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REVIEW

Pharmacotherapy of Ulcerative Colitis: What Role for Mesalamine?

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Abstract: Goals of treatment for ulcerative colitis (UC) include inducing remission, reducing symptom burden, and maintaining disease quiescence. Mesalamine is indicated for the management of mild to moderate ulcerative colitis. There are various dosages, formulations, and mechanisms of delivery that are efficacious and currently utilized in the treatment of UC. Mesalamine therapy (formulation and dosage) should be tailored on an individual basis depending on extent and severity of disease. Newer delivery systems can consolidate dosing regimens and possibly increase compliance. In general, mesalamine has been well tolerated with minimal side effects. In addition, mesalamine has been postulated to play a role in the chemoprophylaxis of colon cancer in patients with ulcerative colitis.

Keywords: ulcerative colitis, mesalamine, delivery systems

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Introduction

Current treatments for ulcerative colitis (UC) are aimed at inducing remission, reducing symptom burden, and maintaining disease quiescence. Mesalamine, in particular, has a crucial role in the management of UC; however, the form of medication, the type of mesalamine delivery system used, and the dosage of mesalamine necessary are important factors which need to be determined on an individual basis depending on the severity and extent of disease present (proctitis, proctosigmoiditis, left-sided colitis, extensive/pancolitis). Patients with mild to moderate UC have the best results with mesalamine for both induction and maintenance therapy. Patients with severe UC should be initially treated with other medications including corticosteroids, immunomodulators, or biologic therapies to induce a remission. Once the patient is significantly improved, mesalamine may be useful in maintenance of remission. Here, we review the data for the role of mesalamine in UC.

Mechanism of Action

Sulfasalazine and mesalamine (5-aminosalicylic acid) have become the core treatments for the management of mild to moderately active UC. Sulfasalazine is available in an oral tablet form while mesalamine is available in a number of oral and rectal (topical) formulations including tablets, micropellets, suppositories, and enemas.

The exact mechanism of action of mesalamine is not fully understood, however, it is believed that the compound acts topically via a direct effect on the colonic mucosa. Many studies have attempted to isolate the underlying mechanism of action, and it appears that there is a multifactorial effect of the 5-ASA medications.[1] These effects are primarily due to the anti-inflammatory and immunosuppressive properties of 5-ASA. These properties include the following: inhibition of prostaglandin and leukotriene synthesis (via inhibition of cyclooxygenase and lipoxygenase respectively), free radical scavenging as a biologic antioxidant, immunosuppressive activity (via inhibition of T-cell proliferation, activation, and differentiation), impairment of white cell adhesion and function (via inhibition of the enzyme aminoimidazolecarboxamidoribonucleotide (AICAR) transformylase), inhibition of proinflammatory cytokine synthesis (IL-1, tumor necrosis factor alpha (TNFα)), and activation of the peroxisome proliferator-activated receptor-gamma (PPAR-γ). PPAR-γ is known to be involved in UC inflammation, and it appears that 5-ASA can act as a synthetic agonist at the PPAR-γ binding site.[2,3]

Free 5-ASA is almost completely absorbed into the systemic circulation at which point it is extensively metabolized and excreted.[3] The development of 5-ASA formulations has thus focused on maximizing delivery to the sites of inflammation in the colonic mucosa while minimizing systemic absorption from the small intestine.[1,5] The first formulation used in the treatment of UC was sulfasalazine (Azulfidine). Sulfasalazine consists of an antibacterial component, sulfapyridine, bonded by an azo bond to a salicylate (5-ASA). Although there is partial absorption in the jejunum, the majority (approximately 90%) of absorption occurs in the colon, where the parent drug is reduced by the bacterial enzyme azoreductase to sulfapyridine and 5-ASA.[6] Coliform bacteria are necessary to produce azo-reductase; therefore, sulfasalazine is primarily active in patients with colonic disease. The free sulfapyridine moiety has been shown to be associated with a number of dose-dependent adverse effects, particularly headache, nausea, dyspepsia, and several non-dose dependent reactions including allergy, agranulocytosis, and aplastic anemia.[5,7] Therefore, other formulations and controlled-release systems were developed to deliver 5-ASA directly to the colon without the sulfapyridine moiety.

Formulations

There have been two main strategies to accomplish this direct colonic delivery: the use of azo-bonded pro-drugs and the use of pH dependent delayed and/or controlled release formulations. In azo-bonded pro-drugs, the 5-ASA is bonded to non-sulfur containing moieties which are inert and produce few side effects. Olsalazine (Dipentum) is a 5-ASA dimer linked by an azo bond whereas balsalazide (Colazal) is a 5-ASA monomer linked to an inert, non-absorbable benzoic acid derivative, 4-aminobenzoyl-B-alanine.[8] Like sulfasalazine, these formulations depend on the bacterial azoreductase produced by the colonic flora to cleave the azo bond. Consequently, these medicines, too, are primarily active in the colon. Although linking 5-ASA to itself would seem to be a good delivery

Table 1. Overview of mesalamine formulations.

Generic name	Trade name	Mechanism of delivery	Mechanism of action	Release location	Tablet size	Daily dose	Average Wholesale Price (AWP)^	AWP per day
Sulfasalazine	Azulfidine	5-ASA azo bond to sulfapyridine	Reduction by colonic bacterial enzyme azoreductase to sulfapyridine and 5-ASA	Colon	500 mg	1–4 g/day divided BID	$0.19 per tablet	$0.38–$1.52
Mesalamine	Pentasa	Timed release	Moisture sensitive, ethycellulose-coated microgranules which results in a pH independent, controlled release formulation	Small bowl, colon	500 mg	2–4 g/day divided QID*	$2.74 per capsule	$10.96–$21.92 per day
	Asacol	pH > 7	Enteric coated, acrylic-based resin (Eudragit S) that dissolves at a pH of 7 or greater	Terminal ileum, colon	400 mg	1.6–4.8 g/day divided TID*	$1.77 per tablet	$7.08–$21.24
	Asacol HD	pH > 7	Enteric coated, acrylic-based resin (Eudragit S) that dissolves at a pH of 7 or greater	Terminal ileum, colon	800 mg	4.8 g/day divided TID*	$3.70 per tablet	$22.20
	Lialda	MMX, pH > 7	Core of liphophilic and hydrophilic matrices which are encapsulated in a pH 7 dependent enteric coating	Colon	1.2 g	2.4–4.8 g/day Once Daily	$5.37 per tablet	$10.74–$21.48
	Apriso	Granules, pH > 6	Release from an enteric coating at a pH of 6 via a proprietary extended–release mechanism	Colon	375 mg	1.5 g /day Once Daily	$2.06 per capsule	$8.24
	Rowasa	Enema	Topical	Rectum, sigmoid	4 g/60 mL	4 g/day	$12.86 per enema	$12.86
	Canasa	Suppository	Topical	Rectum	1000 mg	1 g/day	$14.27 per suppository	$14.27
Balsalazide	Colazal	5-ASA azo bond to inert carrier	Reduction by colonic bacterial enzyme azoreductase	Colon	750 mg	6.75 g/day divided TID*	$1.60 per capsule	$14.40
Olsalazine	Dipentum	5-ASA azo bond to 5-ASA	Reduction by colonic bacterial enzyme azoreductase	Colon	250 mg	1–3 g/day divided BID	$2.30 per capsule	$9.20–$27.60

*Many clinicians use BID dosing to increase adherence. ^Prices obtained from local pharmacies. Generic prices listed where available.
*Actual prices may vary depending on pharmacy coverage benefits and co-pays.

strategy, the resulting molecule can cause diarrhea in some patients, thus limiting its use.

Another strategy used to overcome absorption of 5-ASA in the proximal GI tract is the use of delayed and controlled release formulations of mesalamine. The primary mechanism in utilizing a delayed release formulation is the use of an enteric coated, acrylic-based resin (Eudragit S) that dissolves at a pH of 7 or greater (normally in the terminal ileum).[1] This results in drug delivery to the distal small bowel and colon. Such formulations include Asacol, Salofalk, and Salofalk GranuStix.

Pentasa utilizes moisture sensitive, ethylcellulose-coated microgranules to provide a compound which results in a pH independent, controlled release formulation. Pentasa starts releasing 5-ASA in the duodenum and continues throughout the entire GI tract. Approximately 50% of the mesalamine is released in the small bowel, whereas the remainder is released in the colon.[1,6]

Newer formulations of mesalamine have continued to be developed. Recent technologies have been utilized to address the problem of bolus release with traditional pH-dependent mesalamine formulations. Multimatrix mesalamine tablets (MMX), marketed as Lialda, is a formulation that consists of a core of liphophilic and hydrophilic matrices which are encapsulated in a pH 7 dependent enteric coating. This coating ensures delayed release of the active drug until the terminal ileum, whereas the matrices provide for consistent delivery of 5-ASA throughout the entire colon.[1,9] Lialda also has the benefit of being a high dose, once daily formulation.

Apriso, another formulation which is comprised of extended-release mesalamine granules, is formulated to release from an enteric coating at a pH of 6. This allows delivery to the terminal ileum and colon via a proprietary extended–release mechanism (Intellicor). The outer enteric coating (Eudragit L) dissolves at a pH of 6. 5-ASA containing granules within the coating then swell, allowing for gradual and sustained exposure of the 5-ASA throughout the entire colon.[10]

Pill burden and size can be deterrents to compliance. Many 5-ASA products can be given in twice daily or once daily dosing without losing efficacy. Azo-bonded 5-ASA products and Pentasa can be crushed without affecting delivery profile. Lialda and Asacol HD are relatively large pills and can be difficult for some patients to swallow.

A number of topical therapies including enemas, suppositories, and foams have been developed to deliver mesalamine directly to the distal colon. These therapies are indicated for those patients with active distal UC. The use of enemas allows delivery up to the level of the proximal descending colon, while the use of suppositories can be utilized to treat disease up to 15 to 20 cm from the anal verge. Although efficacious, patients have reported dislike of the rectal formulations secondary to mode of administration, discomfort, retention, and leakage.[5,11,12]

Adverse Effects

As previously noted, sulfasalazine has been associated with various side effects. Dose escalation in particular is limited by hypersensitivity and intolerance to the sulfapyridine moiety. Approximately 15% of patients on sulfasalazine ultimately discontinue the medication secondary to adverse effects.[6] Dose related side effects include nausea, vomiting, dyspepsia, anorexia, and headache.[13,14] Serious complications are rare, and have included agranulocytosis or aplastic anemia (typically occurring in the first two months of therapy), pancreatitis, hepatitis, drug induced connective tissue disease, nephrotoxicity, interstitial nephritis, and reversible abnormal sperm counts or morphology.[6,15] Men should be notified about this effect on sperm; if they plan on conceiving a child, the sulfasalazine should be switched to a mesalamine product at least three months before attempting conception. Additionally, sulfasalazine may impair folate absorption via competitive inhibition of the jejunal enzyme, folate conjugase.[6] Therefore, patients on sulfasalazine should be prescribed folate supplementation of 1 mg/day and 2 mg/day if pregnant.

The tolerability of the various 5-ASA's is known to be broadly similar. They are generally well tolerated, and approximately 80% of those who are unable to take sulfasalazine can use oral mesalamine formulations without complication.[13] Non-dose related side effects for non-sulfur containing 5-ASA's tend to be nausea and headache. Of note, colitis, abdominal pain, and diarrhea can worsen on mesalamine, and in these cases, patients should stop taking the medication. There does not appear to be significant dose dependent toxicity associated with oral mesalamine preparations. There have been, however, rare case reports of nephritis, pancreatitis, pericarditis, pulmonary vasculitis and

pulmonary cavitary nodules, Kawasaki-like syndrome, pneumonitis, and serum sickness-like reaction.[15,16] Although the risk of nephrotoxicity or interstitial nephritis is uncommon, it is suggested that urinalysis and monitoring of the plasma creatinine should be done in the first few months of therapy. Subsequently, a yearly creatinine and urinalysis are recommended.[17,18] Additionally, olsalazine has been associated with diarrhea secondary to its potential to cause chloride secretion in the terminal ileum.[19] The MMX mesalamine formulation has been found to be well tolerated thus far. The adverse-event profile of MMX mesalamine was found to be similar to that reported for placebo in the induction studies.[20,21] The most common treatment related adverse effects were headache, flatulence, and abdominal pain.[22]

Mesalamine and Pregnancy

Sulfasalazine, oral mesalamine, balsalazide, and topical mesalamine are category B and felt to be safe for use when indicated during pregnancy and breastfeeding. The incidence of decreased birth weight, spontaneous abortion, stillbirths, prematurity, or birth defects is similar in children born to mothers taking sulfasalazine compared to the general population.[23] As previously mentioned, it is recommended that patients who are taking sulfasalazine during pregnancy should be on folate supplementation of 2 mg/day. There is limited data on olsalazine (category C) in pregnancy; therefore, an alternate 5-ASA formulation should be chosen.

Treatment of Ulcerative Colitis

Distal colitis

Mesalamine has an integral role in treating UC, and the formulation and dose of mesalamine are important considerations for every patient. Rectally administered 5-ASA preparations are mainstays of effective therapy for ulcerative proctitis and for proctosigmoiditis.[24–26] There are multiple forms of rectal 5-ASA formulations including suppositories, gels, foams, and enemas which are useful in distal disease. Rectal 5-ASA medications have been proven effective in multiple trials with comparison to both placebo and rectal corticosteroids. A large meta-analysis compared rectal 5-ASA with placebo and found a pooled odds ratio favoring rectal 5-ASA for inducing symptomatic, endoscopic, and histologic remission in distal UC (OR 7.71, 6.55, and 6.91 respectively).[27] Of note, the studies in this meta-analysis included both 5-ASA suppositories as well as 5-ASA enemas at varying doses. In terms of the enema dosing, there has not been a dose response effect found in studies of 1 g, 2 g, and 4 g 5-ASA enemas. The conclusion is that the 1 g/day 5-ASA enema is sufficient for treating mild to moderate distal disease.[28]

Small studies have been performed analyzing 5-ASA suppositories versus 5-ASA enemas in patients with ulcerative proctitis.[29,30] There were no differences found in efficacy between the two formulations, though patients did prefer the suppository to the enema. The combination of efficacy, safety, and ease of use has resulted in mesalamine suppositories becoming the preferred treatment for treating active ulcerative proctitis and subsequently maintaining remission.

Oral corticosteroids have long been used in the treatment of moderate to severe pancolitis. Rectal corticosteroids, on the other hand, have been used for distal inflammation. However, compared with topical corticosteroids, rectally administered 5-ASA's were significantly more likely to induce symptomatic remission, with an odds ratio of 2.42.[27] Rectal 5-ASA was superior to rectal corticosteroids in clinical, endoscopic, and histological remission. Mesalamine foams have also been compared to corticosteroid rectal foams for patients with distal UC and have shown improvement in clinical symptoms including rectal bleeding.[31]

Rectal 5-ASA medications have also been compared with oral 5-ASA medicines in the treatment of distal UC and ulcerative proctitis. Gionchetti et al. compared Asacol 2.4 g/day with 5-ASA suppository in patients with active ulcerative proctitis.[32] In this four week study, patients had a greater improvement in the disease activity index (DAI) while taking the suppositories and also had improved clinical, endoscopic, and histologic remission. The DAI is a qualitative rating scale measuring stool frequency, rectal bleeding, mucosal appearance, and physician's rating of disease severity, scored from 0 (normal) to 3 (severe). Because rectally administered 5-ASA is poorly absorbable, it delivers a high level of medication to the appropriate site. Another benefit to rectal 5-ASA is that adverse event rates are almost half compared with oral 5-ASA.[29]

Rectal 5-ASA can not only induce remission in distal UC compared to placebo, rectal corticosteroids,

and oral mesalamine, but can also maintain remission in these patients.[33] Four trials have found 5-ASA enemas and suppositories to be superior to placebo in treating distal UC and a pooled odds ratio of 5.6 was found for maintaining remission.[34–37] The dosing of suppositories was optimal at 1 g/day, but no difference was found amongst the different enema strengths (1 to 4 grams).[27]

Left-sided Colitis

As shown previously, rectal 5-ASA medications are core therapies for induction of remission in ulcerative proctitis and proctosigmoiditis. However, UC can extend proximally and may require different treatment regimens depending on disease extent. 5-ASA suppositories are generally effective at treating the distal 20 cm (rectum and distal sigmoid), while 5-ASA enemas can treat UC up to the splenic flexure. Safdi et al. compared rectal mesalamine enema (Rowasa 4 g/day) versus oral mesalamine tablets (800 mg orally three times daily) versus combination therapy of mesalamine enema and mesalamine tablets in patients with UC which extended to less than 50 cm and had a DAI score of 4–10.[38] Sixty patients were enrolled in this six week double-blind study in which endoscopic and clinical data was collected. At week six, combination therapy produced a greater improvement in total DAI scores (−5.2) than did the mesalamine enema (−4.4) or mesalamine tablets (−3.9) alone. Similar differences had also been seen at week three of the study. Combination-therapy patients also reported an absence of bloody stools significantly sooner than the other individual groups. Thus, for those patients with left-sided mild to moderate UC, a combination of oral mesalamine tablets and mesalamine enemas is recommended to induce remission. Oral therapy may then be used alone to maintain remission.

Extensive Colitis

In those patients with mild to moderate UC whose disease extends proximal to the splenic flexure, oral formulations of mesalamine are standard of care. Sulfasalazine was the first medication discovered, and it provided efficacy in treating patients with mild to moderate UC. Given the propensity for side effects due to sulfasalazine, oral mesalamine has been used preferentially. In these patients, rectal mesalamine can be used in an adjunctive role, as the symptoms of diarrhea and tenesmus are often due to the left-sided disease component. Combination therapy has been shown to be effective in patients with mild to moderate extensive colitis at inducing remission.[39] In a meta-analysis, non-sulfur containing 5-ASA therapies showed a trend toward improved therapeutic benefit versus sulfasalazine for the induction of remission;[40] however, a different meta-analysis found sulfasalazine to be more effective than other 5-ASA medications for maintenance of clinical or endoscopic remission.[41] In general, sulfasalazine and 5-ASA medications are thought to have similar efficacy.[29]

Oral therapy with mesalamine is the mainstay of treatment for maintenance therapy in patients with extensive colitis. Despite the variety of delivery mechanisms employed in the oral formulations, the results of the clinical trials have shown the efficacy of oral medications to be broadly similar, with success in anywhere from 40%–80% of patients.[29] The studies comparing the 5-ASA medications have generally provided mixed results. For example, in one study, balsalazide was found to be slightly more efficacious than Asacol in patients with mild to moderate, active, UC, but two subsequent trials were unable to confirm these findings.[42,43] The clinical response ranges from 50 to 71 percent with olsalazine (2 to 3 g/day), Asacol (2.4 to 4.8 g/day), and Pentasa (2 to 4 g/day).[40,44] Generally, the oral medications begin to work in two to four weeks.

Dosing

There is some debate if there is a dose response effect with 5-ASA. Early studies illustrated that this was indeed the case. One small study of 87 patients with mild to moderate UC demonstrated that Asacol at 4.8 g/day was more effective than 1.6 g/day over a six week trial period.[45] Similarly a dose-response study with Pentasa found that doses up to 4 g/day were more effective than lower doses. The ASCEND (Assessing the Safety and Clinical Efficacy of a New Dose) trials attempted to elucidate this point further. In ASCEND I, 301 patients with mild to moderate UC were enrolled in a six week double-blind study in which patients were randomized to groups of mesalamine 2.4 g/day or 4.8 g/day.[46] Endoscopic and clinical data was obtained throughout the course of the study as well as

via a Physician Global Assessment score (PGA). The PGA was a composite score based on stool frequency, rectal bleeding, patient functional assessment, and endoscopic findings. Quiescent disease was scored as 0, mild (1), moderate (2), or severe (3). A predetermined subgroup analysis was planned to assess those with moderate disease. Treatment success was not found to be statistically different between the two dosage groups (51% of the 2.4 g/day group and 56% of the 4.8 g/day group reached the efficacy end point). In the previously mentioned subgroup analysis, the 4.8 g/day was more effective. Fifty-seven percent of patients given 2.4 g/day and 72% of the 4.8 g/day group achieved treatment success.

In ASCEND II, 386 patients with mild to moderate UC were randomized to mesalamine 2.4 g/day or 4.8 g/day.[47] The primary study population for ASCEND II was the 268 patients with moderate disease who had been randomized to the two drug dosage groups. Seventy-two percent of patients with moderate UC in the 4.8 g/day group compared with 59% of patients with moderate UC in the 2.4 g/day group achieved clinical remission ($p = 0.036$). Thus, the optimal dosing of oral mesalamine depends on extent and severity of disease, as patients with mild disease did well on low dose (2.4 g/day) while those with moderate UC did significantly better with higher dose mesalamine therapy.

The ASCEND III trial studied mesalamine 2.4 g/day versus 4.8 g/day for the treatment of moderately active UC.[48] The design was a non-inferiority study with a primary endpoint of treatment success defined as overall clinical improvement at week six. Seven hundred seventy patients were randomized in a 1:1 ratio to receive the delayed release mesalamine tablets. At week six, 70.2% of patients receiving 4.8 g/day achieved treatment success compared with 65.5% of those who received 2.4 g/day, thus showing no significant difference between the two groups. However, the study found that significantly more patients who received 4.8 g/day compared to 2.4 g/day achieved clinical remission at week three ($p = 0.02$) and week six ($p = 0.04$). Subgroup analyses determined that those with previously difficult to treat UC may do better with 4.8 g/day. In particular, those treated in the past with corticosteroids ($p = 0.05$) or multiple UC medications ($p = 0.01$) showed better improvement with the 4.8 g/day dosing.

Newer Formulations

Clearly mesalamine has a primary role in treating patients with mild to moderate UC, however, compliance has proven to be an important issue given the pill burden. Newly developed mesalamine formulations have attempted to decrease this pill burden, with a goal of improving compliance, and consequently improving symptoms. The Multi Matrix System technology is featured in a delayed-release mesalamine (Lialda). Two randomized double-blind trials were originally completed to prove the efficacy of the new drug.[22] The first compared MMX mesalamine1.2 g twice daily and 4.8 g daily versus placebo for eight weeks for the induction and remission of 280 patients with mild to moderate UC.[20] Both drug groups in this study achieved statistically significant clinical and endoscopic remission compared with placebo (34.1% and 29.2% vs. 12.9%, 2.4 g/day and 4.8 g/day vs. placebo respectively). The second Phase III trial was a randomized double-blind placebo controlled study which assessed 343 patients with active mild to moderate UC, comparing MMX 2.4 g once daily, MMX 4.8 g once daily, Asacol 800 mg three times daily, or placebo.[21] The primary endpoint (clinical and endoscopic remission) at week eight was achieved significantly more often in both MMX groups compared with placebo (40.5 and 41.2% for 2.4 g daily MMX and 4.8 g daily respectively versus 22.1% for placebo). The Asacol group achieved clinical and endoscopic remission in 33 percent of patients, although this was not statistically significant compared with placebo ($p = 0.124$). Neither of these studies suggested a dose-response benefit. Subgroup analyses of these studies have shown that MMX mesalamine was effective, irrespective of disease extent, disease severity, gender, and previous low dose 5-ASA usage. One year follow up studies have shown that MMX mesalamine is effective for maintenance therapy.[49,50] A recent post-hoc analysis studied the MMX mesalamine and its efficacy in both induction and maintenance therapy, as there was an overlap of patients in both trials.[51] This study followed the original patients with active disease through induction therapy (and if necessary, through an extension of induction therapy) and/or maintenance therapy. The study concluded 63.6% of patients who start MMX mesalamine therapy can achieve remission after eight to sixteen weeks of therapy (for some patients, a dose escalation was necessary from 2.4 g

daily to 4.8 g daily). After one year of maintenance therapy, 89.9% of patients were relapse-free. Overall, the study concluded that 56.6% of patients who started MMX mesalamine therapy achieved and maintained remission for twelve months.[52]

Salofalk granules is another once-daily preparation that can be used to induce a remission in mild to moderate UC. Three hundred eighty patients were randomized to receive 3 g/day mesalamine granules once daily or three times daily. Comparable clinical efficacy and remission was obtained between the two groups of patients (remission rates > 70%).[22] Other Phase III studies showed that the efficacy of 3 g/day mesalamine granules was not affected by gender, duration of disease, disease location, or disease duration.[53] Salofalk has also been shown to maintain remission in mild to moderate UC. Six hundred forty-seven patients were randomized to 3 g daily, 1.5 g daily, and 0.5 g three times daily. All of the regimens maintained remission at one year (74.7%, 60.8%, and 68.8% respectively).[54]

A new formulation of balsalazide (5-ASA azo bonded to an inert carrier molecule) was recently studied in patients with mild to moderately active UC.[55] Patients had a Modified Mayo Disease Activity Index (MMDAI) scale between 6 and 10 (with a subscale rating of 2 or greater for rectal bleeding) and were randomized to receive 3.3 g of balsalazide twice daily (6.6 g per day total) or placebo. The primary end point studied was the proportion of patients achieving clinical improvement (>3 point improvement in MMDAI and >1 point improvement in rectal bleeding) after eight weeks of therapy. Two hundred forty-nine patients were randomized to balsalazide or placebo in a 2:1 format. Fifty-five percent in the treatment group versus 40% in the placebo group ($p = 0.02$) achieved overall clinical improvement and specific improvement in rectal bleeding.

Chemoprophylaxis

Besides its role in induction of remission and maintenance of therapy for patients with mild to moderate UC, mesalamine has also been suggested to have a role in chemoprophylaxis for patients with UC. The incidence of colorectal cancer (CRC) is increased in patients with UC, with an overall prevalence of CRC in patients with UC at 3.7%, and a prevalence of 5.4% in those with pancolitis. Risk for patients with UC is a function of duration of disease (risk is 2% at 10 years of disease, 8% at 20 years of disease, and 18% at 30 years of disease).[56] Several other risk factors for CRC (besides duration of disease) have been identified and include extent as well as activity of disease, family history of CRC, primary sclerosing cholangitis, young age at diagnosis, and previous history of adenoma or cancer.[57] Current cancer prevention strategies rely on regular colonoscopy, detection of dysplasia on mucosal biopsies, and proctocolectomy if dysplasia/neoplasia is detected. Chemoprophylaxis with medications has been a source of increasing interest due to the limitations from these previous strategies.

However, the data investigating mesalamine is lacking in the form of large, prospective randomized placebo-controlled studies. This is, in part, due to ethical constraints. Also, an extremely large sample size of patients would be needed given the incidence of CRC in UC patients, and the time (in years) would be substantial.[58] Therefore, the data regarding mesalamine and chemoprophylaxis derives from retrospective and observational studies. A meta-analysis was performed in 2005 by Velayos et al. to determine the effect of mesalamine on CRC.[56] Nine studies (three cohort and six case-control) were found which met the criteria of evaluating and defining exposure to mesalamine in UC patients. In all, 1,932 patients with 334 cases of CRC and 140 cases of dysplasia were studied. Use of 5-ASA was significantly associated with a lower risk of CRC (OR 0.51) as well as with CRC and dysplasia combined (OR 0.51). There was no benefit for the endpoint of dysplasia alone, though. The meta-analysis did find a dose response effect for mesalamine and chemoprevention, as a minimum dose of 1.2 g/day was found to lower the risk of CRC or dysplasia (OR 0.37). A subsequent, small case control study in 2006 compared patients with chronic UC that developed dysplasia with chronic UC patients who did not.[59] Despite the small sample size, there was a reduction in cancer risk with a dose of at least 1.2 g mesalamine per day.

The specific pathophysiology of mesalamine in chemoprevention is unknown, as mesalamine affects multiple pathways which could potentially play a role. Proposed mechanisms include modulation of inflammatory cytokine production, inhibition of cyclooxygenase, inhibition of inducible

nitric oxide synthase, inhibition of nuclear factor kappa β (a transcription factor for multiple genes involved in inflammatory responses and promotion of carcinogenesis via blockade of apoptosis), activation of peroxisome proliferator-activated receptor-γ, and antimicrobial action.[60] 5-ASA's also have antioxidant and free radical scavenger properties that reduce DNA oxidative stress and microsatellite instability.[56]

Despite the observational studies and the likely pathophysiological mechanisms, we do not have conclusive clinical evidence that mesalamine reduces CRC. More studies are needed to assess the dose, duration, and frequency of therapy as well as the indication for mesalamine in those patients with UC on different forms of treatment (biologics or immunomodulators).

Compliance

Clearly mesalamine is effective for mild to moderate UC. However, an important risk factor for UC flares is non-compliance with medication. Rectal formulations are sometimes difficult to tolerate, as they have side effects including anal leakage, burning sensation, and bloating.[5] These delivery mechanisms, while effective, can be intrusive for newly diagnosed young adults who are likely establishing independence as well as personal and intimate relationships at this time in their lives. In terms of oral medications, the inconvenience of frequent daily dosing, in conjunction with the amount of capsules/tablets necessary per day have been identified as key factors in reducing patient compliance with therapy in UC.[61] Patients may find it difficult to be compliant with multiple medications particularly when they are having no symptoms. In fact, male gender, single status, full-time employment, and three times daily dosing have all been identified as independent predictors of non-compliance.[5] Several studies have been performed studying the rates of non-compliance and its impact on disease. One observational study of 94 patients with quiescent UC found that 60% failed to adhere to their prescribed regimen. An average consumption was found to be 70% of the prescribed dosage.[62] Another study prospectively followed 99 patients with quiescent UC for two years and monitored compliance and relapse rates.[63] Compliant patients were more likely to remain in remission than non-compliant patients (89% vs. 39%, $p < 0.001$). Patients who were not adherent had a five-fold greater risk of recurrence than adherent patients (hazard ratio 5.5). In this study, the majority of non-adherent patients cited forgetfulness as the primary cause, while others reported that the number of pills was "too many."

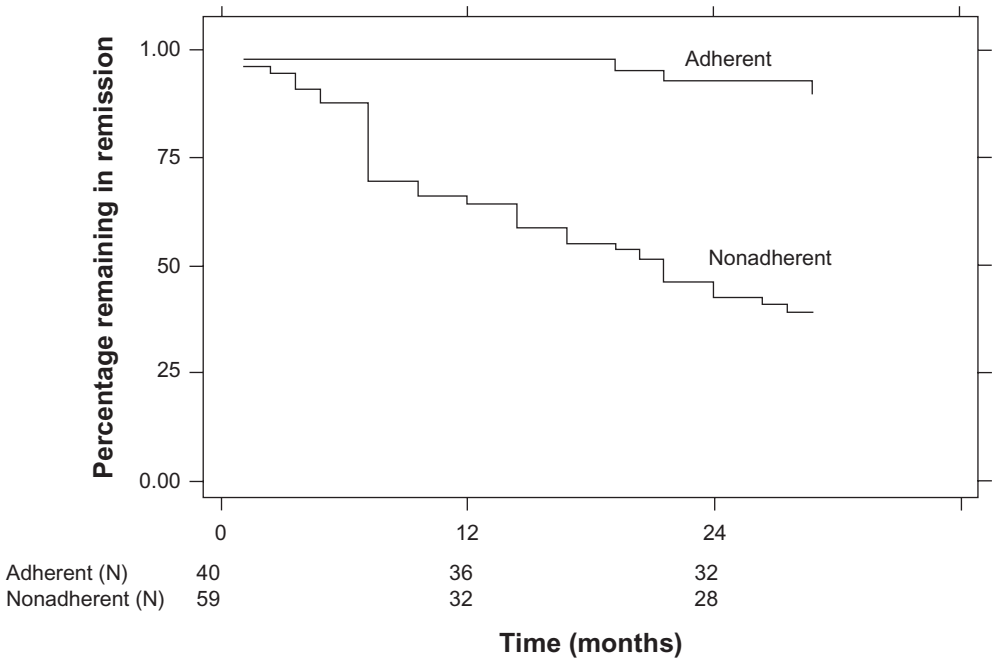

Figure 1. Non-adherence rates and clinical recurrence at 24 monts.
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Cost

Given that UC can be a lifelong condition, the cost of mesalamine must be taken into consideration. This cost is not only measured in pure dollars, but must also take into account quality of life in remission or while flaring along with possible costs and interventions prevented by maintenance therapy. A cost-effectiveness ratio was performed using a Markov model, attempting to compare two disease maintenance strategies over a two year period: 1) no maintenance on 5-ASA, but 5-ASA 4.8 g/day given for flares, 2) maintenance 5-ASA of 2.4 g/day, escalated and maintained at 4.8 g/day after the first flare. In the study, failure to induce remission led to other theoretical treatments such as systemic steroids, biologic therapy, immunomodulator therapy, and surgery.[64] This theoretical model did conclude that 5-ASA therapy decreases the risk of UC flares, but found that the cost of this disease maintenance may be considerable. Multiple assumptions were made to construct the model, and the authors admit that the cost of the quality adjusted life year (QALY) gained is highly dependent on the quality of life during flares of disease, as well as the quality of life experienced during disease remission (while both on or off the 5-ASA medication). The authors concluded that sulfasalazine may be a more cost-effective measure to maintain disease quiescence given its similar efficacy and reduced cost. Admittedly, though, the authors state that the inability to tolerate sulfasalazine is likely to be a significant limiting factor. Another limitation to the model included the inability to account for possible chemoprophylactic properties of 5-ASA medication. Definitive data of chemoprotective benefit would clearly improve the cost-effectiveness of the 5-ASA's.

It is believed, though, that the 5-ASA medications are plausible chemoprotective agents given the observational studies and in-vitro and in-vivo data.[65] Rubenstein et al. performed a Markov model to study the cost-effectiveness of colonoscopic surveillance in the setting of 5-ASA use. The study found that 5-ASA use alone prevented 49% of CRC and that endoscopic surveillance could likely be decreased to every two years as opposed to annually, which could decrease cost, burden on the patients, and need for endoscopic resources. This recommendation, however, is dependent on 5-ASA being efficacious for chemoprevention.

Conclusion

In conclusion, the role of mesalamine is to induce and maintain remission in mild to moderate UC. The specific formulation of mesalamine chosen depends on the location and extent of disease. There are multiple oral formulations with different delivery systems; however all appear to be equally efficacious. Topical 5-ASA's should be used as first-line therapy in distal disease. Combination therapy with oral and topical therapy leads to faster symptom resolution. Higher doses of 5-ASA appear to be better than lower doses in moderate and extensive disease whereas lower doses seem to be as good as higher doses in mild disease. The 5-ASA's have a better safety profile compared to sulfasalazine but are not more efficacious. These drugs are overall well-tolerated with minimal side effects. Newer delivery systems can consolidate dosing regimens and possibly improve compliance. While the evidence supporting mesalamine for therapy in UC is clear and robust, more studies are needed studying the chemoprophylactic properties of mesalamine for the prevention of colon cancer in patients with UC.

Disclosures

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