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REVIEW

Update on the role of modified release mesalamine in the management of ulcerative colitis and Crohn's disease

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Abstract: 5-aminosalicyclates (5-ASA) remain a key first-line therapy for patients with ulcerative colitis (UC). A range of 5-ASA preparations is available and Eudragit-S® coated modified release formulations of mesalamine, such as Asacol®, remain among the most popular choices. We here review the current understanding of the mechanism of action of 5-ASA in inflammatory bowel disease. We evaluate evidence supporting the efficacy and safety of modified release mesalamine for both induction and remission maintenance in UC, including a review of the data from the recent ASCEND studies. We also examine the controversial issue of the role of mesalamine in treatment of Crohn's disease (CD) and highlight data supporting its use following surgically induced remission of CD. Evidence supporting the use of mesalamine as prophylaxis for colorectal cancer and dysplasia will be considered. Finally, recent developments in our understanding of how to use modified release mesalamine in a safe and cost-effective manner are evaluated, including discussion of the importance of studying patient non-adherence as a key component of future studies in this area.

Keywords: mesalamine (mesalazine), 5-aminosalicyclate, ulcerative colitis, Crohn's disease, modified release

Introduction

The therapeutic activity of 5-aminosalicyclates (5-ASA) in inflammatory bowel disease (IBD) was first demonstrated by the use of orally administered sulfasalazine (which is cleaved to its constituent 5-ASA and sulfapyridine moieties by the action of colonic microflora).[1] While sulfasalazine is effective for induction and remission of maintenance in ulcerative colitis (UC), it is poorly tolerated (particularly at higher doses). Most toxicity results from the sulfa component, which is largely systemically absorbed, while 5-ASA remains predominantly in the colon.[2] Indeed it was this observation that led to the hypothesis that 5-ASA was the active therapeutic component and this was confirmed in studies using enemas of the individual constituents.[3] Several alternative strategies have been employed to direct delivery of 5-ASA to the distal intestine including the use of carrier molecules (as employed in the formulation of balsalazide) or the use of dimeric 5-ASA such as olsalazine; however arguably the more popular strategy has been the use of altered release formulations of mesalamine (or mesalazine), the name used for 5-ASA when it is employed alone as a drug. Two broad formulation strategies have been employed; the use of ethyl cellulose coated microgranules employed in the prototype prolonged release formulation Pentasa® and the use of acrylic enteric coating in formulations such as Asacol®, Claversal® and Salofalk®. We will here focus attention more specifically on Eudragit-S® coated modified release mesalamine

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marketed as Asacol® or Asacolon®. We will review briefly data relating to the pharmacology of this preparation before focusing attention on studies of its use for both induction and remission maintenance in UC and Crohn's disease (CD). We will also look at data on safety and tolerability and the evidence to support 5-ASA use for chemoprophylaxis of colorectal neoplasia. We will concentrate particular attention on recent studies and conclude with a summary of our views on the place of modified release mesalamine in current IBD therapy.

Pharmacology of modified release mesalamine

Modified release mesalamine (Asacol®) ensures active drug reaches its principal site of action in the colon by use of a delivery system that involves coating of the active drug in a synthetic polymer. The coating consists of an 80 to 130 μm layer of Eudragit-S®, a resin containing methacrylic acid and methyl methacrylic acid in a 1:2 ratio. This acrylic resin layer is soluble at a pH of 7 or greater, with the result that drug release therefore occurs in the terminal ileum, the initial site during transit through the gastro-intestinal tract where luminal pH exceed neutral. While significant variations in colonic 5-ASA delivery between agents have been observed, modified release mesalamine appears to achieve satisfactory concentrations of mesalamine in colonic tissue.[4] Significant systemic 5-ASA absorption occurs with all oral preparations and absorbed mesalamine is principally inactivated by acetylation in the liver with subsequent urinary excretion of metabolites.[5] Most orally administered modified release mesalamine is, however, excreted by the fecal route.[6] The pharmacokinetics of delayed release mesalamines do not appear altered by the use of acid suppressants[7] and are not altered significantly in patients with diarrhea.[8]

Mechanism of action of 5-ASA

The mechanism of action of mesalamine is far from entirely understood, although a growing understanding of the molecular action of 5-ASA agents has been emerging. It is now well established that 5-ASA drugs have effects on the production and action of a number of key pro-inflammatory cytokines. 5-ASA drugs appear to impair binding of interferon-gamma (IFN-γ) to its receptor[9] and disrupt the action of this key pro-inflammatory chemokine,[10] including blocking of its detrimental effects on gut barrier function.[11] 5-ASA agents reduce *ex vivo* production of interleukin-1 beta (IL-1β) in IBD mucosal biopsies[12,13] and by circulating peripheral blood monocytes[14] and also appear to impair the production of interleukin 2 (IL-2) with consequent effects on proliferation of T-lymphocytes.[15] In addition to their effects on key cytokines, alterations in other key mediators of inflammation have also been described. 5-ASA agents have been noted to have a significant impact on production and activity of eicosanoids – arachidonic acid-derived signaling molecules with important vascular and immunoregulatory effects. 5-aminosalicylic acid reduced *ex vivo* generation of PGE_2 and LTB_4 by colonic mucosa from UC patients in one study[16] and was noted to reduce LTB_4 in another study (where no change in PGE_2 was detected) with an associated reduction in LTB_4 to PGE_2 ratio.[17] Whether these alterations are fundamental to the action of 5-ASA (or merely co-incidental to decreased inflammation by other mechanisms) remains debatable.

There has been interest in the effects of mesalamine on free radical production, another potential mechanism for modulation of intestinal inflammation by these agents. 5-ASA may act as scavengers of superoxide free radicals produced by inflammatory cells[18] and in some studies have shown the ability to abrogate oxidant induced apoptosis of intestinal epithelial cells, with positive associated effects on mucosal barrier integrity.[19]

Exciting recent studies have offered a more profound insight into the precise molecular mechanisms for the anti-inflammatory activity of 5-ASA, namely their ability to activate peroxisome proliferators-activated receptor-gamma (PPAR-γ).[20] PPARs are nuclear receptors which regulate gene expression. PPAR-γ is expressed at high levels in colonic epithelium and appears important in maintenance of mucosal integrity and regulation of immune activation in the intestinal mucosa. However, PPAR activation may only be a piece of the jigsaw and changes in the balance of angiogenic factors in a rat model of UC have now also been elucidated.[21] Recent intriguing data have also highlighted a potential role for 5-ASA in altering gene expression by enteric microflora,[22] a novel hypothesis which could open a new avenue in our understanding of the mechanism of action of these drugs.

Whatever the precise mechanism of action of these agents, there is abundant evidence that they exert a significant *in vivo* anti-inflammatory effect in patients with IBD. We will proceed therefore to review this evidence with particular focus on the efficacy of modified release mesalamine in a therapeutic setting.

Efficacy in treatment of UC

Remission induction in UC

The therapeutic activity of delayed release mesalamine for remission induction in UC has been observed in

placebo-controlled comparisons. An initial study involved 87 patients with mild to moderately active UC randomized to receive Asacol® 4.8 g/day, 1.6 g/day or placebo. Complete response was observed in 24% of patients receiving 4.8 g/day of mesalamine compared to 5% in the placebo group (with partial response in 50% versus 13% with placebo, $P < 0.001$).[23] No significant difference with placebo was observed for the 1.6 g/day dose, though the numbers randomized to this arm were small (n = 11) and the comparison was likely underpowered. A subsequent multi-center trial made a placebo-controlled comparison of modified release mesalamine at two doses (2.4 g/day and 1.6 g/day) to placebo, with 158 patients with mild to moderate UC randomized. This study demonstrated significant improvement by week 6 with both doses of mesalamine ($P = 0.03$ for comparison with 1.6 g/day dose and $P = 0.003$ with 2.4 g/dose), however only at the 2.4 g/dose was a clear difference observed in the proportion of patients who showed worsening (50% in placebo group compared to 19% with mesalamine 2.4 g/day, $P = 0.003$).[24]

Early comparative studies demonstrated that Eudragit coated mesalamine showed similar efficacy to sulfasalazine in patients with active UC but was better tolerated.[25] Comparative studies followed with other 5-aminosalicylates. An initial randomized comparison of balsalazide 6.75 g/day and mesalamine 2.4 g/day in patients with active UC demonstrated higher rates of complete remission at 12 weeks with balsalazide (62% versus 37%).[26] However, a subsequent larger trial of 154 patients did not detect a significant difference in remission rates at 8 weeks between patients receiving balsalazide 6.75 g/day and modified release mesalamine 2.4 g/day.[27]

More recent studies of modified release mesalamine in active UC have focused on dose considerations, co-inciding with development of a new 800 mg modified release tablet marketed in the United States as Asacol HD®. Three studies have now evaluated the comparative efficacy of modified release mesalamine 2.4 g/day (dosed with a traditional 400 mg Asacol® tablet) and 4.8 g/day (dosed with the new 800 mg HD tablet). The first of these studies, ASCEND I, did not identify any overall difference in improvement at week 6 in 301 patients with mild to moderately active UC.[28] However, subgroup analysis in this study suggested an advantage to the higher dose specifically for patients with moderate (as distinct from mild) disease. The second study (ASCEND II) therefore focused on this subgroup (though patients with mild disease were still recruited).[29] In 268 patients randomized with moderately active disease overall improvement (defined as complete remission or clinical response) at week 6 was observed in 72% treated with mesalamine 4.8 g/day compared to 59% treated with the 2.4 g/day dose ($P = 0.036$). The results of a final study (ASCEND III) have recently also been reported.[30] In this study 772 patients with moderately severe UC were randomized to an identical treatment regimen with remission at week 6 somewhat more common in the high dose group (43% compared to 35%, $P = 0.04$), although treatment success overall (the primary end-point) was not significantly different between the two groups. Interestingly, an advantage to high dose therapy was observed in the sub-group of patients previously treated for UC compared to treatment naïve/newly diagnosed patients. Table 1 summarizes the results of the principal controlled trials of the use of modified release mesalamine for remission induction in ulcerative colitis.

Remission maintenance in UC

The efficacy of modified release mesalamine for maintenance of remission has also been extensively evaluated both in comparison with placebo and in comparisons with other 5-ASA. An initial multi-center study evaluated the effectiveness of maintenance doses of mesalamine 1.6 g/day and 0.8 g/day in a placebo controlled comparison.[31] 264 patients with UC in remission for 1 month were randomized with an end-point of endoscopic remission at 6 months defining treatment success. In both intention to treat and per protocol analysis mesalamine at both doses was significantly better than placebo for remission maintenance. Remission was maintained in 70.1% (1.6 g/day) and 63.3% (0.8 g/day) compared to 48.3% in the placebo group in the intention to treat analysis ($P = 0.05$ for comparison with 0.8 g/day dose, $P = 0.005$ for comparison with 1.6 g/day dose) but no significant difference between the two doses of mesalamine was detectable. A subsequent study suggested that the addition of twice weekly rectal mesalamine 4 g to maintenance oral Asacol® 1.6 g/day significantly reduced the risk or relapse at one year (from 69% with oral therapy alone to 39% with combination treatment, $P = 0.036$).[32]

A number of studies have compared modified release mesalamine to sulfasalazine in maintenance therapy. Two early studies both showed equivalence of modified release mesalamine in remission maintenance in UC.[33,34] A subsequent larger study randomized one hundred patients with a longer duration of follow up. This study demonstrated that mesalamine doses of 0.8 and 1.6 g/day were equally effective to sulfasalazine 2 to 4 g/day in remission maintenance with relapse rates at 48 weeks (primary end point) of 38 and 39% respectively.[35]

Table 1 Summary of controlled trials of modified release mesalamine for induction of remission in ulcerative colitis (UC)

Study author	Number randomized	Treatment arm	Comparator arm	Response	Remission	Comments
Schroeder[23]	n = 87	Mesalamine 4.8 g or 1.6 g for 6 weeks	Placebo	50% (4.8 g) 18% (1.6 g) 13% (placebo)	24% (4.8 g) 9% (1.6 g) 5% (placebo)	4.8 g dose superior to placebo
Sninsky[24]	n = 131	Mesalamine 2.4 g or 1.6 g for 6 weeks	Placebo	49% (2.4 g) 43% (1.6 g) 23% (placebo)		Per protocol analysis. Both doses superior to placebo
Green[37]	n = 101	Mesalamine 2.4 g for up to 12 weeks	Balsalazide 6.75 g		62% (Bal) 37% (Mes)	ABACUS Induction Trial Balsalazide appeared superior to mesalamine
Levine[27]	n = 154	Mesalamine 2.4 g for 8 weeks	Balsalazide 6.75 g or 2.25 g		20% (Mes) 23% (Bal 6.75) 19% (Bal 2.25)	No sig. difference noted between balsalazide 6.75 g and mesalamine 2.4 g
Hanauer[28]	n = 301	Mesalamine 4.8 g for 6 weeks	Mesalamine 2.4 g	56% (4.8 g) 51% (2.4 g)		ASCEND I includes patients with mild and moderate UC
Hanauer[29]	n = 386	Mesalamine 4.8 g for 6 weeks	Mesalamine 2.4 g	72% (4.8 g) 59% (2.4 g)	20% (4.8 g) 18% (2.4 g)	ASCEND II rates for n = 286 with moderate disease only
Sandborn[30]	n = 772	Mesalamine 4.8 g for 6 weeks	Mesalamine 2.4 g	70% (4.8 g) 66% (2.4 g)	43% (4.8 g) 35% (2.4 g)	ASCEND III only patients with moderate disease enrolled

Abbreviations: Mes, mesalamine; Bal, balsalazide.

A single randomized study has been reported which compared the relative efficacy of olsalazine and mesalamine.[36] One hundred patients in remission with UC were randomized to olsalazine 1 g/day or mesalamine (Asacol®) 1.2 g/day. Treatment failure at 12 months was observed in 24% in the olsalazine group compared to 46% in the mesalamine group ($P = 0.025$). The relapse rates observed at 1 year (only 12% in the olsalazine group) were less in this single center study than those observed in other similar comparative studies. For example, in a comparative multi-center study of remission maintenance with balsalazide (3 g/day) and modified release mesalamine 1.2 g/day relapse rates of 42% in both treatment groups were reported at 12 month follow-up.[37]

A recent development in technology for mesalamine delivery has been the development of the multimatrix system (MMX), a formulation system which comprises lipophilic and hydrophilic excipients enclosed within a pH-dependent coating to allow gradual release of active drug along the colon.[38] The MMX mesalamine (Lialda®) formulation has demonstrated efficacy for both induction and maintenance in UC[39,40] and results of a head to head comparison with modified release mesalamine for remission maintenance have recently been reported.[41] This study randomized 331 patients with UC to receive either modified release mesalamine (Asacol®) 2.4 g/day with twice daily dosing or MMX 5-ASA 2.4 g/day with once daily dosing with appropriate placebo controls in each case. The proportion of patients in clinical remission at 1 year was similar in both groups (66% versus 68%) with combined rates of clinical and endoscopic remission also similar. Adverse events did not differ between the two study groups. The principal controlled trials for remission maintenance in UC with modified release mesalamine are shown in Table 2.

In summary, therefore, there is a significant body of evidence from randomized controlled trials of the efficacy of modified release mesalamine in both induction and maintenance of remission in UC. This agent generally appears at least as effective as other 5-ASA compounds at comparable doses. Recent developments in 5-ASA delivery technology have not enhanced its effectiveness compared to traditional 5-ASA formulations, though the possibility of once daily dosing may impact on compliance and patient preference.

Efficacy in treatment of CD

While there is a strong general consensus about the important role of 5-ASA in general and mesalamine preparations in particular in the treatment of UC, the proper place of mesalamine in CD therapy is a much more contentious issue.

There has been only one published randomized study of the use of modified release mesalamine in treatment of active CD.[42] Patients with mild to moderately active ileo-colonic CD were randomized to receive mesalamine 3.2 g/day (n = 20)

Table 2 Summary of controlled trials of modified release mesalamine for maintenance of remission in ulcerative colitis

Study author	Number randomized	Treatment arm	Comparator arm	Remission	Comments
Mesalamine Study Group[31]	n = 264	Mesalamine 1.6 g or 0.8 g for 6 months	Placebo	70% (1.6 g) 63% (0.8 g) 48% (placebo)	Intention to treat analysis Both doses superior to placebo
Riley[35]	n = 100	Mesalamine 0.8–1.6 g for 48 weeks	Sulfasalazine 2–4 g	62% (Mes) 61% (SSZ)	Treatment equivalence demonstrated
d'Albasio[32]	n = 69	Mesalamine 1.6 g with twice weekly 5-ASA enema for 12 months	Mesalamine 1.6 g	61% (combo) 31% (oral)	Combination therapy superior to oral mesalamine alone
Courtney[36]	n = 100	Mesalamine 1.2 g for 12 months	Olsalazine 1 g	54% (Mes) 76% (Ols)	Olsalazine superior to mesalamine
Green[37]	n = 99	Mesalamine 1.2 g for 12 months	Balsalazide 3.0 g	58% (Mes) 58% (Bal)	Treatment equivalence demonstrated
Prantera[41]	n = 331	Mesalamine 2.4 g for 12 months	MMX 5-ASA 2.4 g	66% (Mes) 68% (MMX)	Treatment equivalence demonstrated

Abbreviations: Mes, mesalamine; Bal, balsalazide; SSZ, sulfasalazine; Ols, olsalazine; MMX, multimatrix formulation.

or placebo (n = 18). The study endpoints were remission (CDAI < 150) or response (CDAI > 150 with >70 point reduction from baseline) at 16 weeks. Complete response (remission) was observed in 45% in the treatment group compared to 22% in the placebo group where treatment failure was seen in 72% compared to 35% of the mesalamine-treated patients.

These impressive differences have not, however, been reproduced by larger studies and systematic review has failed to identify convincing evidence for the effectiveness of 5-aminosalicylates for treatment of active CD.[43] Indeed a recent meta-analysis suggested that there was no evidence to support the use of 5-ASA in the maintenance of medically induced remission in CD.[44] However the situation may be somewhat different with surgically induced remission in CD.[45] While most of the studies evaluating the use of mesalamine in post-operative prophylaxis have made use of either prolonged release (ethyl cellulose) or Eudragit-L® coated preparations, some of the most encouraging studies have evaluated the activity of Eudragit-S® coated modified release mesalamine (Asacol®). An initial randomized study of the effect of mesalamine 2.4 g/day following first intestinal resection for CD demonstrated a dramatic difference in both the rates of endoscopic recurrence and symptomatic (clinical) recurrence at 24 months with mesalamine.[46] However the study has been criticized due to the absence of an adequate placebo control with consequent concerns about bias, due to inadequate allocation concealment. A subsequent randomized placebo controlled trial by the same authors evaluated the relative efficacy of modified release mesalamine 4.0 g/day compared to 2.4 g/day when given as post-operative prophylaxis.[47] The study (n = 101) did detect a reduction in the primary end-point, the number of patients with any degree of endoscopic recurrence (Rutgeerts score >0; 62% in the 4.0 g group versus 46% in the 2.4 g/day group, $P < 0.04$). No significant differences were detected, however, in the rates of severe endoscopic recurrence or clinical recurrence at 12 months.

A recent meta-analysis of the effectiveness of a range of interventions for post-operative recurrence has suggested that there is evidence for a modest reduction in the risk of both clinical and endoscopic recurrence with use of mesalamine preparations when used for prevention of post-operative CD recurrence.[48] The number needed to treat to prevent a single clinical recurrence is 12, which raises concerns about the cost-effectiveness of mesalamine in this context. On the other hand, it can be argued that mesalamine is safe and well tolerated, in contrast to other agents suitable for use in prevention of CD recurrence. Indeed, safety issues with mesalamine, especially those relevant to modified release formulation are what we will go on to consider next.

Safety and tolerability in IBD

Data from controlled trials have showed that modified release mesalamine is generally well tolerated in treatment of IBD. A slight excess of gastro-intestinal side-effects such as nausea, dyspepsia and diarrhea has been reported in some placebo controlled trials (see Table 3) though without a significant dose relationship.[24] However, in larger long term trials of modified release mesalamine dosed at 4.8 g/day

Table 3 Common adverse effects of delayed release mesalamine in a large randomized placebo controlled trial[24]

Adverse effect	Placebo	Mesalamine 1.6 g/day	Mesalamine 2.4 g/day
Vomiting	2%	2%	0%
Nausea	2%	2%	4%
Dyspepsia	0%	0%	2%
Diarrhea	0%	0%	4%
Gas	4%	2%	4%
Rash	4%	4%	0%
Headache	14%	15%	4%

treatment is well tolerated with low rates of withdrawal due to adverse effects.[29,30] Meta-analysis suggests that the tolerability of other 5-ASA including mesalamine is generally superior to sulfasalazine[49] and that withdrawals due to adverse events are not significantly greater than for placebo.[49] Rare serious adverse events associated with delayed release mesalamine have, however, been reported including blood dyscrasias, pancreatitis, pneumonitis, pericarditis and hepatitis. A paradoxical worsening of colitis is observed infrequently with all 5-ASA drugs, a phenomenon that is not well understood. One of the most feared and contentious side effects of 5-ASA is the rare risk of interstitial nephritis. While chronic interstitial nephritis has been reported in association with modified release mesalamine therapy,[50] there have also been reports in IBD patients in the absence of 5-ASA therapy[51] and both disease activity and 5-ASA therapy have been associated with renal tubular dysfunction in IBD patients.[52] To date there is no evidence of any difference between 5-ASA preparations in terms of risk of renal dysfunction.[53,54] While some authors have made recommendations for close monitoring of renal function in IBD patients initiating 5-ASA therapy,[55] this remains controversial and others have argued that renal dysfunction is exceptionally rare and that monitoring is not warranted.[56]

Role in chemoprophylaxis of colorectal neoplasia

While the principal reason for mesalamine prescribing remains the induction and maintenance of disease remission in IBD, particularly UC, there has been increasing interest into its potential role in prevention of neoplasia complicating chronic colitis. Few authors now dispute that there is an increase in the risk of colorectal cancer (CRC) in patients with UC and that the incidence increases progressively with disease duration, such that cancer risk may be as high as 8% by 20 years and 18% by 30 years from diagnosis of colitis.[57] A number of epidemiological studies have suggested that 5-ASA use by UC patients maybe be associated with a reduced incidence of CRC. A nested case control analysis of data from a large primary care database in the UK found the odds ratio (OR) of CRC was decreased in regular (compared to irregular) 5-ASA users (adjusted OR 0.60, 95% confidence interval [CI] 0.38 to 0.96) and was negatively associated with the number of prescriptions for both sulfasalazine and mesalamine filled in the preceeding 12 months.[58] Another UK case control study with over 100 cases of UC-associated CRC made similar findings with the OR of CRC significantly reduced with 5-ASA use, particularly mesalamine (OR 0.19, 95% CI 0.06 to 0.61).[59] This study also highlighted that regular clinic visits with a hospital doctor were also protective and there has been debate about whether 5-ASA use/adherence is merely a surrogate for better compliance with other aspects of health maintenance. This may partially explain the failure of some other case control studies to identify a significant association between cancer risk and preceding 5-ASA use.[60] It is possible that differences in the application of endoscopic surveillance for IBD associated dysplasia in different countries or geographical areas might influence how important an anti-neoplastic effect mesalamine or other 5-ASA have in a given population. The balance of evidence, however, appears to suggest that 5-ASA are protective in reducing risk of CRC but their effect on the incidence of dysplasia requires ongoing evaluation.[61] Given the significant costs associated with treatment of CRC, it is important that the impact of 5-ASA be fully understood and factored into any pharmaco-economic analysis of their use. Indeed, this is an area that we will now go on to evaluate in more detail.

Recent developments in use of modified release mesalamine

There has been increasing focus recently on the pharmaco-economic aspects of 5-ASA use in UC. Cost-effectiveness studies of 5-ASA therapies in UC have highlighted that both cost per flare prevented and cost per quality of life adjusted year (QALY) gained with maintenance 5-ASA treatment is substantial. It has even been suggested that 5-ASA maintenance may only be cost-effective in the case of sulfasalazine (where monthly drug costs are substantially lower than for other 5-ASA preparations).[62] However, healthcare costs can vary substantially both regionally and from country to country and so the findings of such studies can be difficult to apply universally. For example a

cost utility study performed in the UK which specifically examined the relative cost-effectiveness of high dose (HD) modified release mesalamine (4.8 g/day of Asacol HD® 800 mg) versus standard therapy with 2.4 g/day Asacol® with the standard 400 mg preparation came to a very different conclusion.[63] This analysis favored the use of HD mesalamine as more effective, less costly and based on a cost per QALY threshold of £30,000 reported a 72% likelihood that its use was cost-effective. A specific quality of life analysis (using the IBDQ index) on patients enrolled in the ASCEND I and II studies has certainly highlighted significant early improvements in IBDQ scores with modified release mesalamine therapy.[64]

Recent studies have also highlighted the crucial importance of non-adherence in the both the cost and utility of 5-ASA use. A recent systematic review of the impact of 5-ASA non-adherence in UC pays particular attention to the cost of associated flares.[65] Based on data from six 5-ASA RCTs they observed relative risk of flare in excess of 3.65 in non-adherent patients. Despite the additional expenditure on medications in adherent patients, overall co-morbidity adjusted healthcare costs were greater in non-adherent individuals.

Given the high levels of non-compliance with maintenance therapy reported by UC patients,[66] there has been significant interest in devising methods to improve adherence. Data on compliance in patients taking delayed release mesalamine have highlighted specific factors associated with non-compliance.[67] Logistic regression revealed 3-times daily dosing (OR, 3.1; 95% CI, 1.8 to 8.4] and full-time employment (OR, 2.7; 95% CI, 1.1 to 6.9) to be independent predictors of non-compliance. Interestingly, clinical depression was the only independent predictor of complete non-compliance (OR, 10.5; 95% CI, 1.8 to 79.0), highlighting the importance of identifying and treating co-morbid mood disorders in IBD patients in order to maximize the quality of their care. Based on this data, aiming for a once or twice daily dosing regime would certainly appear worthwhile. However, while dosing frequency certainly appears important other intervention may be considered to minimize non-adherence. Physician's time spent in education and use of other simple behavioral strategies may also constitute important adjuncts.[68] Non-adherence is clearly an important issue in how 5-ASA drugs are used, with both significant clinical and economic consequences. Future studies of 5-ASA should ideally ensure that non-adherence is included as a key outcome component.

As well as consolidating our understanding of how best to use mesalamine in treatment of UC and possibly in CD, there may be additional novel therapeutic avenues that merit evaluation. Future studies may be useful to examine new indications for mesalamine outside of IBD therapy, including the use of modified release mesalamine in other inflammatory disorders of the colon such as diverticulitis.[69] There has even been interest in potentially beneficial effects of the anti-inflammatory properties of mesalamine in functional bowel disorders.[70]

Conclusion

Modified release mesalamine (Asacol® or Asacolon®) remains among the most popular 5-ASA formulations currently in use for the treatment of IBD. There is a significant body of data from clinical trials that modified release mesalamine is more effective than placebo for both induction and remission maintenance in UC and this agent compares favorably with other 5-ASA in comparative studies. Several recent studies have been helpful in clarifying optimal use of this agent in UC. Recent data suggest that twice daily modified release mesalamine therapy with 4.8 g/day may be more effective than 2.4 g/day in remission induction in UC patients with disease of moderate severity, although the differential effect is modest at best. Recent maintenance studies demonstrate that at equivalent doses, twice daily modified release mesalamine is as effective as once daily MMX mesalamine. The choice between these agents is likely to be determined, therefore, by factors such as cost and patient preference. It remains to be seen, however, whether once daily dosing has a clinically significant advantage over twice daily dosing with regards to long-term rates of 5-ASA compliance. There is a paucity of data to support mesalamine use in treatment of active CD or in maintenance of medically induced remission. However, there are data for a modest benefit for mesalamine in maintenance of surgically induced remission, although the number needed to treat to prevent a single clinical recurrence is approximately twelve. There are insufficient studies to determine whether any 5-ASA formulation is superior to another in this context. The real question is whether use of mesalamine is cost-effective in the post-operative setting in CD and this issue remains open for debate and further study. There are conflicting data on the cost-effectiveness of mesalamine as maintenance treatment for UC and this is an area that merits further careful evaluation. Cost-effectiveness analysis should probably also incorporate an understanding of the likely chemo preventive properties of mesalamine, as this may be an important consideration in how and why these agents are used into the future.

Disclosures

The authors disclose no conflicts of interest.

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