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Maintenance of remission of ulcerative colitis: a comparison between balsalazide 3 g daily and mesalazine 1.2 g daily over 12 months

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SUMMARY

Background: Despite widespread use of aminosalicylates as maintenance treatment for ulcerative colitis (UC), patients still report troublesome symptoms, often nocturnally.

Aim: To compare the efficacy and safety of balsalazide (Colazide) with mesalazine (Asacol) in maintaining UC remission.

Methods: A randomized, double-blind comparison of balsalazide 3 g daily (1.04 g 5-ASA) and mesalazine 1.2 g daily for 12 months, in 99 (95 evaluable) patients in UC remission.

Results: Balsalazide patients experienced more asymptomatic nights (90% vs. 77%, $P = 0.0011$) and days (58% vs. 50%, N.S.) during the first 3 months. Balsalazide patients experienced more symptom-free nights per week (6.4 ± 1.7 vs. 4.7 ± 2.8; $P = 0.0006$) and fewer nights per week with blood on their stools or on the toilet paper, mucus with their stools or with sleep disturbance resulting from symptoms or lavatory visits (each $P < 0.05$). Fewer balsalazide patients relapsed within 3 months (10% vs. 28%; $P = 0.0354$). Remission at 12 months was 58% in both groups. Similar proportions of patients reported adverse events (61% balsalazide vs. 65% mesalazine). There were five serious adverse events (two balsalazide, three mesalazine) and four withdrawals due to unacceptable adverse events (three balsalazide, one mesalazine), of which one in each group was also a serious adverse event.

Conclusions: Balsalazide 3 g/day and mesalazine 1.2 g/day effectively maintain UC remission and are equally well tolerated over 12 months. At this dose balsalazide prevents more relapses during the first 3 months of treatment and controls nocturnal symptoms more effectively.

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammation of the large bowel, affecting ≈ 160 per 100 000 of the population.[1] It is characterized by periods of acute relapse and intervals of remission. Maintenance therapies for UC aim to reduce the frequency and severity of the acute attacks, maintain and prolong remission of symptoms and control mucosal inflammation. The choice of treatment is determined by the extent of the disease.[2] Maintenance doses of oral aminosalicylates (e.g. sulphasalazine, olsalazine, mesalazine) are typically prescribed to control both distal and extensive colitis in remission.[2]

Sulphasalazine is well established as a maintenance treatment for UC.[3] However, 20–40% of patients experience side-effects, including nausea, anorexia, skin rashes, blood dyscrasias and male infertility.[4–7] Because most adverse reactions are attributed to the

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sulphapyridine carrier, with 5-aminosalicylic acid (5-ASA or mesalazine) being identified as the therapeutic moiety,[8, 9] the development of alternative therapies has continued over the last 25 years.

Asacol (SmithKline Beecham Pharmaceuticals, Welwyn Garden City, UK), a delayed-release mesalazine formulation with a pH-dependent acrylic resin coating,[10] is a widely prescribed maintenance treatment for UC. Despite the widespread use of delayed-release mesalazine, especially in patients intolerant of sulphasalazine,[11, 12] there is still some concern over its nephrotoxic potential[13] and maintenance studies have reported that ≈ 40% of patients relapse within 6–12 months of commencing treatment.[14, 15] Even if patients remain in 'disease remission', inadequate symptom control, which can result in disturbed sleep and undesirable side-effects are commonly reported problems at routine clinic visits. Inadequate night-time control of symptoms may be interpreted to indicate inadequate control of underlying inflammation. Sleep disturbance and fatigue have been identified by patients as important factors in determining their quality of life.[16, 17] Thus there still remains the clinical need for a better alternative treatment strategy for these patients.

Balsalazide (Colazide; Astra Pharmaceuticals, Kings Langley, UK) is a novel 5-ASA prodrug, in which 5-ASA is linked via an azo bond to 4-aminobenzoyl-β-alanine (4-ABA), an inert and biologically inactive carrier molecule.[18] Colonic release of 5-ASA results from azo-bond cleavage by bacterial azo-reductases. Balsalazide is more effective and better tolerated than sulphasalazine in the acute and maintenance treatment of UC.[5, 6, 19] Balsalazide is also more effective than mesalazine in the treatment of disease exacerbations,[20] and is better tolerated than mesalazine in patients intolerant of sulphasalazine.[21] Due to the minimal systemic absorption of the parent compound or its metabolites, balsalazide lacks nephrotoxic potential.[18] For balsalazide to be preferred as an alternative first line maintenance therapy for UC, either superior efficacy to mesalazine with no compromise in patient tolerability and safety or a better patient tolerability and safety profile with no reduction in efficacy, must be demonstrated. To date no studies have compared balsalazide directly with mesalazine in the maintenance treatment of UC.

The present study compared balsalazide 3 g daily (equivalent to 1.04 g 5-ASA), a suitable dose for maintenance treatment,[22] with delayed-release mesalazine (5-ASA) 1.2 g daily, the dose typically prescribed for maintenance treatment, in terms of efficacy and tolerability in the maintenance treatment of inactive UC. The primary efficacy variable of the study was to determine the proportion of patients in remission after 3 and 12 months. Secondary objectives of the study were to assess the proportion of symptom-free days and symptoms over 3 months according to patient diary card information.

MATERIALS AND METHODS

Patients

Twenty centres in the UK and one centre in the Republic of Ireland participated in the study. The duration of the clinical phase was from August 1993 to March 1997. Patients gave written informed consent and Local Research Ethics Committee approval was obtained. Patients were aged between 18 and 80 years with UC symptoms requiring treatment with maintenance therapy. All patients were therefore asymptomatic (none or only mild symptoms, Table 1) and had a sigmoidoscopic grade of 0 or 1 (Table 2). The grade of UC was verified by sigmoidoscopy or colonoscopy no more than 3 days before initiation of the study therapy. All patients had experienced a relapse involving haemorrhagic mucosa, as verified by sigmoidoscopy, and remission was declared up to a maximum of 1 year

Table 1. Definition of patient overall evaluation of symptoms

Symptoms	Definition
Mild	Aware of symptoms, easily tolerated, no interference with normal activities.
Moderate*	Occasional interference with normal activities.
Severe*	Frequent interference with normal activities.

* Excluded at entry.

Table 2. Definition of ulcerative colitis sigmoidoscopic grades

Grade	Sigmoidoscopic appearance
0	Normal, vascular pattern clearly visible.
1	Erythema with loss of vascular pattern.
2	Erythema with loss of vascular pattern plus contact bleeding.
3	Erythema with loss of vascular pattern plus spontaneous bleeding.
4	Erythema with loss of vascular pattern plus frank ulceration.

(0–365 days) before entry to the study. Patients with coexisting Crohn's disease, idiopathic proctitis or non-inflammatory bowel diseases were excluded from the study. Patients were excluded if they had: received oral or intravenous steroids within the last month, received immunosuppressants within the last 3 months, required the daily use of a rectal steroid to maintain remission, used rectal steroids outside the product licence within the last 2 weeks, received in the last 14 days a dose of 5-ASA releasing compound from which more than 1.2 g 5-ASA/day was available. Patients were excluded if they were unable to discontinue treatment with a rectal 5-ASA preparation on entry to the study.

Materials

Balsalazide (Colazide; Astra Pharmaceuticals, Kings Langley, UK) was supplied as hard gelatin capsules containing balsalazide 0.75 g (manufactured by Penn Pharmaceuticals Ltd, Tredegar, Gwent). Mesalazine (Asacol; SmithKline Beecham Pharmaceuticals, Welwyn Garden City, UK) was supplied as tablets containing mesalazine 0.4 g coated with Eudragit S (an acrylic-based resin). Placebos of identical appearance to the balsalazide capsules and mesalazine tablets were manufactured by Penn Pharmaceuticals Ltd. Patients received two capsules (balsalazide/placebo) and one tablet (mesalazine/placebo) every morning and two capsules (balsalazide/placebo) and two tablets (mesalazine/placebo) every evening.

Study design

The study was a randomized, multicentre, double-blind, double-dummy, parallel group comparison of balsalazide 1.5 g b.d. or mesalazine 1.2 g daily (0.4 g o.m. (once in the morning) plus 0.8 g o.n. (once at night)) for 12 months.

Clinical assessments

At entry, patients underwent a physical examination and sigmoidoscopic examination (within 3 days of the start of study therapy) to grade the macroscopic appearance of the rectal mucosa (Table 2). Data regarding UC disease history, previous disease complications and demographic characteristics were collected. The patients' overall evaluation of symptoms during the previous 3 days was assessed (Table 1).

Patients returned to the clinic after 3, 6, 9 and 12 months of treatment for a general examination and assessment of symptoms, compliance and adverse events. Compliance was assessed by verifying the amount of returned medication. Adverse events were assessed by asking the patient a standard open health question at each clinic visit. Details on the severity, duration and causal relationship to the study drug were also recorded. Sigmoidoscopic examination was repeated after 3 months, on completion of the study at 12 months or upon withdrawal/discontinuation. Patients discontinued on relapse. A symptomatic relapse was defined as the recurrence of moderate or severe symptoms on the patients' overall evaluation. Patients who presented with grade 3 or 4 UC on sigmoidoscopy, in the absence of symptoms, were classified separately as suffering an asymptomatic relapse and were discontinued from the study. Specific criteria for discontinuation also included: at the wish of the patient/investigator, treatment with excluded medication, non-compliance with the study protocol, the development of an excluded medical condition, any unacceptable adverse event or a complication of UC requiring active intervention.

Routine haematology, clinical chemistry and a urinalysis test were performed at entry and on completion of the study. A stool sample was taken if the patient relapsed to determine whether infection was the cause of the presenting symptoms.

Diary card assessments

Patients recorded UC symptoms, other medical problems, the use of other medicines and visits to their general practitioner on a daily diary card for the first 3 months of the study. Three months was considered the maximal duration to ensure patient compliance for diary card completion. The following variables were recorded in the morning (AM) and evening (PM): number of visits to the lavatory to pass stool, blood on stools, blood on toilet paper, mucus, abdominal pain, need to go to the lavatory and other symptoms interfering with sleep (AM only), symptoms interfering with normal daily activities (e.g. work, meals, recreational activities) (PM only), other relevant symptoms. Patients were considered completely free of symptoms if the responses to all the above variables (excluding the number of visits to lavatory) was none or no, as appropriate.

Statistical analysis

The analyses were based on an all-patients-treated approach.

Diary card data were compared between treatments by the Wilcoxon rank sum test, using the last 7 days of diary card data prior to the 3-month visit to summarize the individual daily assessments, with patients required to have at least 4 days of recorded data in this period to be eligible for analysis. The percentage of days (AM and PM diary card assessments for each day) and nights (AM diary card assessments only) with no symptoms was calculated for each patient based on all available diary card data, and compared between treatments using the Wilcoxon rank sum test.

Survival analysis was used to compare the time to relapse between treatments. Patients discontinuing the study in remission had time censored data for the purposes of the survival analysis. Life table estimates and 95% confidence intervals of 3 and 12 month relapse rates were calculated for each treatment group using the Kaplan–Meier estimates of relapse on day 91 and 365, respectively, and the time to relapse compared between treatments by the log rank test. The proportion of patients with a relapse of symptoms necessitating a clinic visit prior to the scheduled 3-month visit was compared between treatments using the chi-squared test. The proportion of patients in symptomatic remission who had sigmoidoscopically diagnosed UC after 3 and 12 months was compared between treatments by Fisher's exact test. A Cox regression model was fitted to the data, to identify prognostic factors significantly associated with symptomatic relapse after 3 and 12 months (logistic analysis). Changes in blood pressure, pulse and weight from entry to relapse or completion were compared between treatments using the Wilcoxon rank sum test. Changes in laboratory assessments from entry to relapse or completion were analysed by the Wilcoxon rank sum test. The percentage of compliant patients was compared between treatments by Fisher's exact test. The proportion of patients attending their GP surgery during the first 3 months of treatment was compared between treatments by the chi-squared test.

The proportions of patients who did not complete the study for any reason, and the proportions of patients discontinuing the study as a result of a treatment failure were compared between treatments by a chi-squared test. The number of patients reporting adverse events was compared between treatments by a chi-squared test. The proportion of adverse events with a probable or possible relationship to the study medication and the percentage of patients who discontinued due to intolerance to treatment were compared between treatments by Fisher's exact test.

All *P*-values relate to two-tailed significance tests and comparisons were deemed to be statistically significant if the *P*-value was less than 0.05. Multiple statistical testing was not considered be an issue in these analyses because each analysis was performed on separate data.

RESULTS

Ninety-nine patients were randomized into the study and 95 patients (49 balsalazide, 46 mesalazine) provided evaluable data; four patients in the mesalazine group were excluded from all analyses because they were lost to follow-up after their initial entry visit (Figure 1). Treatment groups were comparable at randomization for baseline demographic characteristics (Table 3) and UC history (Table 4).

Diary card assessments

Diary card data were available for 88 patients (46 balsalazide, 42 mesalazine). Treatment with balsalazide provided patients with significantly better relief of night-time symptoms during the first 3 months of their treatment. This included significantly fewer nights per week with blood on the stools or on the toilet paper, mucus associated with the stools and less sleep disturbance caused by the need to go to the lavatory or by their symptoms (Figure 2). No significant differences were observed for any of the daytime diary card assessments. There was no significant difference between the two groups in daytime (balsalazide 2.63 ± 2.29, mesalazine 2.26 ± 1.62; $P = 0.6045$) and night-time (balsalazide 0.27 ± 0.67, mesalazine 0.45 ± 0.81; $P = 0.0592$) stool frequency. Overall, after 3 months of treatment patients receiving balsalazide were benefiting from more nights per week completely asymptomatic and undisturbed by their disease (6.4 ± 1.7 vs. 4.7 ± 2.8; $P = 0.0006$). On average, in the first 3 months of treatment, patients in the balsalazide group experienced more nights (AM assessments only) completely asymptomatic (mean 90% vs. 77%; $P = 0.0011$). There were also quantitative differences between the two groups with respect to the number of

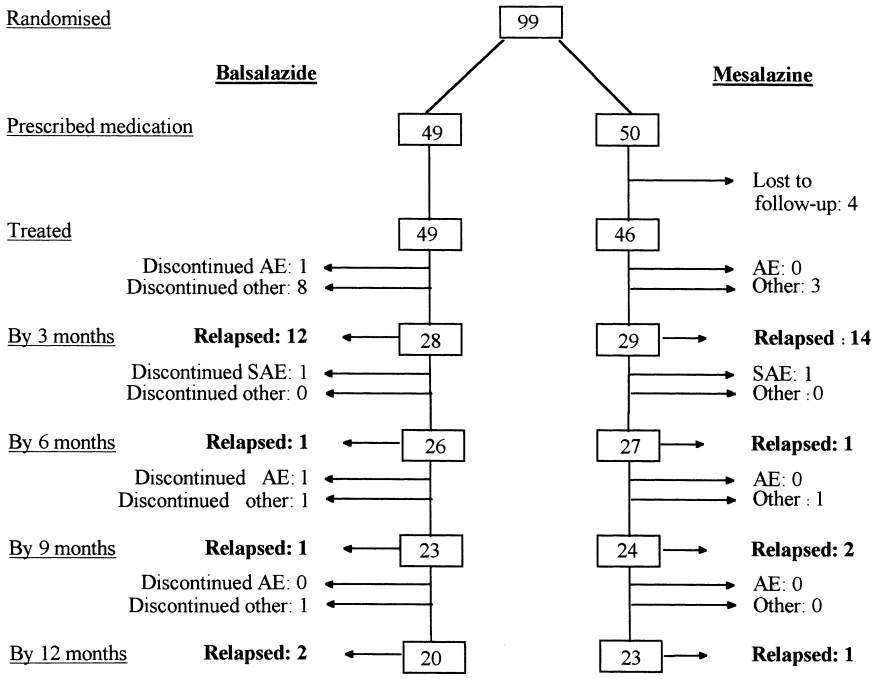

Figure 1. Flow diagram showing patient progress during the study.

Table 3. Patient characteristics at entry

Characteristic	Balsalazide (n = 49)	Mesalazine (n = 46)
Gender (Male:Female)	32:17	24:22
Age (years):	43.3 ± 12.5 (20–70)	46.4 ± 13.4 (21–76)
Height (cm):	170.9 ± 8.8 (145–198)	168.9 ± 9.4 (152–188)
Weight (kg):	76.2 ± 14.3 (53–124)	74.5 ± 13.5 (46.6–99.7)
Smoker (Yes:No)	9:40	3:43
Daily tobacco consumption (g)	8.7 ± 5.8	5.7 ± 4.0
Weekly alcohol consumption (units) (n):		
Teetotal	10	12
Up to 13 units	30	27
14–27 units	6	7
28 + units	3	0

Values are means ± standard deviation with ranges indicated in brackets.

Table 4. Patient ulcerative colitis history, symptoms and sigmoidoscopic examination at entry

Characteristic	Balsalazide	Mesalazine
Remission declared on entry to the study (Yes:No): n (%)	29 (59): 20 (41)	28 (61): 18 (39)
Time since remission declared (days): Mean ± s.d. (n) *(Only patients in remission prior to entry visit)*	67.4 ± 49.6 (20)	69.8 ± 70.5 (18)
Duration of sigmoidoscopically proven ulcerative colitis (months): Mean ± s.d. (n)	67.9 ± 79.2 (49)	61.1 ± 79.0 (46)
Number of acute attacks in last year: Mean ± s.d. (n)	1.5 ± 0.9 (49)	1.4 ± 0.8 (46)
Previous ulcerative colitis complications (Yes:No): n (%)	13 (33): 26 (67)	6 (17): 30 (83)
Previous use of mesalazine:balsalazide in last year: n (%)	30 (61):17 (35)	19 (41): 20 (43)
Symptoms at entry: (None: Mild): n (%)	21 (43): 28 (57)	22 (48): 24 (52)
Ulcerative colitis grade at entry: (Grade 0: 1): n (%)	24 (49): 25 (51)	26 (58): 19 (42)

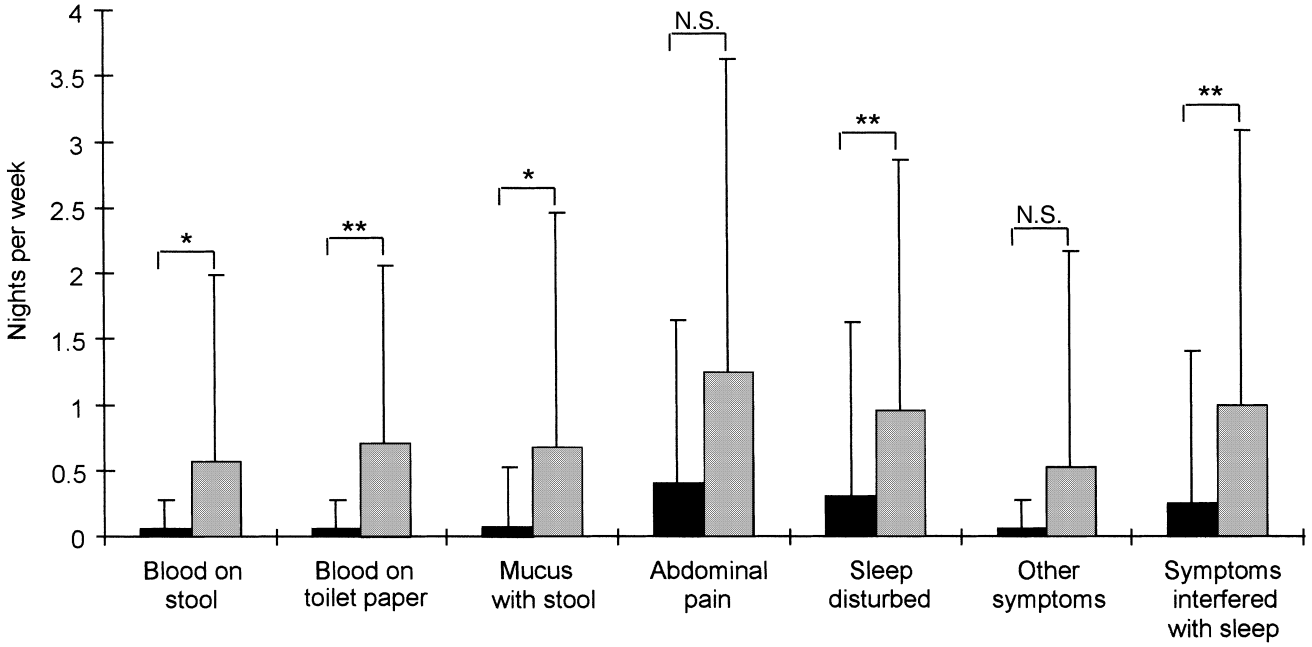

Figure 2. Frequency of night-time diary card symptoms. Frequency of night-time diary card symptoms reported by patients during the week prior of the 3-month visit assessment. Between treatment comparisons: blood on stools $P = 0.0241$; blood on toilet paper $P = 0.0054$; mucus with stool $P = 0.0183$; abdominal pain $P = 0.0502$; sleep disturbed by the need to go to the lavatory $P = 0.0072$; other symptoms experienced $P = 0.0995$; symptoms interfered with sleep $P = 0.0090$. Number of nights per week with no nocturnal symptoms: balsalazide 6.4 ± 1.7, mesalazine 4.7 ± 2.8; $P = 0.0006$.

Number of patients reporting absence of symptoms (basalazide, mesalazine): no blood on stools 40/42, 30/38; no blood on toilet paper 40/42, 28/38; no mucus with stool 41/42, 31/38; no abdominal pain 36/42, 26/38; no sleep disturbed by the need to go to the lavatory 39/42, 26/38; no other symptoms experienced 40/42, 32/38; no symptoms interfered with sleep 40/42, 28/38.

N.S. = not significant, $P < 0.05$, $^{**}P < 0.01$. Mean ± standard deviation presented. ■ Balsalazide; □ Mesalazine.

asymptomatic days (AM and PM assessments) (mean 58% balsalazide vs. 50% mesalazine; $P = 0.3995$, N.S.) and GP visits during the first 3 months of treatment (14% balsalazide vs. 26% mesalazine; $P = 0.201$, N.S.), neither of which achieved statistical significance.

Clinical efficacy

The percentage of patients with a relapse of symptoms necessitating a return visit to the clinic in advance of the scheduled visit at 3 months was significantly lower in the balsalazide group compared to the mesalazine group (5/49 (10%) vs. 13/46 (28%); $P = 0.0354$). The survival analysis at 3 months demonstrated that 79% (95% CI: 66.2–92.6%) of the patients treated with balsalazide remained in remission compared to 65% (95% CI: 49.8–80.7%) of the mesalazine group, although the difference did not achieve statistical significance ($P = 0.1053$). An equal proportion of patients in each treatment group remained in remission by 12 months (survival analysis 58%; $P = 0.4275$) (Figure 3).

Sigmoidoscopic examinations revealed that haemorrhagic mucosa (grade 2–4, Table 2) was present in similar small proportions of patients with none or only mild symptoms at their 3-month and 12-month or final visit assessments. These patients were classified as having experienced an asymptomatic relapse (3 months: 5% balsalazide vs. 3% mesalazine, $P = 1.00$; 12 months: 6% balsalazide vs. 4% mesalazine, $P = 1.00$).

Patients' overall evaluation of their symptoms on entry to the study was identified by logistic analysis as a factor significantly associated with a symptomatic relapse by 3 months ($P = 0.0256$) and 12 months ($P = 0.0114$). Patients were more likely to relapse by 3 and 12 months if they had mild rather than no symptoms on entry to the study (3 months: 37% vs. 14%, 3.1 times greater risk;

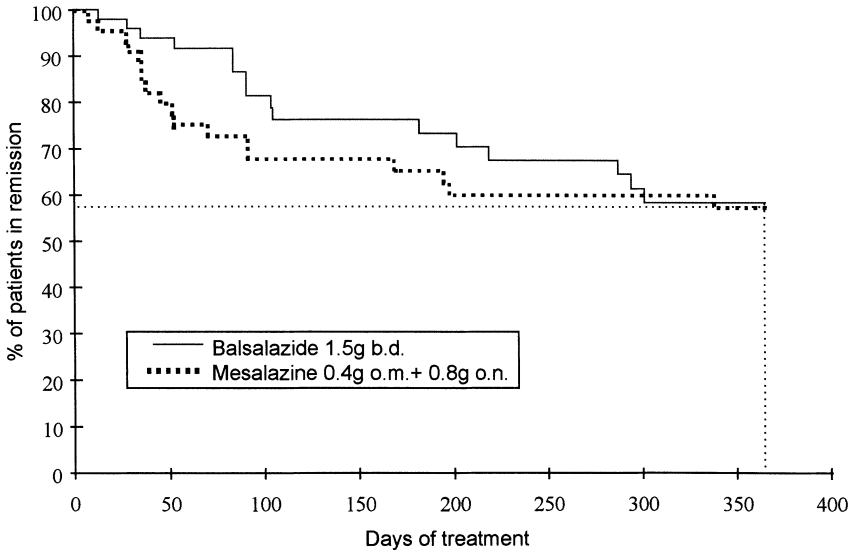

Figure 3. Survival distribution of time to symptomatic relapse for 12 months of treatment. Remission rates for patients after 12 months of treatment with balsalazide 3 g/day or mesalazine 1.2 g/day. Estimates at 12 months based on All-Patients-Treated analysis: Balsalazide 58% of patients in remission (95% CI: 42.3%, 74.3%), mesalazine 58% of patients in remission (95% Cl: 42.5%, 72.6%). Relapses beyond day 365 are not presented graphically because the tail of the survival distribution is unstable due to the small number of patients still at risk at the later time-points.

12 months: 54% vs. 25%, 2.7 times greater risk). Other factors, including time since remission was declared, duration of diagnosed UC, UC sigmoidoscopic grade at entry to the study, age, and alcohol and tobacco intake, were not found to influence remission.

Tolerability and safety

The total exposure of patients to balsalazide was 9634 days and to mesalazine 10 063 days ($P = 0.8919$, N.S.). A similar proportion of patients was compliant with the dosing regimen in each group (85% balsalazide, 93% mesalazine; $P = 0.3109$).

Fifty-seven per cent (56/99) of patients did not complete the study (29 balsalazide, 27 mesalazine; $P = 0.6865$), the main reason being treatment failure. Treatment failures included those patients who withdrew from the study as a result of a complication of their UC requiring intervention and patients who suffered a relapse of UC (symptomatic or asymptomatic relapse) (16 balsalazide, 18 mesalazine; $P = 0.8330$). No relapse was associated with a positive stool culture result. One mesalazine patient withdrew from the study after complaining of urgency and an increased frequency of bowel movements. However, these symptoms had resolved by the time the patient attended the clinic; therefore the discontinuation was not considered by the investigator to be the result of a treatment failure. Other reasons for study discontinuation included non-compliance with the study protocol (two balsalazide, five mesalazine) and unacceptable adverse events (three balsalazide, one mesalazine). Ten patients (eight balsalazide, two mesalazine) who were erroneously included in the study were also withdrawn; six patients receiving balsalazide and two patients receiving mesalazine had no sigmoidoscopic verification that their last relapse had involved haemorrhagic mucosa and two patients receiving balsalazide were not practising adequate contraception; one of these patients also had no sigmoidoscopic verification that the last relapse had involved haemorrhagic mucosa.

There were no significant differences in blood pressure, pulse and weight measurements between the treatment groups ($P > 0.2$) during the course of the study. Comparisons of changes in biochemical and haematological laboratory variables during treatment identified a significant difference between treatments for one parameter, alanine aminotransferase (ALAT). ALAT decreased by an average of 2.29 IU/L in the balsalazide group, whereas an average increase of 1.83 IU/L was observed in the mesalazine group ($P = 0.0183$). This difference was considered unlikely to have any clinical significance. In addition, no significant changes in urinalysis results or plasma urea and creatinine levels were observed during treatment, confirming that there was no renal impairment in either group of patients.

Sixty-one per cent (30/49) of patients in the balsalazide group and 65% (30/46) in the mesalazine group reported adverse events ($P = 0.8317$). The total number of adverse events, recorded without assessment of causal relationship to treatment, was 96 in the

balsalazide group and 98 in the mesalazine group. The most common adverse events reported were headaches, gastrointestinal symptoms (abdominal pain and diarrhoea), respiratory infections, abnormal laboratory tests (related to UC disease), pain (in various parts of the body) and flu-like disorders. In the investigators' opinion, 20% of the adverse events reported by patients in the mesalazine group and 19% in the balsalazide group had a probable or possible association with treatment. Two patients in the balsalazide group discontinued due to an unacceptable adverse event, suggestive of treatment intolerance. One patient experienced mild intermittent headaches which became severe and the other patient experienced severe headaches and lethargy.

Five serious adverse events were reported during the study; the three serious adverse events in the mesalazine treated group were a suspected urinary tract infection, a severe complication of UC and a death resulting from a cardiac arrest and ischaemic heart disease. The two serious adverse events reported in the balsalazide group were a fracture of the left scaphoid bone and a Spigelian hernia.

DISCUSSION

Patients receiving ulcerative colitis maintenance treatment and thus termed as being in 'disease remission' frequently report inadequate symptom control, often nocturnally, which can ultimately result in disturbed sleep. Whilst inadequate night-time control of symptoms can indicate an incomplete control of underlying inflammation, more importantly for the patient, sleep disturbance and fatigue adversely influence their quality of life.[16, 17] From a patient's perspective therefore, better control of night-time symptoms remains an important treatment goal for any ulcerative colitis maintenance therapy.

The collection of diary card data allows an accurate daily record of patients' symptoms to be maintained between clinic visits. The analysis of such records is very important because it may highlight important subtle or more gradual changes in symptoms which patients may not spontaneously report at clinic visits. The diary card data collected during this study have demonstrated a significant therapeutic advantage for balsalazide for at least the first 3 months of treatment.

The significant differences in favour of balsalazide have emerged despite the asymmetric dosing regimen used for the mesalazine patients (0.8 g o.n. mesalazine (5-ASA) vs. 1.5 g o.n. balsalazide (equivalent to 0.52 g 5-ASA)). The bias towards evening dosing of mesalazine did not appear to protect against night-time symptoms. Effective treatment of the underlying disease allows patients to cope with their illness.[17] Inflammatory bowel disease patients have indicated that the most important factors impacting upon their quality of life are stool frequency and consistency, abdominal pain, flatulence, the presence of blood, sleep disturbance and overall fatigue.[16, 17] Consequently, the improved control of night-time symptoms and reduced sleep disturbance experienced by the balsalazide treated patients in this study may translate into a better overall quality of life for these patients.

Balsalazide provided a therapeutic advantage over mesalazine in this study, in that fewer patients relapsed before 3 months (10% vs. 28%). The relapse for these patients was detected as a result of the patients' symptom severity necessitating an unscheduled clinic visit. Although this advantage was no longer statistically significant at the 3-month time point (after the scheduled 3-month clinic visit) (79% vs. 65% in remission), the difference between treatments in the early stages may still be of clinical relevance and may indicate that balsalazide delays UC relapse. A treatment which delayed relapse would mean such patients would suffer fewer relapses in the long term, leading to improvements in quality of life, potentially fewer NHS consultations and predisposing to potentially lower overall treatment costs.

The 12-month remission rates observed for mesalazine in this study are comparable but not identical to those generally reported for 5-ASA releasing compounds.[3, 15, 19] Comparable remission rates to those observed in this study have been reported in studies using similar doses of balsalazide in the maintenance of remission of UC. McIntyre *et al.*[19] reported that 51% of patients receiving balsalazide 3 g remained in remission after 6 months of treatment. Green *et al.*[22] demonstrated that 77% of patients receiving balsalazide 3 g were in remission after 12 months of treatment, a higher remission rate than in this study.

There is a general problem with comparing relapse or remission rates in different studies, because the definition of relapse often differs from study to study. In addition, some studies report only crude relapse/remission rates whilst other researchers present survival analyses. Relapse rates also depend on UC history and symptoms at entry, which may also vary between

groups of patients in different studies. Such factors must therefore be taken into account when comparing the results of different studies. In this study survival relapse rates were used to analyse remission rates, based on whether the patient had suffered a symptomatic relapse, a totally patient-led assessment. This was considered to be the most appropriate end-point because current approaches to clinical management are determined by the severity of the patients' symptoms rather than histological severity of inflammation.[2]

The logistic analysis at both 3 and 12 months highlighted that only patients' symptoms influenced time in remission as opposed to the time since the patients' last relapse or duration since initial diagnosis. Because the patients' overall symptoms appear to be highly predictive of underlying disease activity, as confirmed by the low frequency of asymptomatic relapses in this study and the study by Misiewicz *et al.*,[3] then the results may be interpreted to indicate that maintenance therapy should not be initiated in clinical practice until a patient is truly in symptomatic remission. Patients in symptomatic remission are not sigmoidoscopically screened at routine clinic visits. Patient-led management is more acceptable not only to patients but also to physicians, because routine examinations are time-consuming during a clinic and impractical due to constraints on health resources. Patient-led disease management predisposes towards a transfer of responsibility for the routine care of patients to nurse practitioners, resulting in economic benefits for the NHS.

It has been suggested that no distinction can be made between the efficacy of different ways of delivering 5-ASA when equimolar doses are given in trials of mild-to-moderate disease or maintenance of remission.[23] In this study dose equivalence was not quite achieved. The dose of balsalazide prescribed in this study (3 g) yielded 1.04 g of 5-ASA compared to 1.2 g 5-ASA available from the delayed-release mesalazine. Despite this bias in favour of mesalazine in terms of 5-ASA equivalence, advantages were still observed in favour of balsalazide. Higher doses of balsalazide may provide advantages in the maintenance of remission.

It has been postulated that any difference in efficacy between the various preparations must be related to their ability to deliver 5-ASA, the active therapeutic moiety, to the colon.[9] It would be expected that 5-ASA delivery from delayed-release mesalazine should be reliable in patients with inactive disease because the factors affecting 5-ASA release (intestinal pH, gastric emptying or transit time[24]) would be relatively normal and stable. As an azo compound, balsalazide relies only upon bacterial azo-reduction and colonic transit.[24] The results of this study suggest that this may be a slightly more reliable release mechanism in UC patients even when the disease is inactive. Whether the differing pharmacokinetic properties of the 5-ASA releasing drugs can wholly or partly explain the efficacious advantages of treating patients with balsalazide rather than mesalazine will require further investigation.

Finally, the results of this study have demonstrated equivalent tolerability of balsalazide and mesalazine in terms of similar proportions of patients experiencing adverse events (61% vs. 65%, respectively) and withdrawing from the study as a result of an unacceptable adverse event (6% vs. 2%, respectively). Patient tolerability is an important clinical measure because it represents a true reflection of the level of patient acceptability of the treatment. No consistent changes in urinalysis results or plasma urea or creatinine levels were observed in either treatment group suggesting no evidence of renal impairment in either group of patients. However, patients treated with mesalazine experienced three adverse events related to the renal tract, one of which (haematuria) the investigator considered to be possibly caused by the study medication. However, the relatively small number of patients in this study is not sufficient to establish the nephrotoxic potential of mesalazine. No adverse events related to kidney function were reported by patients in the balsalazide group.

This study has confirmed that balsalazide 3 g daily is at least as effective, and equally well tolerated and accepted by patients as a long-term maintenance treatment for UC, as delayed-release mesalazine 1.2 g daily. The results also show a therapeutic advantage for balsalazide in delaying relapse and maintaining more complete remission, especially in respect of night-time symptoms. Previous work has also confirmed that balsalazide 6.75 g daily is more effective than mesalazine 2.4 g daily in the treatment of a disease exacerbation.[20] Balsalazide should therefore prove to be an effective treatment in the long-term management of ulcerative colitis, allowing patients to manage their disease symptoms by tailoring the dose of balsalazide accordingly.

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