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Mesalazine preparations for the treatment of ulcerative colitis: Are all created equal?

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The therapeutic effect of mesalazine occurs topically at the site of diseased colonic mucosa. A myriad of oral mesalazine preparations have been formulated with various drug delivery methods to minimize systemic absorption and maximise drug availability at the inflamed colonic epithelium. It remains unclear whether different oral mesalazine formulations are bioequivalent. This review aims to evaluate the differences between mesalazine formulations based on the currently available literature and explore factors which may influence the selection of one agent above another.

Key words: Colitis; Ulcerative; Drug delivery systems; Mesalamine; Sulfasalazine; Therapeutic equivalency

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Core tip: Various formulations of oral mesalazine are available for management of mild to moderate ulcerative colitis. Selection of the most appropriate formulation requires tailoring of the therapy to the individual and must incorporate factors such as disease distribution, efficacy, side effect profile, pill burden, patient preference and health economics.

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Abstract

Oral mesalazine (also known as mesalamine) is a 5-aminosalicylic acid compound used in the treatment of mild to moderate ulcerative colitis, with high rates of efficacy in induction and maintenance of remission.

INTRODUCTION

Ulcerative colitis is a chronic idiopathic inflammatory bowel disease (IBD) characterised by intestinal inflammation confined to the superficial mucosal layer. It may involve the rectum only, the distal colon

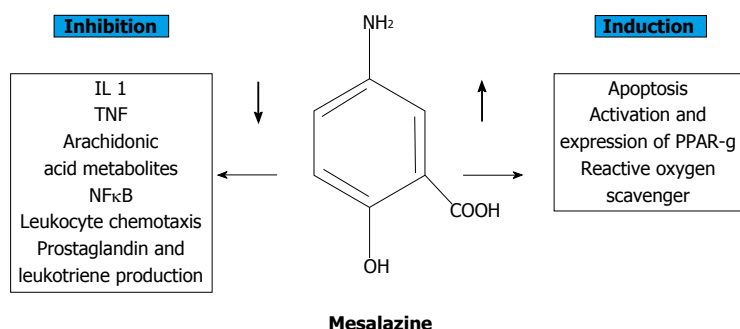


Figure 1 Proposed mechanism of action of mesalazine at the colonic mucosa. IL: Interleukin; NFκB: Nuclear factor κB; PPAR: Peroxisome proliferative activated receptor; TNF: Tumour necrosis factor.

or the entire colon, typically in a contiguous fashion. Classical symptoms of ulcerative colitis include bloody diarrhoea, urgency and tenesmus. Mesalazine, a 5-aminosalicylic acid compound (5-aminosalicylate, or 5-ASA), is most often used as the first line therapy for mild to moderate ulcerative colitis^[1]. However, the exact mechanism of action of mesalazine remains poorly elucidated. It is believed to exert a negative effect on the cyclooxygenase and lipoxygenase pathways, thereby reducing the formation of pro-inflammatory prostaglandins and leukotrienes^[2,3]. The peroxisome proliferator activated receptor-γ is also implicated in colonic inflammation and has been identified as a target of 5-ASA action^[4]. Furthermore, mesalazine may have antioxidant properties that reduce tissue injury and play a part in inhibition of T cell activation and proliferation^[5,6] (Figure 1).

Oral mesalazine compounds have proven efficacy for inducing and maintaining remission in patients with ulcerative colitis^[7,8]. Mesalazine exerts therapeutic effect through local topical activity at the inflamed mucosa^[9]. Oral mesalazine in unaltered form is almost entirely absorbed by the small intestines, with very little intact drug reaching the colon^[10,11]. Hence, the main goal of the various formulations currently available on the market is to optimise drug delivery to the affected colon and minimise systemic absorption. This promotes maximal therapeutic efficacy at the lowest possible dose, which in turn reduces side effects.

It remains unclear whether individual mesalazine formulations have differential effects in certain IBD patient subgroups. Anecdotally in the clinical setting, the choice of mesalazine appears at best to be rather experimental or idiosyncratic, and at worst, based on ambit claims by pharmaceutical representatives and/or advertisement, rather than evidence-based. In the absence of quality head to head comparative trials in appropriately selected patients, claims that one formulation is superior to another may be spurious. Nevertheless, physicians are often tasked with selecting a suitable mesalazine compound for their patients. These decisions require tailoring of the therapy to the individual and must incorporate factors such as disease distribution, efficacy, side effect profile, pill burden, patient preference and health economics. Hence, this review aims to

evaluate the current literature relating to potential therapeutic differences between mesalazine formulations and thus inform an evidence-based approach to optimal mesalazine use in patients with ulcerative colitis.

DELIVERY MECHANISMS

Azo-bonded prodrugs

In these formulations, mesalazine is synthesized as a prodrug, binding *via* an azo bond to either a transporter molecule or another mesalazine molecule. This prevents absorption of the drug in the upper gastrointestinal tract. The azo bond is subsequently cleaved by bacteria containing azoreductase in the colon, releasing the active mesalazine component (Table 1).

Sulfasalazine (Azulfidine®, Salazopyrin®, Pyralin®, Pfizer Inc, New York, NY) was one of the first aminosalicylates shown to be effective in the induction and maintenance of remission in ulcerative colitis^[12,13]. It consists of a mesalazine and a sulfapyridine molecule bound by an azo bond, which is cleaved upon exposure to colonic bacteria. Mesalazine is the active moiety and sulfapyridine acts as an inactive carrier molecule^[14,15]. Systemic absorption of sulfapyridine is responsible for many of the adverse effects associated with sulfasalazine^[16]. Approximately 20% of patients are intolerant^[17].

Other azo-bonded prodrugs have been formulated with alternative carrier molecules, in an attempt to reduce side effects. Olsalazine sodium (Dipentum®; UCB Pharma, Slough, United Kingdom) is comprised of two mesalazine molecules also connected by an azo-bond. Balsalazide disodium (Colazide®, Fresenius Kabi AG, Hamburg, Germany; Colazal®, Salix Pharmaceuticals Inc, Morrisville, NC) consists of mesalazine bound to 4-aminobenzoyl-β-alanine. Both agents have been shown to be effective in treatment of patients with ulcerative colitis^[18,19].

pH dependent formulations

Other mesalazine preparations encapsulate the active drug in an enteric coat in order to control the site of drug release. The enteric coating consists of a resin film designed to release mesalazine only at a designated pH, thereby preventing premature disintegration in the

Table 1 Summary of drug delivery mechanisms

Formulations	Generic name	Proprietary names	Mode of delivery	Site of drug release
Azo-bonded prodrugs	Sulfasalazine	Azulfidine®; Salazopyrin®; Pyralin®	Mesalazine bound to sulfapyridine	Colon
	Olsalazine	Dipentum®	Two mesalazine molecules bound together	Colon
	Balsalazide	Colazide®; Colazal®	Mesalazine bound to 4-aminobenzoyl-β-alanine	Colon
pH dependent	Mesalazine	Asacol®; Mesren®	Eudragit-S coating (dissolves at pH ≥ 7)	Terminal ileum, colon
		Salofalk®; Mesasal®; Claversal®	Eudragit-L coating (dissolves at pH ≥ 6)	Mid ileum to colon
		Salofalk Granules®	Eudragit-L coating and matrix core	Mid ileum to colon
Time dependent	Mesalazine	Pentasa®, Pentasa® granules	Microspheres encapsulated within an ethylcellulose semi-permeable membrane	Duodenum to colon
MMX	MMX mesalazine	Lialda®; Mezavant XL®; Mezavant®	Enteric coating (dissolves at pH ≥ 7). MMX of lipophilic and hydrophilic excipients	Terminal ileum and entire colon

MMX: Multi-matrix system.

acidic environment of the stomach and proximal small bowel. Asacol® (Tillotts Pharma AG, Ziefen, Switzerland) and Mesren® (Ivax Pharmaceuticals Limited, Runcorn, Cheshire, United Kingdom) are manufactured with a methacrylate copolymer coating, Eudragit-S. This coating dissolves at pH ≥ 7, releasing the active drug in the terminal ileum and colon. Salofalk® (Dr Falk GmbH, Freiburg, Germany), Mesasal® (Aspen Pharmacare, NSW, Australia) and Claversal® (Merckle GmbH, Ulm, Germany), comprise mesalazine enclosed within an Eudragit-L coating which disintegrates at pH ≥ 6, thus preferentially releasing the drug throughout mid to distal ileum and colon^[20]. A potential issue with this mode of delivery is that colonic pH, although highly variable, is overall reduced in patients with inflammatory bowel disease^[21]. It has been postulated that the lowered colonic pH may impede the release of 5-ASA from the pH dependent enteric coating and reduce its efficacy. Certainly, it is recommended that pH dependent formulations should not be co-administered with lactulose or other medications which lower colonic pH.

Time dependent formulations

Pentasa® (Ferring Pharmaceuticals, Copenhagen, Denmark) adopts an alternative method of drug delivery consisting of microspheres of mesalazine encapsulated within an ethylcellulose semi-permeable membrane. This structure allows time and moisture dependent release of the active drug, independent of the luminal pH. Mesalazine is theoretically distributed gradually throughout the gastrointestinal tract from the duodenum to the rectum^[22]. This in turn may be of therapeutic value in patients with small bowel Crohn's disease^[23]. In ulcerative colitis, the efficacy of Pentasa® has been demonstrated in multiple studies, including one randomised control trial where 64% of patients maintained remission after 12 mo of Pentasa® 4 g/d compared with 38% of patient who received placebo ($P = 0.0004$)^[24].

Granule formulations

There is data to suggest that improved efficacy in patients with moderate ulcerative colitis may be achieved with a higher daily dose of mesalazine^[25]. In

order to reduce pill burden and encourage adherence, both Pentasa® and Salofalk® (Dr Falk GmbH, Freiburg, Germany) are available as loose micro granules, packaged into sachets. This allows a higher drug dose to be administered without increasing pill burden and thus attempts to enhance patient tolerability. Furthermore, this formulation may be especially advantageous in patients who have difficulty ingesting large quantities of tablets.

Multi-matrix system

Mezavant® (Lialda®, United States), Mezavant XL® (United Kingdom and Ireland), Shire Pharmaceuticals Inc, Wayne, PA) is a once daily formulation of mesalazine which adopts a multi-matrix system (MMX). Mesalazine is incorporated into a lipophilic matrix which is in turn dispersed within a hydrophilic matrix. The tablet is enterically coated and dissolves at pH ≥ 7, in the terminal ileum. The hydrophilic matrix is then exposed to intestinal fluid and swells to form a viscous gel mass. This viscous gel potentiates slow diffusion of the active drug from the tablet core and thereby enabling slow controlled release of mesalazine throughout the entire length of the colon^[26]. Kamm *et al.*^[27] evaluated the efficacy of MMX mesalazine in patients with active ulcerative colitis and found it to be significantly superior to placebo in inducing remission.

COMPARISON OF MESALAZINE FORMULATIONS

Pharmacokinetics

The ideal mesalazine formulation would minimise systemic absorption in the upper gastrointestinal tract and maximise delivery of the active drug to the colonic mucosa. Ingested 5-ASA is acetylated by the N-acetyltransferase 1 (NAT 1) enzyme in intestinal epithelial cells to form the inactive metabolite N-Ac-5ASA. This metabolite is then either absorbed systemically and excreted in the urine or secreted back into the colonic lumen and excreted in the faeces. Some 5-ASA is also absorbed directly into the bloodstream and undergoes metabolism by the NAT 1 enzyme in liver cells, followed

by elimination in the urine^[11,28].

The assorted delivery technologies used by mesalazine formulations have a direct bearing on their pharmacokinetics. The drug release profile of MMX mesalazine has been compared with pH-dependent formulation Asacol® using radioactive labelling. MMX mesalazine tablets began to disintegrate earlier than Asacol®, at an average of 4.8 h compared to 6.2 h respectively. Complete disintegration occurred at 17.4 h for MMX mesalazine compared with 7.3 h for Asacol®, implying a more prolonged release of 5-ASA with MMX mesalazine. This allows slow and controlled distribution throughout the entire colon. In contrast, Asacol® released the active drug more rapidly, predominantly in the right colon. Consequently, disease distribution may be an important factor to consider in selection of mesalazine agents, with MMX mesalazine potentially more appropriate for patients with distal colitis.

The rate of intestinal transit may also impact the pharmacokinetics of different oral mesalazine preparations, and hence their efficacy. Faecal excretion of 5-ASA was evaluated in healthy volunteers after administration of laxatives to induce diarrhoea and accelerate intestinal transit. Diarrhoea resulted in a marked increase in faecal loss of the pro-drugs, sulfasalazine and olsalazine, indicating insufficient time for activation of the pro-drug by colonic bacteria^[29]. In comparison, pH and time dependent formulations (Pentasa® and Salofalk®) appeared to maintain adequate release of 5-ASA despite accelerated intestinal transit^[29,30]. Similarly, Das *et al.*^[31] evaluated this theory in the clinical setting by administering sulfasalazine to patients with active and inactive ulcerative colitis. The serum levels of sulfapyridine, a byproduct of sulfasalazine metabolism, were then measured as a marker of drug activation. Patients with active disease had lower systemic levels of sulfapyridine compared with patients with inactive disease, suggesting less sulfasalazine had been activated to release the 5-ASA molecule. As such, pro-drug formulations like sulfasalazine may potentially be less effective in the setting of active ulcerative colitis due to diarrhoea and accelerated intestinal transit, given their reliance on exposure to colonic bacteria for activation.

Efficacy

Comparing the efficacy of various oral mesalazine formulations is problematic as patient populations in each study differ in terms of disease severity, disease distribution and primary end points. Direct comparative studies have only identified minor yet inconsistent differences in efficacy between agents. In a randomised double-blind study of patients with active ulcerative colitis, balsalazide was found to be significantly more efficacious in inducing remission and better tolerated than the pH dependent formulation (Asacol®)^[32]. Two subsequent studies, however, were not able to reproduce these results^[33,34].

The influence of enteric coating on efficacy has also been evaluated. Gibson *et al.*^[35] demonstrated in

a randomised double-blind trial that Eudragit-L (pH-dependent) and ethylcellulose-coated (time-dependent) mesalazine tablets achieved comparable rates of clinical remission after 8 wk of therapy. In contrast, another study by Ito *et al.*^[36] found that pH-dependent formulations were significantly more effective than time-dependent formulations in patients with proctitis-predominant ulcerative colitis.

As discussed, MMX mesalazine utilises multi matrix technology in an attempt to release 5-ASA in a controlled manner. Pharmacokinetic studies also suggest a more prolonged duration of drug release, theoretically enabling active drug delivery to more distal regions of the colon. Prantera *et al.*^[37] compared MMX mesalazine 2.4 g/d to Asacol® 2.4 g/d as maintenance therapy in 331 patients with left sided ulcerative colitis. After 12 mo, the two formulations were comparable in maintaining clinical and endoscopic remission based on clinician assessment, 60.9% and 61.7% respectively. However, based on patient diary records of symptoms, including stool frequency and rectal bleeding, 62.2% of patients treated with MMX mesalazine maintained remission compared with 51.5% treated with Asacol ($P = 0.053$)^[37]. Although not statistically significant, there is a trend to suggest that MMX mesalazine may be more efficacious in patients with left sided ulcerative colitis. The disparity between clinician assessment and patient records may be a reflection of under reporting of symptoms during clinical consultations.

It is apparent that studies have to date delivered incongruent results regarding the efficacy of different oral mesalazine agents. A Cochrane review by Feagan and Macdonald^[8] in 2012 aimed to accrue currently available data and compare the efficacy and safety of oral mesalazine formulations in ulcerative colitis. The meta-analysis did not show any statistically significant difference in efficacy between the various preparations of mesalazine in induction of remission. Interestingly, in maintenance of remission, sulfasalazine was significantly superior to other oral mesalazine agents, with 43% of sulfasalazine patients relapsing compared with 48% of patients treated with other oral mesalazine preparations (12 studies, 1655 patients; RR = 1.14, 95%CI: 1.03-1.27)^[7]. However, it must be highlighted that comparative reviews should be interpreted with caution, as they may not account for patient population and study design variability between different trials. Given the paucity of direct comparative trials with adequate power, the relative efficacy of different oral mesalazine formulations cannot be definitively concluded. Patient characteristics, such as disease distribution nevertheless, do anecdotally influence clinicians towards the selection of a particular agent.

Safety

Mesalazine is generally well tolerated, with similar side effect profiles between different formulations. The rate of adverse events is estimated to be in the range of

20%-30%^[38]. The most common side effects include arthralgia, myalgia, flatulence, abdominal pain, nausea, diarrhoea and headache. Rare but serious side effects include interstitial nephritis and pancreatitis.

Of the mesalazine formulations, olsalazine more commonly causes diarrhoea, with up to 29% of patient experiencing this side effect^[39,40]. This has been attributed, at least in part, to the presence of the azo bond, which has prosecretory effects on rabbit mucosa *in vitro*^[41].

As expected, sulfasalazine is poorly tolerated compared with other mesalazine formulations. A meta-analysis found 28% of patients treated with sulfasalazine experienced adverse events compared with 15% of other mesalazine agents (RR = 0.48, 95%CI: 0.37-0.63)^[8]. In addition, it is also associated with agranulocytosis, a rare but potentially fatal haematological condition^[42]. As a result, sulfasalazine is increasingly superseded by the newer generation oral mesalazine formulations. Patients who do not tolerate sulfasalazine may benefit from switching to an alternate mesalazine agent that does not contain the sulfapyridine moiety, which is believed to cause the majority of side effects.

Adherence

The natural history of ulcerative colitis entails a remitting and relapsing clinical course. Maintenance therapy is important in prevention of disease recurrence. Non-adherence, defined as taking less than 80% of prescribed medications, ranges between 40% to 72% in patients with ulcerative colitis^[43,44]. This is particularly problematic in patients with quiescent disease, as the benefit of therapy is less obvious. Patients who are non-adherent have a five-fold greater risk of disease recurrence than adherent patients^[45].

Determinants of adherence are varied and patient-specific. Risk factors for non-adherence include male sex, single status, full-time employment, and thrice daily dosing^[44]. Dosing regimen is one facet of this multifactorial issue. A meta-analysis by Claxton *et al*^[46] suggested that less frequent dosing is associated with higher adherence. Multi-dose regimens and large pill burdens have been identified as major barriers to adherence in ulcerative colitis^[47]. Formulations such as MMX mesalazine with once daily (OD) dosing or granule-based preparations with lower pill burden should in theory assist adherence.

OD dosing was compared with conventional dosing in a meta-analysis by Ford *et al*^[48] in 2011. Rates of adherence were not significantly different between the two groups. Similarly, in the meta-analysis by Feagan and Macdonald^[7], OD dosing did not result in improved adherence compared with conventional dosing. The most plausible explanation for this finding is that medication adherence in most clinical trials is artificially higher due to the intensive clinical supervision and reinforcement, thus not necessarily a true reflection of real-world clinical practice. OD dosing of mesalazine is still promulgated as the preferred option for reducing pill

burden and promoting adherence.

Cost effectiveness

Ulcerative colitis is a chronic disease which requires prolonged therapy to maintain remission. This can place a substantial financial burden on the patient or the healthcare provider. On a per tablet basis, novel formulations of oral mesalazine are often presumed to be more expensive. Yet, Prenzler *et al*^[49] analysed the cost effectiveness of Mezavant® compared with Asacol® and showed a 76% probability for cost savings and a gain of 0.011 quality adjusted life-years (QALYs) with Mezavant®. A similar United Kingdom analysis of Mezavant® and Asacol® found a 62% chance of cost savings and a gain of 0.011 QALYs with Mezavant®^[50]. Both these models suggest that Mezavant® may be a cost effective option amongst oral mesalazine formulations.

CHANGING MESALAZINE FORMULATIONS

Although mesalazine is overall an effective therapy in ulcerative colitis, not all formulations are appropriate for each individual patient. The clinical decision to change from one preparation to another is often influenced by factors including clinical response, tolerability, pill burden, compliance, cost and patient preference. (See Figure 2) An important clinical dilemma is whether patients who have failed one formulation of mesalazine should be switched to an alternate preparation, or should the lack of response to one formulation be considered a class effect.

In a small study, 9 ulcerative colitis patients with endoscopic evidence of active disease despite treatment with Asacol® 2.4 g/d were changed to Pentasa® 4.0 g/d. Following twelve weeks of treatment, there was a significant reduction in the endoscopic severity of disease^[51]. It is important to highlight, however, that the dosages of the two mesalazine formulations were not equimolar. In another study, sub-analysis of two MMX mesalazine trials identified a pooled population of patients with active mild to moderate ulcerative colitis, who were switched from an existing oral 5-ASA (≤ 2.0 g/d) to 2.4 g/d or 4.8 g/d of MMX mesalazine. After 8 wk, significantly more patients treated with 4.8 g/d (37.5%, $P < 0.05$) and numerically more patients treated with 2.4 g/d (31.8%) achieved endoscopic remission compared to placebo (20.9%)^[52]. Similarly, two small pilot studies also evaluated 87 patients who were inadequately maintained on mesalazine and switched to OD dosing Salofalk® granules. After 6 mo of therapy, 70% of patients demonstrated improved ulcerative colitis severity scores (Walsley Index). There was also a 60% reduction in hospital visits due to flare of disease, 45% reduction in family doctor visits and 50% reduction in steroid usage^[53]. In addition, Motoya *et al*^[54] reported a retrospective analysis of 46 patients with active ulcerative colitis, who were switched from a

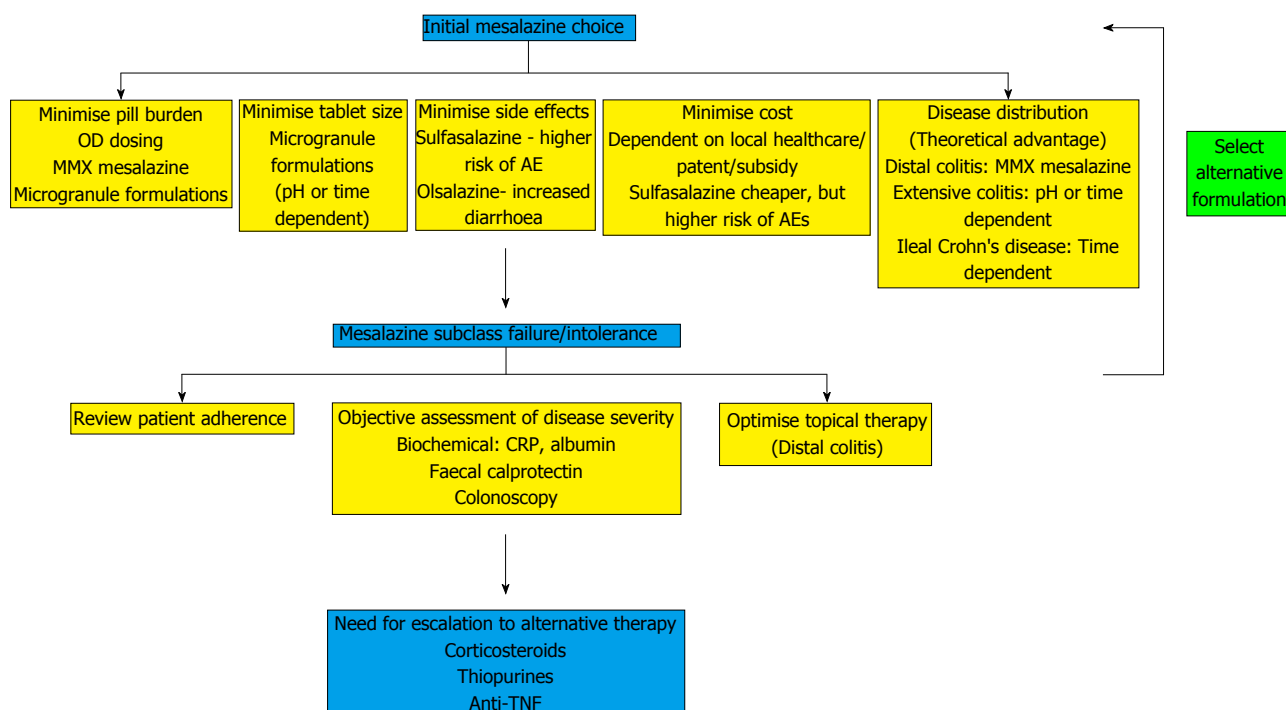


Figure 2 Algorithm for selection of mesalazine formulations. Anti-TNF: Anti-tumour necrosis factor; AEs: Adverse events; MMX: Multi-matrix system; OD: Once daily; CRP: C-reactive protein.

time-dependent mesalazine formulation (4.0 g/d) to a pH dependent formulation (3.6 g/d) due to inadequate clinical response. At 8 wk, 50% of patients achieved clinical remission, with a significant reduction in the Lichtiger clinical activity index. These studies suggest that patients with poor response to one formulation of oral mesalazine may benefit from switching to an alternate preparation, although the data remains sparse and warrants further investigation.

On the other hand, patients who have stable disease on a particular mesalazine formulation should not change preparations as it may destabilise disease control. Robinson *et al*^[55] found in a retrospective study that stable patients who switched mesalazine formulations had a 3.5 fold greater risk of relapse compared to those who did not switch. This indicates that the mesalazine formulations are not bioequivalent and disruptions to maintenance mesalazine should be avoided.

CONCLUSION

In summary, oral mesalazine remains the cornerstone of management of mild to moderate ulcerative colitis. Various formulations have been developed in an attempt to optimise drug delivery to the region of active disease. Each differ in terms of enteric coating, site of drug release and mode of drug delivery, and thus are not interchangeable. Failure of one formulation, should not negate future use of the entire drug class. Although there is a lack of consistent comparative data to confidently state the superiority of one formulation over another, there are theoretical advantages of each formulation to provide some limited guidance. Ultimately, the choice

of mesalazine formulation should be tailored to each individual patient, taking into consideration disease distribution, tolerability, adherence and cost effectiveness.

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