bolus-release 5-ASA formulations are highest in the right-sided colon, whereas in the left-sided colon, concentrations are much lower. A cross-sectional study of American outpatients with quiescent UC (25) found that only 40% were adherent to maintenance mesalazine therapy. Several community-based studies have reported nonadherence rates in IBD patients ranging from 43% to 72%. Nonadherence to medication has important clinical implications in UC and CD patients, including increased risk of relapses, possible risk of developing CRC and the health care costs of managing poor disease control (25-28).

#### Increased risk of relapse

In a cohort study of 99 patients with quiescent UC (29), whose adherence to 5-ASA medication was monitored for two years, 39 patients experienced a recurrence of their symptoms, of whom 32 (82%) were nonadherent to their prescribed medication. Patients who did not adhere to their medication had a greater than fivefold risk of disease recurrence than adherent patients (hazard ratio 5.5; 95% CI 2.3 to 13;  $P < 0.001$ ). The reasons for nonadherence to their prescribed regimen were the following: 21 patients (30%) said there were too many pills, 14 (20%) believed they did not need so much medication and 35 (50%) reported that they 'just forgot'. The investigators also found that patients with quiescent UC who failed to adhere to their prescribed 5-ASA regimen had a 61% chance of relapse compared with only 11% among patients who adhered to their prescribed therapy – a difference that was statistically significant ( $P = 0.001$ ). It is possible, but unlikely, that patients who relapse more often do not take their medication because they believe it is ineffective (30).

#### Increased risk of developing CRC

Patients with IBD affecting the colon are at an increased risk of developing CRC. The risk of developing CRC increases with the extent and duration of UC and is associated with a lifetime risk of approximately 20% (31). In addition, data from population-based studies indicate that CD patients have an increased risk of CRC similar to that of UC patients. Prevention strategies such as surveillance, drug treatment, and regular doctor visits are warranted and probably effective. In a 10-year cohort study of 175 patients with UC, Moody et al (32) demonstrated that the incidence of CRC was significantly higher ( $P < 0.001$ ) in patients (31%) who did not adhere to or discontinued sulfasalazine therapy, compared with only a 3% incidence in those who continued with long-term treatment.

These results were confirmed in a case-control analysis conducted by Van Staa et al (33) using a study population of 18,969 patients. Regular users, defined as having six or more 5-ASA prescriptions in the previous 12 months, were found to have a lower risk of CRC than irregular users (crude OR 0.7, 95% CI 0.44 to 1.03; adjusted OR 0.60, 95% CI 0.38 to 0.96). These results show some reduction in the risk of CRC developing in UC patients who adhere to regular 5-ASA use. Furthermore, conclusions from a systematic review and meta-analysis of nine observational studies involving almost 2000 patients (34) also supported the protective role of 5-ASA against CRC development. More rigorous randomized controlled trials are unlikely, and the effect size of this protection may be debated and can be variable. Chronic inflammation may be the trigger for the colitis-dysplasia-carcinoma sequence; 5-ASA may mitigate this process by decreasing inflammation, and may act in a more direct way by promoting apoptosis in neoplastic cells by decreasing epithelial cell turnover.

#### Increased health care costs

Strategies to improve adherence are important to reduce the high direct and indirect costs of a relapse. The high percentage of nonadherent patients who have a relapse was associated with a two- to threefold increase in the costs for nonhospitalized cases, with a 20-fold increase in costs for hospitalized cases compared with quiescent cases of IBD (35). Over a six-month period, the total direct cost of caring for patients with IBD ranged from UK £73 (approximately US \$129) to UK £33,254 (US \$58,980). The mean cost of care over six months for patients with UC was UK £1,256 (US \$2,228) and, while only 67 (14%) patients with IBD required hospitalization during the six-month assessment period, they accounted for 49% of the total secondary care costs.

### STRATEGIES TO OPTIMIZE DOSE AND ADHERENCE OF 5-ASA IN IBD: 'NEW' 5-ASA FORMULATIONS

The ideal therapy would be an oral formulation, with fewer tablets, requiring less frequent dosing and no side effects. More recently, the introduction of promising new mesalazine formulations (Table 2), offering high-dose and less frequent or once-daily dosing regimens is likely to enhance patient compliance. These include mesalazine 800 mg tablets (Asacol, Procter & Gamble Pharmaceuticals, USA), 1.2 g multimatrix (MMX) system mesalazine tablets (Lialda, Shire Inc, USA), and 2 g (Pentasa) and 3 g 5-ASA granule sachets (Salofalk).

**TABLE 2**  
**New developments in 5-aminosalicylic acid delivery mechanisms**

Formulation	Clinical trial	Author (reference)
Mesalamine (800 mg tablets)	Asacol*, ASCEND I, II and III	Hanauer et al (37,38) Sandborn et al (39)
Mesalazine micropellets (pH dependent)	Pentasa <sup>†</sup> (once daily)	Dignass and Veerman (45) Farup et al (46)
	Salofalk <sup>‡</sup> (once daily)	Kruis et al (48)
Multimatrix (combined hydrophilic/lipophilic matrices)	Multimatrix mesalamine	Kamm et al (40,43) Lichtenstein et al (41)

\*Procter & Gamble Pharmaceuticals, USA; <sup>†</sup>Shire Inc, USA; <sup>‡</sup>Axcan Pharma Inc. ASCEND Assessing the Safety and Clinical Efficacy of a New Dose of 5-ASA (37-39)

### Asacol (800 mg tablet)

Earlier clinical trials comparing the efficacy of 1.6 g/day versus 4.8 g/day mesalamine (Asacol) in patients with mild to moderately active UC showed no definite differences in efficacy between the doses, although systematic reviews have shown a small benefit for higher doses in induction (36).

Recently, the Assessing the Safety and Clinical Efficacy of a New Dose of 5-ASA (ASCEND) I and II trials (37,38) used a new 800 mg tablet formulation of Asacol, comparing 4.8 g/day of delayed-release mesalamine with 2.4 g/day. In the first trial (ASCEND I) (37), 301 patients with mild to moderately active UC were randomly assigned to receive oral mesalamine 2.4 g/day (400 mg tablets) or 4.8 g/day (800 mg tablets). The primary endpoint was the proportion of patients who achieved complete remission or a clinical response to therapy. Overall improvement occurred in 51.3% of patients (77 of 150) treated with Asacol 2.4 g/day and 55.9% of patients (76 of 136) treated with 4.8 g/day ( $P=0.4411$ ).

In the second trial (ASCEND II) (38), the design was amended to restrict the entry criteria to only 268 patients with moderately active UC. Seventy-two per cent of patients receiving mesalamine 4.8 g/day achieved treatment success at week 6, compared with 59% of those who received 2.4 g/day ( $P=0.036$ ). The results of this study suggest that an acceptable strategy may be that patients with mildly active UC be treated initially with Asacol 2.4 g/day and patients with moderately active UC with 4.8 g/day using the 800 mg tablets – such a high dose in moderately active UC may also provide modestly faster symptom relief (38).

The recent ASCEND III (39) study confirmed the clinical benefit of delayed-release mesalamine 4.8 g/day in patients with moderately active UC. The overall improvement at week 6 was higher with the 4.8 g/day dose only in subgroups of patients who had received previous treatment with oral mesalamine, rectal therapies, steroids or multiple medications. The ASCEND program confirmed that high doses of 5-ASA were well tolerated and safe.

### MMX mesalamine (1.2 g tablet)

MMX mesalamine (MMX Lialda, USA; Mezavant XL, United Kingdom and Ireland, Mezavant, rest of Europe, Shire Pharmaceuticals Inc); offers a novel, high-strength (1.2 g/tablet) delivery system, and has been used in patients with active, mild to moderate UC. This delivery system uses lipophilic and hydrophilic matrices enclosed in a gastroresistant, pH-dependent coating to facilitate prolonged exposure of the colonic mucosa to the active moiety. The delivery system has been likened to

an absorbant sponge gradually breaking up and releasing 5-ASA throughout the colon.

The results of two large studies reported by Kamm et al (40) and Lichtenstein et al (41) have shown that MMX mesalamine 2.4 g/day (given once daily or as 1.2 g twice daily) or 4.8 g/day once-daily is well tolerated and efficacious for the induction of clinical and endoscopic remission in patients with active, mild to moderate UC. The UC disease activity index score in these studies was modified by assigning the friability parameter a score of 2. Approximately 64% of patients in these studies did not achieve strictly defined remission by endoscopic and clinical parameters by eight weeks of treatment with MMX mesalamine. Those not achieving remission after eight weeks were treated with steroids or other immunosuppressive therapies (42).

In a long-term, open-label, phase III study, Kamm et al (43) evaluated the effect of prolonged, high-dose, oral 5-ASA treatment over 12 months. The remission rate was similar to that observed in the parent study (57% to 61.5%). The eight-week extension part of the study suggests that some patients who appear refractory to 5-ASA may require only an extended treatment with the high-dose MMX mesalamine (4.8 g/day) as an alternative to step-up steroid therapy.

The current licensed dose of MMX mesalamine for the induction of remission in patients with active, mild to moderate UC is two to four 1.2 g tablets administered once daily. The recommended dose for the maintenance of remission is 2.4 g once daily (44).

### Once-daily 5-ASA granules

Pentasa or Salofalk granules are micropellet formulations of 5-ASA preferred by some patients, especially those reluctant to swallow relatively large tablets.

In a recent multicentre, investigator-blinded, randomized controlled trial, patients with mild to moderate UC in remission were randomly assigned to a 2 g sachet of mesalazine granules (Pentasa) once daily or a 1 g sachet of mesalazine granules twice daily. At one year, 74% and 64% of patients in the once-daily and twice-daily groups, respectively, maintained clinical and endoscopic remission. Once-daily dosing was clinically superior to, and had a higher adherence than twice daily dosing (45). Farup et al (46) compared the efficacy of an equal dose of a prolonged-release granule formulation of mesalazine (4 g/day, Pentasa sachet) divided into twice daily versus four times daily, with that of prolonged-release mesalazine tablets at two doses of 0.5 g four times daily in 227 patients with mild to moderately active UC. Granules were as effective as tablets, and twice-

daily dosing was as effective as more frequent dosing (46). Once again, the study was designed to confirm the noninferiority of the granule formulation to the tablet formulation. In another study, the pharmacokinetic profile of 5-ASA for Pentasa sachets administered 4 g once daily was also similar to that of 2 g given twice daily. Patient compliance was 97% (47).

Salofalk is a multiparticulate, granular formulation of mesalazine, with an enteric, acid-resistant film coating that enables prolonged release in the colon. This formulation is easier to swallow than enteric-coated tablets and may be preferred by some patients.

In a recent multicentre phase III trial, Kruis et al (48) demonstrated that once-daily dosing with mesalazine 3 g (Salofalk granules, Falk Pharma, Germany) was as effective as three-times daily dosing with mesalazine 1 g for the treatment of active UC. A total of 380 patients were evaluated for efficacy and safety by intention-to-treat analysis, with 79.1% in the once-daily dosing group and 75.7% in the three-times daily group achieving remission ( $P < 0.0001$  for noninferiority). Of interest is the significantly greater therapeutic effect of the once-daily dosing in proctosigmoiditis patients. This supports the hypothesis that once-daily dosing leads to higher luminal peak concentrations in the distal colon and that mesalazine granules are well suited for oral treatment of distal disease. In fact, most patients with UC tend to prefer the oral over the rectal route of administration (48).

#### Rectal-oral 5-ASA combination therapy

Rectally administered 5-ASA has also been shown to be superior to placebo for the maintenance of remission of distal UC (49-52). A meta-analysis (53) has demonstrated the superiority of rectal 5-ASA over placebo for maintenance of remission in UC at one year (OR 15.2; 95% CI 4.7 to 55.9).

Rectal 5-ASA is superior to rectal steroid therapy. In addition to patients with left-sided UC of mild to moderate severity, combined therapy also enhances the benefit in patients with extensive, mild to moderately active UC. In a randomized double-blind study performed in 127 ambulatory patients with extensive mild/moderate active UC (54), all subjects received oral mesalazine 4 g/day (twice daily dosing) for eight weeks. During the initial four weeks, they received an additional enema at bedtime containing 1 g of mesalazine or placebo. Remission was achieved in 44% of the mesalazine enema group versus 34% of the placebo enema group at four weeks ( $P = 0.31$ ), and in 64% (95% CI 50% to 76%) of the mesalazine enema group versus 43% of the placebo enema group at eight weeks ( $P = 0.03$ ) (54).

Similar studies with other preparations of 5-ASA, especially the new formulations, are required to demonstrate whether combination oral-rectal therapy offers benefit. Whether such combination therapy offers advantage over simply increasing the dose of oral preparation also requires further study.

#### Rectal 5-ASA therapy

Foam and gel preparations are generally better tolerated than liquid enemas. Adherence requires motivation and some training, as well as choice of the most appropriate delivery device. Increased dosing regimens do not generally enhance the benefit of rectal delivery and once-daily is sufficient. Inflammation at the distal rectum may require the use of a 5-ASA suppository.

**TABLE 3**  
**Treatment approach in ulcerative colitis using 5-aminosalicylic acid (5-ASA)**

Induction of remission
Mild extensive: Oral 5-ASA + rectal 5-ASA
Mild distal: Rectal 5-ASA
Moderate extensive: High dose 5-ASA + rectal 5-ASA for 2 weeks; if unresponsive, start steroids
Moderate distal: Rectal 5-ASA + oral 5-ASA, or rectal 5-ASA + rectal steroids
Maintenance of remission
Once-daily regimen for convenience in all patients
Distal disease: Maintenance rectal 5-ASA

## CONCLUSIONS

Mesalazine, mesalamine or 5-ASA are the first-line therapy for patients with mild to moderate UC and remain the mainstay of maintenance therapy. Current delivery formulations, such as oral and rectal 5-ASA, present many limitations including inconvenience, poor-adherence dosing (number of tablets) and dose frequency (three to four times daily dosing), lack of efficacy in all types of UC and CD, and poor patient acceptability. Therefore, twice-daily dosing is common and once-daily dosing is now a reality. The use of 5-ASA preparations in the management of UC is summarized in Table 3.

Nonadherence to a prescribed regimen of 5-ASA has been shown to dramatically increase the risk of relapse, resulting in decreased quality of life and increased health care and personal costs. Adherence to 5-ASA therapy has also been associated with a possibly reduced risk of CRC. Indeed, the benefit of 5-ASA in the primary prevention of dysplasia and CRC in UC has been established and generally accepted despite the lack of double-blind, randomized studies.

New formulations of mesalazine have been developed and show promise in improving compliance and efficacy. These new 5-ASA formulations, with less frequent or once-daily administration, and with different delivery systems include micropellet and MMX oral formulations, as well as rectal gel and once-daily suppository formulations, have demonstrated efficacy in active mild to moderately active UC and in the maintenance of remission. Although more robust evidence is necessary, it is likely that 5-ASA preparations will be widely used for chemoprevention of CRC in UC and, as such, probably should also be used in colonic CD. Several studies have also demonstrated that these novel formulations are safe, offer a simplified dose regimen, and result in improved quality of life and possibly compliance in patients, with pharmacoeconomic benefits. In the future, new 5-ASA preparations with more effective PPAR-gamma modulation are anticipated. It is likely that higher doses of the new formulations will be tested again for efficacy in CD as well.

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