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Mesalamine in the treatment and maintenance of remission of ulcerative colitis

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Abstract

Ulcerative colitis (UC) is a chronic disease of the GI tract that is characterized by mucosal inflammation in the colon. Mesalamine (mesalazine) is a 5-aminosalicylic acid compound that is the first-line treatment for patients with mild-to-moderate UC. There are multiple formulations of mesalamine available, primarily differentiated by their means of delivering active mesalamine to the colon. Mesalamine has been demonstrated in randomized controlled trials to induce both clinical response and remission, and maintain clinical remission, in these patients. It has few serious adverse effects and is generally well tolerated by patients. The main areas of uncertainty with use of mesalamine in patients with UC center on the optimal dose for induction of response, how to maintain patient adherence and the role of mesalamine in cancer chemoprophylaxis. Generic forms of mesalamine have yet to be approved by regulatory bodies in the USA.

Keywords

5-ASA; inflammatory bowel disease; mesalamine; ulcerative colitis

Ulcerative colitis (UC) is a chronic inflammatory disorder of the GI tract of unknown etiology. It most commonly affects teenagers and young adults, but can occur in any age group. It has a prevalence of 238 per 100,000 in the US adult population and an incidence rate of 2.2–14.3 cases per 100,000 person-years in North America [1]. The clinical course for patients with UC is one that follows a relapsing and remitting course, with symptoms of bloody diarrhea, rectal urgency and abdominal pain [2]. Diffuse mucosal inflammation involves the rectum in 95% of cases, and may extend proximally, involving parts, or all, of the colon [3]. In addition, patients may suffer from extraintestinal manifestations of UC, including episcleritis, scleritis, uveitis, peripheral arthropathies of small and large joints, erythema nodosum, pyoderma gangrenosum, axial arthropathies, sacroilitis, ankylosing spondylitis and primary sclerosing cholangitis. There is an increased risk for colorectal cancer (CRC) with longstanding inflammation, with risks reported as being 0.5–1% per year [4].

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Treatment options for patients with UC involve either chronic medical therapy to suppress intestinal inflammation or a colectomy (surgical removal of the colon) to remove the diseased organ [5]. Medical options are divided into agents used to achieve a clinical response and remission (induction agents), and those used to maintain clinical remission (maintenance agents), although some agents can be used for both situations. Since there is no known 'cure' for UC, most patients take maintenance medical therapy to prevent disease relapse. Colectomy is reserved for those with disease refractory to medical therapy or those who develop complications. Medical management usually involves a 'step-up' approach, starting with topical or oral agents, and ascending to more complex agents, with risk of more serious adverse effects, in those who do not respond to first-line agents [2].

The type and formulation of therapy recommended for patients with UC is dependent on both the location of the disease and the degree of severity. In some patients, the inflammation is limited to the rectum only (distal), but other affected individuals have colonic disease that extends along the length of much of the colon (extensive). Topical (rectal) therapy is the starting point for patients with disease limited to the left colon, with oral therapy added on in patients with more extensive disease [2]. For active distal (rectum and sigmoid colon) disease, the US and European professional bodies recommend topical therapy with mesalamine, hydrocortisone or budesonide [2,6]. Oral mesalamine or sulfasalazine is necessary for patients with disease extending beyond the left colon. Using topical and oral mesalamine together is more effective than either alone in these patients [7]. Patients who are refractory to the above may require oral prednisone or induction therapy with infliximab. Severe active UC should be treated with intravenous steroids, cyclosporine or infliximab [8].

Once clinical remission has been achieved, mesalamine suppositories or enemas are recommended for maintenance of remission in patients with proctitis [5]. Oral 5-aminosalicylic acid (5-ASA) formulations will be required for patients with more extensive disease. If the patient fails to maintain remission with 5-ASA agents, 6-mercaptopurine (6-MP), azathioprine or infliximab may be used. Corticosteroids are not efficacious in maintenance treatment and are not recommended for long-term treatment [9]. The American Gastroenterology Association (AGA) recommends using azathioprine or 6-MP to reduce or avoid long-term corticosteroid use [9].

The US mesalamine market is estimated to be worth US$1.4 billion, and this figure is rising continuously, with newer formulations being developed [10]. More than 88% of all UC patients receive treatment with 5-ASA. The US oral 5-ASA market is led by Warner-Chilcott's Asacol®, which had a 40% share of the oral 5-ASA market in 2010, down from 52% in 2009. This decline is likely due to in-roads made by newer mesalamine formulations. Shire's Lialda® and Ferring's Pentasa® account for 34% of the market (ĩ20 and 14%, respectively). Apriso (Salix) and Asacol HD (Warner-Chilcott) had 6 and 9% market share, respectively, in 2010 [10].

The European markets are variable within each country [10]. Overall, in the UK, Germany, Spain, Italy and France, Asacol has a 21% share of the oral 5-ASA market. In the UK, Asacol has a 56% share, while Pentasa has a 25% share. Germany is dominated by Dr Falk's Salofalk® at 56%, followed by Shire's Mezavant® at 17% and Merkle Recordati GmbH's Claversal® at 15%. In Spain, Claversal and Pentasa dominate, with 41 and 46% of the market share, respectively. Pentasa leads in France at 78%, and Norgin B.V.'s Fivasa® had a 19% share in 2010. The reasons for the variability in use of different mesalamine formulations in different countries cannot be explained by clinical efficacy data.

Pharmacology

Pharmacokinetics & metabolism

Mesalamine is a 5-ASA compound used in induction and maintenance therapy of UC. It was discovered as the active anti-inflammatory moiety of sulfasalazine, which has been used to treat ulcerative colitis since the 1940s [11]. Sulfasalazine contains mesalamine bound to sulfapyridine via an azo bond, which is released by bacterial azoreductase in the small bowel and colon. Sulfapyridine is inactive, but is absorbed in the colon and is mostly responsible for hypersensitivity reactions and adverse effects associated with sulfasalazine [12]. Overall, 30% of the unbound 5-ASA is then absorbed rapidly in the small intestine, metabolized locally and by the liver to N-Ac-5ASA (an inactive metabolite) by N-acetyltransferase 1 (NAT 1), which is present in intestinal epithelial cells and liver. It is then excreted in the urine as free 5-ASA and N-Ac-5-ASA [11].

In a systematic review of the pharmacokinetic profiles of oral mesalamine formulations (Table 1), the mean T_{max} of Asacol was 5.3–14.7 h, that of Pentasa was 3.5h and that of Salofalk/Mesasal ® was 4.5–5.5 h (median 6.5 h) [13]. C_{max} values were as follows: Asacol mean 2.1–10.5 or median 6.5–39.2 nmol/ml; Pentasa mean 6.5 nmol/ml; Salofalk/Mesasal mean 10.9 or median 8.5nmol/ml. The mean and median area under the curve (AUC) for Asacol were 21.5–25.1 nmol/ml × h and 25.5–306.9 nmol/ml × h; mean for Pentasa: 28.5 nmol/ml × h; and for Salofalk/Mesasal mean of 38.3 nmol/ml × h or 18.3–21.5 nmol/ml × h. Both C_{max} and AUC were higher with larger doses.

Urinary excretion of total 5-ASA over 24–96 h were: Asacol mean 10–35% or median 18–40%; Pentasa mean 15–53% or median 23–34%; and Salofalk, Mesasal and Claversal mean 27–56% or median 31–44% [13]. Fecal excretion over 24–96 h for Asacol was a mean of 40–64% or median 20–56%; Pentasa mean of 12–51% or median 39–59%; and Salofalk, Mesasal and Claversal mean 37–44% or median 23–35%.

It should be noted that these studies were mostly performed in healthy volunteers, with some inactive and active UC patients. As a result, the pharmacokinetics detailed above may not be accurate in the setting of active colitis, as gastrointestinal motility and transit may be decreased with inflammation [14].

Pharmacodynamics

Mesalamine's mechanism of action in UC is unclear, but it appears to have a topical effect [11]. 5-ASA is believed to interact with damaged epithelium, be converted to acetyl-5-ASA (inactive acetylated form), and then absorbed and excreted into the urine or excreted into stool. Another proposed mechanism of action of 5-ASA is via inhibition of IL-2 production in peripheral mononuclear cells and thereby inhibiting T-cell proliferation, altering cell adhesion expression pattern, inhibiting antibody production and mast cell release, and interfering with macrophage and neutrophil chemotaxis [15]. 5-ASAs may also decrease IL-1 and TNF, induce apoptosis of lymphocytes and regulate NF-κB [16,17].

PPAR-γ is a transcription factor that modulates the inflammatory response of monocytes and macrophages by inhibiting the production of nitric oxide (iNOS) and macrophage-derived cytokines, such as TNF-α, IL-1 and IL-6 [18]. Normally highly expressed in the colon, it is significantly reduced in inflamed mucosa from patients with UC, which is restored by topical rosiglitazone, a PPAR-γ ligand [19]. Recent data have suggested a role for mesalamine as an additional ligand of PPAR-γ, which may explain some of its pharmacologic effects [20].

Drug-delivery systems

Drug delivery of mesalamine to the colon is dependent upon gastric emptying, small-intestinal transit, intraluminal pH and the coating [21]. Oral ingestion of pure mesalamine leads to rapid uptake in the proximal GI tract (stomach and small intestine) and subsequent acetylation and excretion in urine and stool [12]. Since mesalamine's pharmacological effects are based on topical contact with the colonic mucosa in UC, efficient delivery of mesalamine to the colon necessitates prevention of its absorption in the proximal GI tract. Currently, there are several different formulations of 5-ASA medications, which can be differentiated based on their means of delaying release of mesalamine until it reaches the colon (Table 2) [22–24]. Since there is an ascending pH gradient from the proximal to the distal intestinal tract (low pH in the stomach and upper small bowel; higher pH in the distal small bowel and colon), some delivery systems have an enteric coating that dissolves when the pH rises above a certain threshold [22]. Eudragit® S resin (Evonik; used in Asacol and Lialda/Mezavant) is a pH-sensitive polymer that disintegrates at a pH >7, allowing the drug to be released in the terminal ileum or cecum. By contrast, Eudragit® L resin (used in Claversal, Salofalk and Apriso) breaks down at a pH ≥6, thus releasing the active drug throughout the jejunum, terminal ileum and colon [21]. Lialda/Mezavant capsules contain additional lipophilic and hydrophilic matrices Multi Matrix System (MMX) within the Eudragit S capsule, with the goal of allowing slower diffusion of the drug through the colon [25]. Apriso also contains a polymer matrix coated with Eudragit L, designed to gradually distribute mesalamine throughout the colon [26].

Pentasa is a mesalamine formulation that has a pH-independent delivery mechanism. This formulation consists of mesalamine microgranules coated in a moisture-sensitive ethylcellulose semi-permeable membrane, which allows it to be released in a pH-independent fashion, beginning in the duodenum and continuing throughout the intestinal tract [27].

Aside from the mode of encapsulation of mesalamine (acrylic or ethylcellulose), the other strategy used to accomplish sustained delivery of mesalamine to the colon is to use pellets/granules instead of simple tablets. *In vitro* studies of mesalamine have reported that tablets have a higher rate of dissolution than pellets, but the time to reach the ileocecal region is similar for both formulations [22]. The area under the plasma concentration–time curve from time zero to time t for pellets was significantly lower than for tablets, suggesting a more gradual release of 5-ASA from pellets.

Clinical efficacy

Induction of remission

For patients with active UC, all mesalamine formulations approved in the USA have been shown to induce clinical response and/or remission in randomized controlled trials (RCTs) (Table 3). Clinical response rates of 60–70% and clinical remission rates of 40–70% have been reported in these studies over 6–8 weeks [28,29]. Endoscopic healing (improvement in, or resolution of, mucosal damage seen at endoscopy) occurs in 30–80% of patients treated with mesalamine within 6–8 weeks [30]. Meta-analyses of these induction studies concluded that the mean remission rate with mesalamine was 42%, compared with 24% in placebo-treated patients [28]. There was no difference between the type of 5-ASA used and the efficacy of achieving remission. A meta-analysis determined that 58.7% of 647 patients receiving high- or standard-dose 5-ASA did not achieve remission, whereas 69.8% of 368 patients receiving low-dose 5-ASA failed to achieve remission [29]. While there was a significant difference in remission rates in patients receiving high-dose versus low-dose Asacol (80 vs 68%, respectively), there was no significant difference in high-dose versus low-dose Pentasa administration (44 vs 48%, respectively) [29]. Whether or not higher

doses of mesalamine are superior to lower doses in induction of remission is unclear. Data from mesalamine RCTs initially suggested no difference in overall remission rates between dosing groups [31–34]. However, a recent *post-hoc* analysis of symptom scores from those studies concluded that a dose of 4.8 g per day produced a faster time to symptom resolution (19 vs 29 days), and a greater proportion of patients taking the higher dose achieved remission within 14 days (43 vs 30%) [35]. Higher dose mesalamine was also noted to produce significantly better mucosal healing rates at week 6 than the lower dose (80 vs 68%) [36]. Mucosal healing rates were significantly higher in patients with left-sided colitis on the higher dose of mesalamine; while there was a trend towards higher mucosal healing rates in all patients on higher dose mesalamine, it was not statistically significant. It appears from the cumulative comparative data on mesalamine dosing that 2.4 g is sufficient in many patients with mild disease, but 4.8 g may quicken the time to remission and provide superior results in some subgroups [37]. Whether the additional costs of treating all patients with higher dose mesalamine to achieve faster remission and higher mucosal healing rates is a cost-effective approach is unknown, but warrants analysis.

It should be noted that there are a range of clinical scoring systems and definitions for both clinical and endoscopic remission used in published RCTs. In fact, there are over 15 different scoring systems used in UC clinical trials, with no single scoring system or end point used universally in all trials [38]. Thus, there are few studies that allow direct comparisons of different mesalamine formulations. ‘Remission’ for one RCT may have a different definition in a comparator compound’s RCT. One RCT reported no difference between similar doses of pH-dependent release and timed-release mesalamine formulations in induction of remission of active UC [39].

Topical 5-ASA is recommended for mild-to-moderate distal disease in the sigmoid colon or rectum. A systematic review of topical 5-ASA has confirmed the efficacy of rectal 5-ASA in inducing remission, and is superior to rectal corticosteroids or placebo [40]. There was no dose–response relationship, and a combination of oral and topical 5-ASA was more effective than either alone. Four formulations are available – suppositories, gels, foams and liquid suspensions (enemas), but only suppositories and suspensions are available in the USA. All four are equally efficacious in treating proctitis, and all but suppositories are equally efficacious in treating disease localized distal to the splenic flexure [40]. Topical therapy, alone or in combination with oral therapy, is superior to oral therapy alone in achieving earlier remission and maintaining remission for up to 1 year [40].

Quality of life (QoL) is greatly impacted in patients with UC – important factors include severity of symptoms and effectiveness of medical or surgical therapies [41]. The Inflammatory Bowel Disease Questionnaire (IBDQ) is validated in assessing QoL, and has been used to evaluate QoL in patients with UC [42]. QoL was collected in the ASCEND I and II trials (randomized, active controlled trials evaluating the efficacy and safety of delayed-release oral mesalamine – 2.4 vs 4.8 g daily). Patients had significant improvement in QoL from baseline at weeks 3 and 6 [36]. Those with moderately active disease treated with mesalamine had greater improvements in mean IBDQ scores than those treated with placebo, regardless of dose.

Maintenance of remission

Once remission has been attained, mesalamine therapy has a key role in preventing symptom relapse (Table 4). In a meta-analysis by Ford *et al.*, when comparing 5-ASA with placebo, 42.4% of 642 patients on 5-ASA relapsed compared with 65% of 454 patients on placebo [28]. A study comparing Lialda 2.4 g daily and Asacol 2.4 g daily found no significant difference between the two drugs in maintaining clinical remission (68 and 65.9%, respectively) [43]. In patients receiving Asacol alone at 0.8 g per day, 58.8%

remained in remission, compared with 65.5% of those receiving Asacol 1.6 g per day and 39.7% of patients receiving placebo [44]. At 1-year follow-up, 54% of patients on Pentasa were in continued remission as opposed to 46% of patients on sulfa-salazine [45]. Maintenance studies of Apriso reported that 78.9% of patients on Apriso maintained remission compared with 58.3% of the placebo group [26]. The US FDA-approved doses for maintaining remission are as follows: Asacol 1.6 g daily; Lialda 2.4 g daily; and Apriso 1.5 g daily.

Safety profile

RCT adverse drug reactions

Mesalamine is generally very safe and well tolerated by patients. Reported adverse events include nausea or vomiting, headache, abdominal pain and rash [46]. A paradoxical exacerbation of diarrhea has also been described, which usually occurs early after initiation of therapy [47]. In RCTs, 13–73% of patients taking mesalamine compounds experienced some sort of side effect, while placebo-related events occurred in 22–61% of patients [28]. One study examined the optimal dose of mesalamine in UC, as well as its efficacy and safety in the clinical trial setting [32]. Of 321 patients taking varying dosages of mesalamine, 12 patients experienced side effects, with seven requiring hospitalization for worsening UC. There was one case each of elevated liver enzymes, pancreatitis, deafness, hemolytic anemia and pneumonia. No deaths were reported. Overall, tolerability was rated as very good or good by 82% (1.5 g/day), 88% (3.0 g/day) and 75% (4.5 g/day) of patients. Among these three groups, there was no difference in the number and severity of adverse events. Other side effects reported with mesalamine are listed in Table 5.

Post-marketing safety signals

A study from the UK examined serious adverse reactions to mesalamine from 1991 to 1998 [48]. During this period, 2.8 million prescriptions for mesalamine were issued; there were 29 reported cases of interstitial nephritis, 18 cases of pancreatitis, 12 skin reactions, eight cases of hepatitis and 48 reports of blood dyscrasias. Such reports are dependent on physician reporting of adverse events to regulatory bodies, so they may underestimate the true prevalence or include cases that were causally unrelated.

Acute pancreatitis is a rare but serious complication of 5-ASA treatment. Morbidity of 25% and mortality of 5% has been reported in acute pancreatitis. Initially, pancreatitis was attributed to the sulfa moiety of sulfasalazine; however, it still occurs with 5-ASA medications that lack the sulfapyridine component [49]. It has been postulated that 5-ASAs may increase pancreatic duct permeability or that patients with inflammatory bowel disease (IBD) have increased susceptibility to 5-ASA compounds. A study from the UK found that acute pancreatitis was seven-times more likely to occur with mesalamine than sulfasalazine, at doses ranging anywhere from 800 mg per day to 5 g per day [48]. A French study of Pentasa reported the incidence of pancreatitis to be 1 per million days of treatment, with most cases occurring within the first 6 weeks of therapy, which was independent of the dose and improved after cessation of the drug [50]. It is known that patients with IBD have a higher risk of pancreatitis than the background population, so it is unclear whether these rare events are due to the disease or the medication.

Nephrotoxicity is another rare but documented adverse effect of mesalamine treatment. A systematic review found that the mean rate of nephrotoxicity is 0.26% per patient-year [51]. Although approximately 50% of cases of 5-ASA-induced interstitial nephritis occur within 1 year of initiating treatment, it may occur at any time, from less than 1 month to more than 80 months after starting treatment [52]. Unfortunately, it is difficult to detect early with urinalysis, and currently there are no screening methods other than monitoring serum

creatinine level. While in animals nephrotoxicity is dose dependent, as in acute pancreatitis, interstitial nephritis has reportedly occurred in patients taking doses of 0.5–0.75 g/day [53]. Its exact mechanism is unknown, and it appears to have an indolent, chronic, progressive course, which can prevent diagnosis for several months. Nephrotoxicity can be reversed if identified early on, with better recovery rates the earlier 5-ASA is discontinued. There are anecdotes of renal function recovery with steroids and a trial of high-dose steroids may be attempted if there is no improvement with drug withdrawal [54].

Drug-induced liver injury (DILI) may also occur but is extremely rare – the reported incidence is as low as 3.2 cases per million prescriptions in the UK [55]. Cholestatic injury with and without immunoallergic features and cross-reactive hypersensitivity reactions to sulfsalazine have been described.

In 2010, the FDA revised Asacol from pregnancy Category B to Category C owing to the presence of dibutyl phthalate (DBP), an inactive ingredient, in the coating [101]. The daily intake of DBP from the maximum dose of Asacol is 21 mg daily. The discovery of DBP in Asacol was surreptitiously discovered in a population-based study of urine DBP levels; one subject who had extremely high levels of DBP was noted to be taking Asacol [56]. Studies in humans have reported that *in utero* exposure to phthalates in general has anti-androgenic effects on the fetus [57,58]. Whether the presence of low levels of DBP in Asacol has implications for patients is unknown.

Finally, it is worth noting the potential interaction between mesalamine and azathioprine/mercaptopurine, which are often used in combination in patients with UC. Azathioprine and 6-MP are metabolized to produce varying amounts of 6-methylmercapto-purine (6-MMP) and 6-thioguanine nucleotides (6-TGN) in humans; 6-MMP has been associated with liver toxicity and 6-TG with leukopenia [59]. Patients treated with both mesalamine and azathioprine in combination have been reported to have higher 6-TG levels, with the subsequent development of leukopenia in case reports [60,61]. There are conflicting data from cohort studies as to whether this pharmacokinetic interaction has practical implications for clinical care [62,63].

Mesalamine use in clinical practice

Mesalamine is now firmly established as the first-line agent for treating active UC and maintaining clinical remission. As its use has become widespread in the gastroenterology community, a number of topics beyond its efficacy and safety data have been the subject of study in clinical practice.

Mesalamine as chemoprophylaxis against CRC

The cumulative lifetime risk of developing CRC in patients with UC has been reported to be as high as 10–20% in historical cohorts, with risk factors including extent, age of onset, duration of disease, severity of inflammation over time, presence of primary sclerosing cholangitis and family history of CRC [4]. More contemporary data suggest that the overall population-based risk of CRC in patients with UC is much lower, with a prevalence as low as 1.3% over 15 years in patients with IBD [64]. Since the risk of CRC has been associated with chronic inflammation in this setting, an anti-inflammatory agent such as mesalamine would be expected to have chemoprophylaxis properties [65]. *In vitro* studies of mesalamine have reported reduced proliferation and increased apoptosis of CRC cells, and activation of cell cycle checkpoints and DNA-repair processes via the β-catenin and the TGF-β1 signaling pathways [66,67].

Case–control studies of patients with colon cancer and UC have reported conflicting data on the impact of 5-ASA on the risk of CRC [68–70]. A meta-analysis of observational studies found that the use of 5-ASA was associated with a lower risk of CRC (odds ratio [OR]: 0.51; 95% CI: 0.37–0.69) in a pooled analysis of nine studies [71]. The reduced risk was obtained with regular use and at least 1.2 g of mesalamine daily. In this analysis, pooled results concluded that while 5-ASA may reduce a combined end point of cancer/dysplasia, it was not protective against dysplasia itself. However, only two studies included dysplasia alone as an end point, so further evaluation would be necessary to determine whether the reduction in CRC occurs as a result of a reduced risk of dysplasia. A Canadian population-based study in patients with UC taking oral 5-ASAs did not find any protective effect of 5-ASA [72]. In fact, in subjects who used 5-ASA for at least 7.5 years (n = 493), the hazard ratio for CRC was 2.74 (95% CI: 1.04–7.23; p = 0.041) in this study. 5-ASA use may have been a surrogate for more active disease in this cohort. A major problem with the studies examining the relationship between exposure to 5-ASAs and CRC is that they are observational studies, which are prone to bias [65]. Unfortunately, current observational studies are lacking in terms of cohort size, long-term follow-up, methods of data collection, and a lack of data regarding drug exposure and the extent and severity of disease over time. A prospective RCT of 5-ASA in prevention of polyps in adults with a history of polyps also did not show a chemoprotective effect of 5-ASA in this setting [73].

Mesalamine adherence

Efficacy is dependent upon adherence to medication regimens, which has been reported to be only 40–60%, by self-report and urinary drug measurements, in patients prescribed mesalamine [74,75]. These self-reports may even underestimate the extent of nonadherence, as self-reporting typically overestimates an individual's adherence. Factors associated with noncompliance include male gender, younger age, South Asian ethnicity, full-time employment and multiple dosing schedules [76,77]. When patients were interviewed for their reasons for nonadherence, a variety of barriers to adherence were reported, including lifestyle, risk of side effects and financial factors [78]. Lack of compliance has also been shown to have a fivefold increased risk of relapse, increased risk of hospitalization and surgery, and increased costs [79,80].

A number of approaches have been examined to improve patients' mesalamine adherence. One study comparing standard care and a nurse-delivered patient support program found that there were no significant differences between compliance in both groups over 6 months [81]. However, a study based on urine 5-ASA levels reported that patient education and counseling prevented patients from becoming nonadherent over 12 months [82]. As single-dosing maintenance regimens have become available, the assumption has been that these simplified regimens will improve adherence to mesalamine. Once-daily mesalamine has been shown to be as effective as twice-daily dosing, with improved patient compliance in those with reduced pill burden [83]. It is clear that many prescribers, pharmacists, payers and pharmaceutical companies can all play a role in addressing some of the factors that influence patient adherence to mesalamine, as the factors involved for patients are complex [77].

Regulatory affairs

Mesalamine is approved by the FDA for both induction and maintenance of remission in patients with UC [84]. Table 6 summarizes the clinical trial criteria on which each mesalamine formulation was approved. As can be seen, Asacol was approved based on endoscopic criteria, and Pentasa, Lialda and Apriso were approved based on a combined clinical/endoscopic score. The main regulatory issue in the USA is the criteria for future approval of generic mesalamine. Congress passed the Hatch-Waxman Act (Drug Price

Competition and Patent Term Restoration Act) in 1984, which allows sponsors to apply for approval of generic medications without having to provide independent evidence of safety and efficacy for the proposed generic drug. The generic applicant must demonstrate that the proposed generic contains the same active ingredient as, and is 'bioequivalent' to, a reference listed drug. For mesalamine, the big issue has been how to assess bioequivalence for generic versions of Asacol and Pentasa. Since mesalamine is thought to act locally, rather than systemically, traditional pharmacokinetic studies of absorption may be inadequate to demonstrate bioequivalence for generic mesalamine formulations. In August 2010, the FDA decided that applicants for generic versions of mesalamine must demonstrate bioequivalence to Asacol or Pentasa through a combination of pharmacokinetic studies and *in vitro* dissolution testing (dissolution of mesalamine formulations over a range of GI pH levels), but not comparative clinical studies [102]. Balsalazide, which is another 5-ASA for treatment of UC, has been available in generic form since 2007 in the USA, after approval of the generic version as 'therapeutic equivalent' to the pioneer compound (Colazal®, Salix Pharmaceuticals, Inc.). Generic versions of balsalazide had a sevenfold higher market share than Colazal in 2010 (7 vs 1%). The FDA-approved generic is approximately a quarter of the cost of the pioneer agent (Colazal).

In Europe, the EMA is responsible for evaluating applications for European marketing authorizations for medications derived from 'biotechnology and other high-tech processes'. Otherwise, all other medications are evaluated and marketed in each individual country in accordance with their national procedures, which occurs for mesalamine. The EMA is not involved unless there is a disagreement between countries about the authorization or use of the medication due to public safety concerns.

Conclusion

Mesalamine is safe and effective in the induction and maintenance of remission in mild-to-moderate UC. In addition, it has been shown in clinical studies to induce mucosal healing and improve QoL, and has a favorable safety profile. The potential for mesalamine as a chemoprophylaxis agent against CRC is appealing, but the evidence to support its role in this setting is conflicting at present. In addition, a major issue in maintenance of remission is low adherence to mesalamine in practice. Adherence may improve with simplified dosing schedules for maintenance of remission. Given the different study designs and differing formulations of mesalamine, comparative efficacy is also difficult to determine, but some studies have provided guidance in this regard [85]. Since UC is a disease that begins in the rectum and extends proximally, the rectum should also be a target for therapy, regardless of the extent of disease. Rectally applied mesalamine has been shown to have higher mucosal concentrations than oral administration alone [86].

Expert commentary

Mesalamine is a safe and effective anti-inflammatory treatment, both in inducing and maintaining remission in patients with UC. It can induce mucosal healing and, in doing so, should reduce the risk of hospitalizations, the need for colectomy and the risk of CRC in the long term. However, this assumes patients actually take the drug as prescribed. The market has evolved from a single market leader in the USA to five currently FDA-approved formulations of mesalamine with similar efficacy and safety. The marketing of these competitors has focused on issues such as patient adherence and convenience, which were not historically a prominent topic in mesalamine outcomes. The introduction of newer formulations has also led to an expansion in research on secondary outcomes, such as mucosal healing, costs, adherence and cancer prevention, in what was a previously sedate field. The development of higher-dose, simplified regimens for maintenance of remission

should improve patient compliance and comfort, leading to increased rates of remission. Costs remain an issue for patients and third-party payers, as the costs of mesalamine have remained similar across all formulations over the last 20 years.

Five-year view

The patent for the original mesalamine formulation, Asacol, is anticipated to expire in July 2013 in the USA. If generic manufacturers can provide evidence of bioequivalence with pioneer formulations, it is likely that in many cases payers will transition to cheaper generic versions for patients with UC. Future indications for mesalamine may also include diverticulitis, segmental colitis associated with diverticular disease, microscopic colitis and chemoprophylaxis. However, further clinical study is required prior to the expansion of the current FDA-approved indications.

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Key issues

- Mesalamine has anti-inflammatory effects that aid in the healing of mild-to-moderate ulcerative colitis.
- Multiple formulations of mesalamine exist, to facilitate release in the small intestine and/or colon.
- Mesalamine has been shown to be safe, with a side-effect profile comparable to that of placebo, in addition to being efficacious in inducing and maintaining remission in ulcerative colitis.
- Adherence is a major issue with mesalamine, due to pill burden and dose scheduling.
- The role of mesalamine as chemoprophylaxis against colorectal cancer remains to be clarified.

Table 1

Pharmacokinetics of oral mesalamine preparations.

Formulation	T_{max} (mean)	C_{max} (mean)	AUC (mean in nmol/ml × h)	Fecal excretion over 24–96 h (mean [%])	Urinary excretion (mean [%])
Asacol®	5.3–14.7 h	2.1–10.5 nmol/ml	21.5–25.1	40–64	10–35
Pentasa®	3.5 h	6.5 nmol/ml	28.5	12–51	15–53
Salofalk®/Mesasal®	4.5–5.5 h	10.9 nmol/ml	38.3	37–44	27–56

AUC: Area under the curve.

Data taken from [13].

Table 2

Different 5-aminosalicylic acid delivery systems, formulations and sites of 5-aminosalicylic acid release.

Trade name	Standard dose	Delivery method	Site of 5-ASA release†	Formulation
Mesalamine, Asacol®, Ipocol®	2.4–4.8 g	pH-dependent; soluble at pH ≥ 7	Terminal ileum, colon	Coated with Eudragit® S resin
Claversal®, Salofalk®	1.5–3 g/day	pH-dependent; soluble at pH ≥ 6	Jejunum, ileum, colon	Coated with Eudragit® L resin
Pentasa®	4 g	Delayed release through ethylcellulose coat	Duodenum, jejunum, ileum, colon	Microgranules coated in semi-permeable ethylcellulose
Lialda®	2.4–4.8 g	pH-dependent; soluble at pH >7	Terminal ileum, colon	Multi Matrix System matrices
Apriso®	1.5 g	pH-dependent; soluble at pH ≥ 6	Colon	Eudragit L-coated granules containing polymer matrix

† Site of release is theoretical.

5-ASA: 5-aminosalicylic acid.

Data taken from [21].

Table 3

Efficacy of mesalamine in inducing remission of ulcerative colitis.

Formulation	End point	Response rate
Lialda®	Clinical (UCDAI ≤1) and endoscopic remission (sigmoidoscopy score reduction of 1 or more points from baseline)	8-week complete mucosal healing rate of 32% in MMX mesalamine groups (either 2.4 g/day or 4.8 g/day) compared with 16% on placebo
Asacol®	Endoscopy score of 0 or 1: mucosal healing	At 6 weeks, 80% of patients achieved mucosal healing on 4.8 g/day, while 68% of those on 2.4 g/day achieved this
Pentasa®	Clinical and endoscopic remission	At 8 weeks, 44 and 48% of patients receiving 2 and 4 g achieved remission by endoscopy, compared with 31% on placebo
Apriso®/Salofalk®	Clinical and endoscopic remission	After 8 weeks, patients receiving 3 g daily had remission rates of 66%, similar to those receiving 4.5 g daily (56%)

MMX: Multi Matrix System; UCDAI: Ulcerative Colitis Disease Activity Index.

Data taken from [28].

Table 4

Efficacy of mesalamine in maintaining remission of ulcerative colitis.

Formulation	End point	Response rate
Lialda®/Mezavant®†	Clinical (UCDAI) and endoscopic remission	68% of patients in the Lialda (2.4 g/day) and 65.9% in the Asacol (2.4 g/day) groups remained in clinical remission; 60.9 and 61.7% remained in endoscopic and clinical remission
Asacol®	Clinical and endoscopic remission	At 6 months, 39.7% of patients receiving placebo remained in remission; while 58.8% of those receiving 0.8 g/day of mesalamine and 65.5% of those receiving 1.6 g/day remained in remission
Pentasa®	Clinical and endoscopic remission	At 12 months, 54% of patients on Pentasa had ongoing remission, 46% of patients on Salazopyrin® maintained remission; Pentasa had no reported side effects whereas multiple side effects were recorded with Salazopyrin
Apriso®	Relapse-free patients based on revised Sutherland Disease Activity Index	At 6 months, 78.9% of patients on Apriso remained relapse free, compared with 58.3% of the placebo group

† Mezavant is the European trade name for Lialda.

UCDAI: Ulcerative Colitis Disease Activity Index.

Data taken from [28].

Table 5

Adverse events reported in 245 patients with mesalamine.

Adverse effect	Frequency (%)
Headache	35
Abdominal pain	18
Eructation	16
Pain	14
Nausea	13
Pharyngitis	11
Dizziness	8
Asthenia	7
Diarrhea	7
Back pain	7
Fever	6
Rash	6
Dyspepsia	6
Rhinitis	5
Arthralgia	5
Hypertonia	5
Vomiting	5
Constipation	5
Flatulence	3
Dysmenorrhea	3
Chest pain	3
Chills	3
Flu syndrome	3
Peripheral edema	3
Myalgia	3
Sweating	3
Colitis exacerbation	3
Pruritus	3
Acne	2
Increased cough	2
Malaise	2
Arthritis	2
Conjunctivitis	2
Insomnia	2

Data taken from [101].

Table 6

US FDA clinical efficacy criteria for mesalamine formulation approval.

Formulation	Date of FDA approval	Description of trial(s)	Primary end point	Duration of study
Asacol®	01/31/1992	Randomized, double blind, placebo controlled	Clinical remission via sigmoidoscopic improvement	6 weeks
		Randomized, double blind, placebo controlled	Maintenance of remission via sigmoidoscopic appearance	6 months
		Randomized, double blind, double dummy, controlled equivalence study vs sulfasalazine	Maintenance of remission via sigmoidoscopic appearance (Asacol was nonsignificantly inferior to sulfasalazine)	6 months
Pentasa®	05/10/1993	Randomized, double blind, placebo controlled	Induction of clinical remission, combination of physician global assessment and sigmoidoscopic index	8 weeks
Lialda®	01/16/2007	Randomized, double blind, placebo controlled	Clinical remission defined as UCDAI score ≤1, with score 0 for rectal bleeding and stool frequency and sigmoidoscopy score reduction ≥1 point from baseline	8 weeks
Apriso®	10/31/2008	Randomized, double blind, placebo controlled	Maintenance of remission. Relapse free at end of study defined as a Sutherland Disease Activity Index rectal bleeding subscale score ≥1 and mucosal appearance subscale score ≥2. Symptoms of UC flare or restarting UC medications also counted as relapse	6 months

UC: Ulcerative colitis; UCDAI: Ulcerative Colitis Disease Activity Index.

Data taken from [84].