

Review article: balsalazide therapy in ulcerative colitis

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SUMMARY

Balsalazide is a 5-aminosalicylic acid (mesalazine) pro-drug which has an inert carrier molecule instead of the sulfapyridine moiety of sulfasalazine. It is designed to deliver 5-aminosalicylic acid to the colonic mucosa without the sulfapyridine-associated side-effects encountered with sulfasalazine.

Several studies have confirmed the efficacy and patient tolerance of balsalazide. When compared to mesalazine at equivalent doses, it induced symptomatic and

complete remission of acute ulcerative colitis in a greater proportion of patients. In particular, patients with resistant left-sided disease were shown to have a higher probability of achieving remission. Balsalazide was beneficial in patients with troublesome nocturnal symptoms. It has a similar efficacy in maintaining remission when compared to sulfasalazine and mesalazine. The advantage of balsalazide over other 5-aminosalicylic acid compounds is its superior patient tolerability with minimal side-effects.

INTRODUCTION

Sulfasalazine (SSZ) is a well-established treatment for ulcerative colitis.^{1,2} Since the drug's introduction nearly half a century ago for the treatment of rheumatoid arthritis,³ the side-effect profile has become well known.^{4–6} Following the demonstration that the anti-colitic activity of SSZ lay in the 5-aminosalicylic acid (5-ASA, mesalazine) moiety,^{7,8} the search for an alternative way of releasing oral 5-ASA in the colon began in earnest with the aim of finding a 5-ASA compound that is as efficacious as SSZ but without the high incidence of side-effects. A number of different methods for administering oral 5-ASA have been devised accordingly.

(i) Azo compounds (e.g. SSZ, olsalazine, balsalazide). In the case of SSZ, 5-ASA and sulfapyridine molecules are joined together and, in the case of olsalazine, two 5-ASA molecules are azo-bonded. Balsalazide is a

pro-drug in which a 5-ASA molecule is linked via a diazo-bond to 4-aminobenzoyl-B-alanine (4-ABA), an inert and biologically inactive carrier molecule. All three drugs are released in the colon as a result of azo-bond cleavage by colonic bacterial azo-reductases.

(ii) Mesalazine delayed-release agents (Eudragit-coated). In these preparations, the 5-ASA moiety is coated in a pH-dependent resin. For Eudragit-L-coated mesalazine (Salofalk), this breakdown occurs at pH 6.0 and above, and for Eudragit-S-coated mesalazine (Asacol), at pH 7.0 and above. Thereby these compounds deliver the active 5-ASA to the colonic mucosa.

(iii) Mesalazine slow-release formulation (e.g. Pentasa). In this preparation, mesalazine microgranules are coated with an ethylcellulose membrane. Tablets contain multiple granules, which disperse in the gut, providing a slow, steady release of free 5-ASA from the upper small bowel downwards.

Over the last decade, Eudragit-S-coated mesalazine has been widely used in clinical trials and has gained much popularity in the UK due to its efficacy and fewer side-effects. In recent years, the pro-drug balsalazide has been the focus of attention as an alternative to SSZ.

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Although balsalazide was first developed in 1983 and has undergone animal and human studies,⁹ this drug was not licensed until recently.

For this review of the use of balsalazide in ulcerative colitis, a *Medline* literature search was undertaken using the key words, ulcerative colitis, 5-aminosalicylic acid, sulfasalazine, mesalazine, mesalamine, olsalazine, balsalazide sodium, covering all the literature listed in *Index Medicus* between 1966 and 2000. The product monograph was consulted and all the references quoted in the various relevant papers were reviewed.

PHARMACODYNAMIC AND PHARMACOKINETIC PROFILE

The possible mechanisms by which salicylates exert their therapeutic benefit in patients with ulcerative colitis include alteration of the mucosal prostaglandins, inhibition of the synthesis and release of pro-inflammatory mediators, alteration of intestinal microflora, inhibition of the cellular functions of natural killer cells, mast cells, neutrophils, mucosal lymphocytes and macrophages, and scavenging of reactive oxygen metabolites.¹⁰ Animal studies as well as human pharmacokinetic studies have confirmed the suitability of the balsalazide molecule as an efficient pro-drug source of luminal 5-ASA in the colon with minimal systemic absorption of both the parent compound and its metabolites.^{9, 11, 12} After a 2 g oral dose of balsalazide, the parent compound and its metabolites can be detected in serum only at low concentrations (below 2 µg/mL), and 72% of the carrier molecule 4-ABA is recovered in the faeces.⁹ This contrasts with SSZ which, after a 2 g dose, yields 85% of the carrier molecule sulfapyridine in the urine, indicating significant systemic absorption. Thus, from this and other studies,¹² balsalazide appears to have the favourable pharmacodynamic characteristics of efficient release of 5-ASA in the colonic lumen with much lower systemic absorption of both the parent molecule and its carrier molecule 4-ABA.

CLINICAL TRIALS: IN ACUTE ULCERATIVE COLITIS

There have been five studies of the use of balsalazide in acute ulcerative colitis. Only one study has been published in a full paper,¹³ and the results of the rest are available in abstract form.^{14–17}

Green *et al.* compared high dose balsalazide 6 g/day with SSZ 3 g/day in a prospective double-blind trial recruiting 40 patients with either acute relapse or first presentation of ulcerative colitis.¹⁴ Seventeen of 22 patients (77%) who received balsalazide were in remission at 12 weeks compared with 11 of 18 (61%) on SSZ. Five patients on SSZ were withdrawn from the study due to intolerance compared with none on balsalazide ($P = 0.021$). This study showed that high dose balsalazide is an effective therapy for ulcerative colitis, and is better tolerated than SSZ.

Mansfield *et al.* compared balsalazide 6.75 g/day with SSZ 3 g/day in a double-blind randomized trial in 37 patients with newly diagnosed ulcerative colitis.¹⁵ Assessment of the patients who completed 8 weeks of treatment (balsalazide, 17 patients; SSZ, six patients) showed similar improvement in clinical, sigmoidoscopic and histological appearances. Intolerance to therapy, necessitating withdrawal from the trial, was seen in one of 20 patients on balsalazide and in eight of 17 patients on SSZ ($P = 0.02$). This study concluded that high dose balsalazide is better tolerated than SSZ and more successful in the initial management of ulcerative colitis.

In a different study, Green *et al.* randomized 57 patients with newly diagnosed or relapsed colitis to receive double-blind therapy with either SSZ 3 g/day or balsalazide 6.75 g/day for 12 weeks.¹⁶ Once again, it was found that the remission rates for the balsalazide treated group (81%) were as good as those of the SSZ treated group (61%) or better. No patient on balsalazide was withdrawn due to adverse reactions or intolerance, while 10 patients on SSZ (34%) were withdrawn for this reason.

The first trial comparing balsalazide with another 5-ASA compound was conducted by Levine *et al.*, who reported a multicentre, double-blind, dose-response trial of balsalazide and mesalazine in patients with mild to moderately active ulcerative colitis.¹⁷ An 8-week trial was conducted to assess balsalazide 6.75 g/day compared with balsalazide 2.25 g/day or mesalazine 2.4 g/day. After 8 weeks, balsalazide 6.75 g/day was at least as effective as mesalazine 2.4 g/day and significantly more effective than balsalazide 2.25 g/day for improving symptoms of disease and quality of life in 154 patients (number per group not stated). The percentages of patients who showed improvement at 8 weeks with balsalazide 6.75 g/day, mesalazine 2.4 g/day and balsalazide 2.25 g/day, according to the physician's

global assessment, were 74%, 62% and 51%, respectively. Sigmoidoscopic improvement occurred in 79%, 61% and 53%, improvement in rectal bleeding occurred in 65%, 53% and 32%, and reduction in stool frequency occurred in 59%, 58% and 29% of patients. Although improvements in the patient's functional assessment (71%, 61% and 54%) and in abdominal pain (41%, 44% and 31%) were greater in patients receiving balsalazide 6.75 g/day or mesalazine 2.4 g/day as compared with patients receiving balsalazide 2.25 g/day, the difference in response rates did not attain statistical significance. Patient quality of life scores improved by 40.4, 39.1 and 22.1 points in each group. Complete response rates (not defined) were low in all treatment groups (23%, 19% and 20%). Sigmoidoscopic improvement occurred more rapidly in patients treated with balsalazide 6.75 g/day than in those treated with mesalazine 2.4 g/day (56% vs. 32% of patients improved after 2 weeks, $P = 0.016$). All the above studies have been published only in abstract form.

Recently, the results of a randomized, double-blind study by Green *et al.*, comparing balsalazide 6.75 g/day with mesalazine 2.4 g/day administered for 12 weeks to 99 patients with acute ulcerative colitis, was published as a full paper.¹³ Balsalazide ($n = 50$) produced symptomatic remission in significantly more patients than did mesalazine ($n = 49$). A significantly higher number of patients achieved complete remission with balsalazide than with mesalazine after 4 (38% vs. 12%), 8 (54% vs. 22%) and 12 (62% vs. 37%) weeks. Patients treated with balsalazide experienced their first completely symptom-free day sooner than those treated with mesalazine (after a median of 10 vs. 25 days, $P < 0.005$). They also experienced more asymptomatic days (24% vs. 14%). Fewer patients in the balsalazide group reported adverse events (48% vs. 71%).

Summary of clinical data in active ulcerative colitis

The safety and efficacy of balsalazide in the treatment of active ulcerative colitis have been studied in five clinical trials involving several hundred patients. The results of only one trial involving 99 patients have been published as a full paper. Balsalazide has been compared with SSZ, mesalazine and placebo. Compared with the other two 5-ASA preparations, balsalazide has a more favourable risk-benefit profile. Patients tend to achieve remission sooner with less severe adverse events.

CLINICAL TRIALS: MAINTENANCE OF REMISSION IN ULCERATIVE COLITIS

The potential benefits of balsalazide as a means of maintaining remission in ulcerative colitis have been studied in six randomized clinical trials. Unlike the trials in active ulcerative colitis, the majority have been published as full papers. Five of the six studies were randomized and double-blind in design, and of 6 or 12 months' duration.¹⁸⁻²² They included dose range studies and comparisons with SSZ and mesalazine. The sixth study was a double-blind comparison of balsalazide 3 and 6 g, of 2 years' duration,²³ which continued for a further 2 years as an open study.^{24, 25}

The first randomized double-blind study of balsalazide in the maintenance of remission in ulcerative colitis was conducted by McIntyre *et al.* in 1988.¹⁸ In this study, 79 patients with ulcerative colitis in remission were randomized to receive either SSZ 2 g/day ($n = 38$) or balsalazide 2 g/day ($n = 41$) over a 6-month period. The remission rates were similar (SSZ, 63%; balsalazide, 51%). Even at this low dose, 10 patients on SSZ reported side-effects compared to two patients on balsalazide.

In a trial conducted by the German Colazide Study Group, maintenance of remission over 6 months in patients with ulcerative colitis with balsalazide 6 g/day (79%) was similar to that of mesalazine 1.5 g/day (60%) and significantly better ($P = 0.002$) than that with balsalazide 3 g/day (45%) in a randomized, double-blind, multicentre trial in 133 patients.¹⁹

Two other multicentre trials of longer duration and higher doses have been reported.^{20, 21} Giaffer *et al.* randomized 133 patients with ulcerative colitis in remission to receive double-blind therapy with 2 g/day ($n = 65$) or 4 g/day ($n = 68$) of balsalazide.²⁰ This study showed a significantly higher remission rate at 12 months on 4 g/day of balsalazide (64%) compared to 2 g/day of balsalazide (45%), $P < 0.01$. Adverse events were reported by 12% of patients on 2 g/day and by 19% of patients on 4 g/day. Green *et al.* conducted a similar study randomizing 108 patients with ulcerative colitis in remission to receive double-blind balsalazide in a daily dose of either 3 g ($n = 54$) or 6 g ($n = 54$).²¹ Remission rates for both groups were similar (77% vs. 68%) after 12 months of treatment, indicating that 3 g/day may be the optimal dose of balsalazide for the maintenance of remission. The patients in this study were continued on balsalazide and follow-up was extended over the next 3 years. Sixty-seven patients

who were in remission after the first 12 months were crossed over to the alternative dosage of balsalazide and monitored for a further 12 months.²³ Remission rates were again similar with each dosage (69% with balsalazide 3 g/day and 77% with balsalazide 6 g/day). Forty-five patients in remission after the second year of this study were treated for a further 12 months with balsalazide 3 g/day (increased to 6 g/day if symptoms recurred) in a non-blind fashion.²⁴ Remission was maintained in 80% of patients. Patients in remission at the end of the third year received balsalazide 1.5–6 g/day in a non-blind fashion over a further 12 months.²⁵ A plateau appeared to have been reached, indicating that patients at high risk of relapse experienced this in the first 30 months. Over the entire 4-year treatment period, 38% of patients remained in remission.²⁵ There are no prospective studies of this length of time with any other 5-ASA compound. This study shows that balsalazide is efficacious with good patient tolerance. There have been no significant renal, haematological or biochemical events.

Recently, Green *et al.* have compared balsalazide with mesalazine in a randomized, double-blind, multicentre trial in the maintenance of remission in ulcerative colitis.²² Balsalazide 3 g/day ($n = 49$) was associated with significantly more asymptomatic nights (90% vs. 77%, $P = 0.0011$) and significantly less relapse (10% vs. 28%, $P = 0.0354$) than mesalazine 1.2 g/day ($n = 46$) after 3 months. However, similar numbers of patients (58%) were in remission in both groups after 12 months.

Summary of clinical data in the maintenance of remission in ulcerative colitis

Overall, the data from these clinical trials have shown that balsalazide is effective in prolonging remission in ulcerative colitis and that its efficacy and tolerability compare well with SSZ and mesalazine. Additionally, during the first 3 months, balsalazide was found to provide significantly greater nocturnal symptom control, coupled with a lower relapse, compared with mesalazine.

OVERALL SAFETY PROFILE

The most frequently reported adverse events in patients treated with balsalazide were headache (15.3%), abdominal pain (16.2%), dyspepsia (8.3%), nausea

(7.9%), respiratory infection (6.1%), body pain (5.7%), diarrhoea (5.2%) and dizziness (4.8%).¹² The same eight adverse events were also among the most frequently reported with mesalazine, SSZ and placebo. In most cases, the frequency of individual events was higher with SSZ than with balsalazide, whereas the frequencies were similar between mesalazine and balsalazide as well as between balsalazide and placebo.¹²

DISCUSSION

The medical management of ulcerative colitis has improved with the introduction of newer agents mainly in the form of immunosuppressants. Azathioprine and 6-mercaptopurine have an established role in the induction and maintenance of remission in resistant disease, while ciclosporin has shown promising results in severe acute and refractory colitis.²⁶ The new steroid, budesonide, in the form of delayed-release oral medication, as well as enemas, has demonstrated equal efficacy to prednisolone and hydrocortisone with less suppression of endogenous cortisol secretion.^{27–29} Other new agents, such as heparin, probiotics, nicotine patches, eicosanoids (fish oil), thromboxane inhibitors, cytokines, antioxidants and local anaesthetics, are in the research arena.²⁶ Despite the development of new therapeutic agents, 5-ASA remains the cornerstone of treatment for ulcerative colitis.

Balsalazide is a 5-ASA pro-drug that has demonstrable clinical efficacy in the management of acute exacerbations,^{13–17} and in the maintenance of remission in ulcerative colitis.^{18–25} It has been shown to have a significantly superior tolerability profile to that of SSZ.^{14–16, 18} When compared to mesalazine at equivalent doses, it has induced symptomatic and complete remission of moderate to severe ulcerative colitis more quickly and in a greater proportion of patients.¹³ In particular, patients with resistant left-sided disease treated with balsalazide have been shown to have a higher probability of achieving complete remission after 4 weeks than patients with any other disease extent treated with mesalazine.¹³ It has similar efficacy in maintaining remission when compared to SSZ and mesalazine.^{18, 19}

It has been suggested that delayed, pH-dependent release of 5-ASA is less reliable than agents that use the azo-reductase activity of colonic bacteria.³⁰ Theoretically, if gastric emptying, intestinal transit time and luminal pH are altered, the enteric-coated mesalazine

will be less effective. The major advantage of balsalazide over other 5-ASA compounds is its superior patient tolerability with minimal side-effects.¹² Reduction of nocturnal symptoms by balsalazide is an important factor in improving the quality of life of patients.²² Patient compliance is potentially reduced in any medicine that requires frequent administration and has delayed onset of effect. None of the studies reviewed have addressed this, but balsalazide may offer better compliance since it has better patient tolerability and also patients respond sooner and achieve higher rates of complete remission with reduction in nocturnal symptoms. This may negate the disadvantage of frequent dosing with more than one capsule.

No studies have yet compared balsalazide with olsalazine, which is another 5-ASA compound utilizing the azo-bond and theoretically should be as effective as balsalazide. However, diarrhoea seems to be a troublesome side-effect with olsalazine which may compromise patient tolerability and compliance.^{31, 32} The clinical experience and trial data on balsalazide are limited when compared to SSZ and mesalazine. Most of the clinical trials in active ulcerative colitis have been published in abstract form only. Nonetheless, from current evidence, balsalazide appears to be an effective 5-ASA compound with minimal side-effects and high patient compliance.

CONCLUSIONS

Balsalazide is as effective as SSZ and mesalazine in the treatment of acute ulcerative colitis and in maintaining remission in ulcerative colitis. Patients tend to respond sooner and achieve higher rates of complete remission. It has superior patient tolerability with minimal side-effects. It should be particularly considered in the management of ulcerative colitis patients with troublesome nocturnal symptoms and resistant left-sided disease.

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