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Olsalazine versus mesalazine in the treatment of mild to moderate ulcerative colitis

W. KRUIS[1], J.-W. BRANDES[2], S. SCHREIBER[3], D. THEUER[4], B. KRAKAMP[5], E. SCHÜTZ[6], P. OTTO[7], H. LORENZ-MAYER[8], K. EWE[9] & G. JUDMAIER[10]

[1]*Department of Internal Medicine, Evangelisches Krankenhaus Kalk, Cologne, Germany;* [2]*Medizinische Klinik I, Städtisches Klinikum, Braunschweig, Germany;* [3]*University of Klinik, Eppendorf, Hamburg, Germany;* [4]*Heilbronn, Germany;* [5]*Medizinische Klinik I, Städtisches Krankenhaus Merheim, Cologne, Germany;* [6]*Castra Regina Center, Regensburg, Germany;* [7]*Krankenhaus Burgwedel, Burgwedel, Germany;* [8]*Medizinische Klinik I, Städtisches Krankenhaus, Friedrichshafen, Germany;* [9]*I Med. Universitätsklinik, Mainz, Germany; and* [10]*Universitätsklinik für Innere Medizin, Innsbruck, Austria*

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SUMMARY

Aim: To compare the efficacy and tolerability of olsalazine sodium with enteric-coated mesalazine in inducing endoscopic remission in patients with mild to moderate active ulcerative colitis.

Patients and methods: Patients with mild to moderate active ulcerative colitis were randomized to receive either olsalazine sodium, 3 g/day ($n = 88$), or mesalazine, 3 g/day ($n = 80$), for up to 12 weeks.

Results: Of the patients treated with olsalazine sodium, 52.2% achieved endoscopic remission, compared with 48.8% of patients treated with mesalazine. This difference was not significant ($P = 0.67$). There was a non-significant trend for patients with left-sided colitis or a more severe endoscopic grade to achieve remission if they were treated with olsalazine sodium than if they were treated with mesalazine. Both treatments were comparable with respect to clinical activity index and an investigator's global assessment. Seventy patients reported one or more adverse events; adverse events were seen in 45% of olsalazine sodium-treated patients and in 36% of mesalazine-treated patients. Eleven patients treated with olsalazine sodium and nine patients treated with mesalazine withdrew from the study because of adverse events. One patient treated with olsalazine sodium compared with two treated with mesalazine stopped treatment because of diarrhoea. Serious adverse events occurred in three patients treated with olsalazine sodium and in four treated with mesalazine.

Conclusion: Therapeutic effectiveness and tolerance to the treatment did not differ between olsalazine sodium, 3 g/day, and mesalazine, 3 g/day, in inducing endoscopic remission in patients with mild to moderate active ulcerative colitis within 12 weeks of treatment.

INTRODUCTION

Ulcerative colitis has been effectively treated with sulphasalazine for many years. This treatment has, however, been associated with gastrointestinal side-effects, leading to the development of compounds with comparable therapeutic activity but without the propensity to cause as many adverse events. Sulphasalazine consists of 5-aminosalicylic acid (5-ASA) and sulphapyridine linked by an azo bond. The active moiety 5-ASA is released in the colon after bacterial splitting of the azo bond. Many adverse events associated with sulphasalazine have been attributed to the sulphapyridine component.[1]

Correspondence to: Prof. Dr med. Wolfgang Kruis, Evangelisches Krankenhaus Kalk, Buchforststrasse 2, D-51103 Köln, Germany.

When pure 5-ASA is given orally, it is almost totally absorbed by the small intestine.[2] Therefore, methods of delivering 5-ASA to the colonic mucosa have been developed. Two different approaches have been used: (i) in analogy to sulphasalazine the use of prodrugs, which release 5-ASA when they reach the colon (e.g. olsalazine), and (ii) the use of enteric-coated 5-ASA preparations (mesalazine). Coating is performed by the resins eudragit L or S, which release 5-ASA pH dependently at pH > 6 and pH > 7, respectively, or coated microcapsules are constructed which release 5-ASA transit dependently.[1]

This study is the first to compare the use of the 5-ASA prodrug olsalazine with a eudragit L enteric-coated preparation of mesalazine in the treatment of patients with mild to moderately active ulcerative colitis. Olsalazine sodium consists of two molecules of 5-ASA. Many studies have demonstrated that olsalazine sodium is an effective treatment for active ulcerative colitis when compared with sulphasalazine and placebo.[3–9] In two of these studies, as in the present study, olsalazine sodium was used at a dose of 3 g/day.[3, 8]

The mesalazine preparation used in this study is commonly used for the treatment of active ulcerative colitis. This preparation is designed to release active mesalazine in the terminal ileum and proximal colon,[10] and has been shown to have a comparable clinical activity to sulphasalazine in patients with active ulcerative colitis.[11]

The main aim of this study was to compare the effect of treatment with olsalazine sodium with that of a eudragit L coated mesalazine preparation for 12 weeks in bringing patients with active ulcerative colitis into endoscopic remission.

PATIENTS AND METHODS

This was a randomized, double-blind trial comparing the efficacy and tolerability of treatment with olsalazine sodium with that of mesalazine for 12 weeks in patients with mild to moderate active ulcerative colitis. The study was conducted in 17 hospitals and private practice settings in Germany and Austria (see list of participating investigators at the end of this paper).

Patient selection and randomization

Patients were included in the study if they were aged between 18 and 75 years and had a mild to moderate (less than endoscopic score of 4) attack of ulcerative colitis, defined as the presence of visible blood in the stool for at least 3 consecutive days within the first week of the study; one or more stools per day greater than normal in the week prior to the start of the study; and by an endoscopic score of 2 or 3. Randomized patients also had to have a previously established diagnosis of ulcerative colitis extending more than 15 cm, at least one attack of ulcerative colitis in the last 5 years and negative bacteriological and parasitological stool culture. Patients were not allowed to receive oral steroids, immunosuppressives or more than two doses of rectal steroid therapy within 2 weeks of the start of the study. Those who had a history of allergy to salicylates or were on antibiotic treatment lasting for more than 30 days were excluded.

Patients who met the inclusion criteria were consecutively assigned to treatment groups by a central randomization procedure.

Study medication

Patients were treated with either olsalazine sodium (Dipentum; Pharmacia & Upjohn AB, Uppsala, Sweden), 3 g/day or mesalazine (Claversal; SmithKline Beecham, Munich, Germany), 3 g/day for up to 12 weeks. According to a double-blind, double-dummy technique all patients received the same number of tablets, regardless of the study medication or dosage used. The first two doses of the study medication were taken with the evening meal on the day the patient was included in the study.

Olsalazine sodium was supplied as 500 mg tablets. Patients were instructed to take two active tablets of olsalazine sodium immediately after a meal and two placebo mesalazine tablets before a meal, three times a day. The dose of olsalazine sodium was gradually increased from 500 mg/day to 3 g/day during the first week of treatment.

Mesalazine was supplied as 500 mg tablets coated with an eudragit L acrylic-based resin. Patients were instructed to take two active mesalazine tablets before a meal and two placebo olsalazine sodium tablets immediately after a meal, three times a day. Patients took the full dose of mesalazine from the start of the study.

Evaluation

Clinic visits of the patients were required upon entry to the study and after 3, 6, 9 and 12 weeks of treatment.

Investigators telephoned patients after the first 7 days of treatment. Patients who achieved endoscopic remission at weeks 6 or 9 were said to have completed the study. These patients were included in the final analysis.

Primary efficacy variables. At entry to the study, patients were given an endoscopic examination, either by colonoscopy or sigmoidoscopy. Sigmoidoscopy was performed at the end of the study and in those patients who had achieved a good clinical response at the previous visit as assessed by the investigator.

Endoscopic remission was assessed using a five-point scale:[11] normal mucosa with a visible vascular pattern and no granularity or friability (score 0); inactive colitis, pink mucosa, no visible blood vessels, faintly granular but no friability (score 1); oedematous mucosa and erythaema with mild granularity and friability (score 2); marked oedema and erythaema of the mucosa with granularity and friability (score 3); spontaneous bleeding, obvious mucosal ulcers (score 4). Endoscopic remission was defined as a score of 0 or 1 on the above scale.

Secondary efficacy variables. A clinical activity index was used to assess the clinical effectiveness of treatment. The clinical activity index used was a modified version of that described by Rachmilewitz *et al.*[11] The index was calculated as the sum of the total scores of six variables: the number of stools in the last 7 days; the number of bloody stools in the last 7 days; average frequency of abdominal pain/cramp in the last 7 days; temperature due to colitis; presence of extraintestinal manifestations (iritis, arthritis) and laboratory findings (erythrocyte sedimentation rate (ESR), haemoglobin). The clinical activity index score gives an indication of the severity of disease: a score of 6 or higher indicates active disease, whereas a score of less than 1 indicates that a patient is in remission.

At each clinic visit a global assessment of the patient's symptomatic state was made by the investigators using a four-point scale. Patients were graded as having either a good (score 0), average (score 1), poor (score 2) or very poor (score 3) response to treatment.

Safety evaluation

Laboratory assessments were carried out upon inclusion into the study and at 3, 6, 9 and 12 weeks. The following assessments were made: ESR, haemoglobin, leucocyte count, serum alkaline phosphatase, serum gamma-glutamyl transferase and serum creatinine. At the start of the study, the presence of blood and protein in urine was investigated, and the faeces were examined for the presence of *Shigella spp.*, *E. Coli*, *Yersinia spp.* and *Campylobacter spp.*

Adverse events were carefully monitored throughout the entire study and after completion of the study.

Statistical methods

The main objective of the study was to assess whether olsalazine sodium was at least as effective as mesalazine in inducing endoscopic remission. This was assessed using the reverse hypothesis method as described by Blackwelder.[12] In order to be regarded as at least as effective as mesalazine, the 95% lower confidence limit for the observed difference in endoscopic remission rates between olsalazine sodium and mesalazine should not be below − 20% units.

As this was a non-inferiority study a one-sided 95% confidence interval was used (see for example ICH guidelines[12]). When planning the study it was decided that the olsalazine sodium group should not have a remission rate of more than 20% units less than the mesalazine group. Furthermore, it was estimated that 35% in both treatment groups would reach remission. Using a one-sided test at the 5% significance level and a power of 80%, 71 patients were needed in each treatment group, according to the method described by Blackwelder.[12]

Two types of analysis were performed: an intention-to-treat analysis and a per protocol analysis. All randomized patients, with the exception of those who were incorrectly included in the study, constituted the intention-to-treat population. Only patients for whom the results of endoscopic examinations and clinical activity index data were available from both the start and the end of the study and who had not violated the study protocol were included in the per protocol analysis.

Ethical guidelines and GCP compliance

The study was conducted according to the Helsinki Declaration (Hong Kong, 1989) and adhered to good clinical practice (GCP) guidelines. The study was approved by the Ethikkommission, Ärztekammer Nordrhein, Düsseldorf, Germany. All patients gave written informed consent.

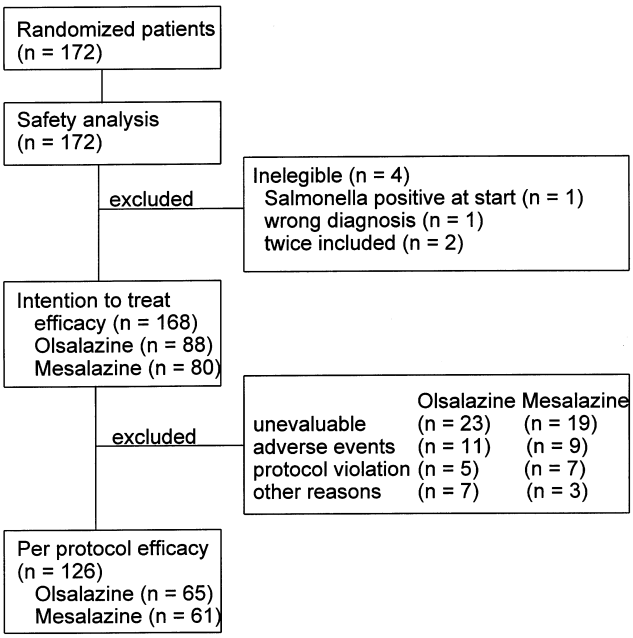

Figure 1. Flow chart of patients included and analysed.

Patient compliance

Compliance was checked by counting the number of tablets returned at clinic visits.

RESULTS

Figure 1 depicts the number of patients included and analysed. Patients were well matched for age, sex, weight, history of ulcerative colitis and initial clinical status (Table 1) and treatment prior to the study (Table 2), which was terminated in each patient before the start. A minor difference between the treatment groups, however, was that more patients (62%) randomized to receive olsalazine sodium had an initial endoscopic grade of 3 at the start of the study than those who were randomized to receive mesalazine (54%, difference not significant).

Intention-to-treat analysis

An overview of some of the results obtained is given in Table 3.

In the intention-to-treat analysis, 52.2% of patients treated with olsalazine sodium, compared with 48.8% of patients treated with mesalazine, achieved endoscopic remission (endoscopic score of 0 or 1). The point estimate of the difference between the remission rates for olsalazine sodium and mesalazine was 3.5% and the lower limit of the one-sided 95% confidence interval was − 9.1%. This figure is above the prespecified limit of

Table 1. Patient characteristics at inclusion (intention-to-treat population)

Characteristic	Olsalazine sodium, $n = 88$	Mesalazine, $n = 80$
Age (years)	41.9 (14.7)	38.5 (14.1)
Sex: Male (*n*)	52	46
Female (*n*)	36	34
Weight (kg)	71.5 (16.1)	72.2 (13.9)
Duration of disease (years)	5.5 (6.2)	5.3 (6.5)
Number of ulcerative colitis attacks	5.3 (5.7)	5.6 (5.9)
Duration of current attack (months)	1.9 (2.3)	2.4 (2.9)
Time in remission (months)	86 (16.0)	77 (24.6)
Extent of disease (*n*):		
Proctosigmoiditis	26 (30%)	20 (25%)
Left-sided ulcerative colitis	31 (35%)	27 (34%)
Sub-total/total ulcerative colitis	31 (35%)	33 (41%)
Clinical activity index ($n = 86$ olsalazine, $n = 76$ mesalazine)	6.19 (2.03)	6.14 (2.22)
Investigator's global assessment		
Good	12 (14%)	10 (12%)
Average	50 (57%)	46 (58%)
Poor	26 (30%)	23 (24%)
Very poor	0	0
Endoscopic grade: 2	33 (38%)	37 (46%)
3	55 (62%)	43 (54%)

Table 2. Treatment prior to the inclusion into the study

Pre-treatment	Olsalazine sodium	Mesalazine
Sulphasalazine	12 (14%)	11 (14%)
Mesalazine	27 (31%)	20 (25%)
Cortisone	1 (1%)	1 (1%)
Olsalazine	7 (8%)	3 (4%)
Combination	8 (9%)	10 (13%)
No ulcerative colitis medication	29 (33%)	32 (40%)
Other ulcerative colitis medication	4 (2%)	3 (4%)

– 20%. Thus, according to the main objective of the study it can be deduced that olsalazine sodium is at least as effective as mesalazine in bringing patients with mild to moderate ulcerative colitis into endoscopic remission at the 5% significance level.

More patients who initially had an endoscopic grade of 2 achieved remission compared with those who initially had an endoscopic grade of 3 (64% vs. 41%, $P = 0.003$). Patients who initially had an endoscopic score of 3 and who were treated with olsalazine sodium showed a numerically higher remission rate than the corresponding patients who were treated with mesalazine (46% vs. 35%, $P = 0.29$).

Endoscopic remission and extent of disease

The rate of endoscopic remission was also assessed according to the extent of disease (Figure 2). Although no significant difference was found in the rate of endoscopic remission in terms of the extent of disease, more patients with left-sided ulcerative colitis achieved endoscopic remission if they were treated with olsalazine sodium (54.8%) than if they were treated with mesalazine (29.6%); a difference of 25.2% was seen between the two groups ($P = 0.053$). Differences were smaller in the group with proctosigmoiditis (7.3%) and in the group with subtotal/total colitis (8.8%), respectively, and both differences were in favour of mesalazine.

Clinical activity index. Clinical activity index data were not reported by six patients upon inclusion in the study, and therefore the change in the clinical activity index was calculated for 162 patients. The clinical activity index decreased in both treatment groups during the course of the study. In patients treated with olsalazine sodium, the clinical activity index was 6.19 ± 2.03 (mean ± s.d.) at the start of the study and 3.30 ± 3.31 at the end of the study. This was a mean decrease of 2.92 ± 3.49. In patients treated with mesalazine, the clinical activity index was 6.14 ± 2.22 at the start of the study and 2.99 ± 3.49 at the end of the study. This was a mean decrease of 3.18 ± 3.11. There was no significant difference in the mean change in the clinical activity index between the two treatment groups ($P = 0.31$). Futhermore, no significant differences in decrease in clinical activity index were found between the two treatment groups for either of the subgroups of patients with left-sided disease or patients with endoscopic grade 3 at baseline.

The clinical activity index was also used to assess how many patients had achieved a clinical remission. A patient was considered to be in clinical remission if the clinical activity index was ≤ 1. A similar number of patients in each treatment group had a clinical activity index ≤ 1; 45.4% of patients treated with olsalazine sodium ($n = 88$) achieved a clinical remission compared with 46.2% of patients treated with mesalazine ($n = 80$).

Table 3. Selected results

Criterion	Olsalazine	Mesalazine
Endoscopic remission rates		
Total	52.2%	48.8%
Only patients with initial endoscopic grade 3	45.5%	34.9%
Proctosigmoiditis	57.7%	65.0%
Left-sided colitis	54.8%	29.6%
Subtotal/total colitis	45.2%	54.6%
CAI: decrease from start to end of the study	2.92 ± 3.49	3.18 ± 3.11
Clinical remission (CAI ≤ 1)	45.4%	46.2%
Investigator's global assessment at the end of study: 'good'	60.2%	52.5%

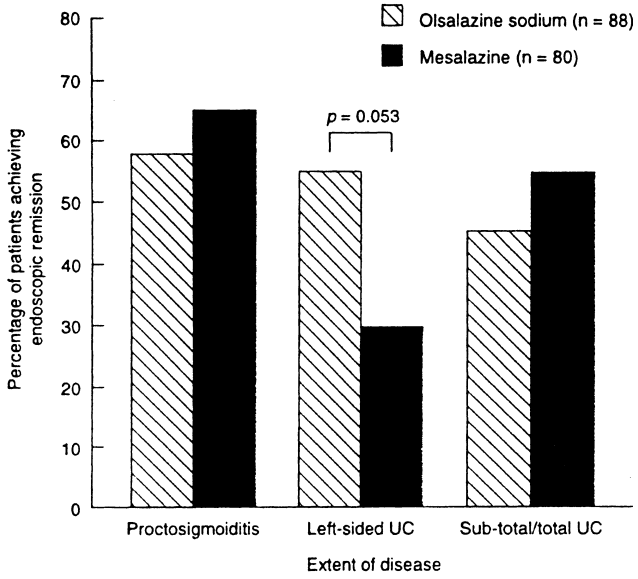

Figure 2. Rate of endoscopic remission in patients treated with olsalazine sodium and mesalazine according to the extent of disease (intention-to-treat population).

Investigator's global assessment. At the end of the study the investigator's global assessment of the symptomatic state was good (60%), average (19%), poor (19%) and very poor (1%) in the group treated with olsalazine sodium. The corresponding figures associated with mesalazine treatment were 52%, 31%, 14% and 3%, respectively. There was no statistically significant difference between the two treatment groups.

Per protocol analysis

Endoscopy was performed both at inclusion and at termination of the study in 126 patients (olsalazine 65, mesalazine 61). These patients were included in a per protocol analysis which showed results similar to those of the intention-to-treat analysis; both olsalazine sodium and mesalazine produced comparable improvement in the endoscopic remission rate. The rate of remission was slightly, but not significantly, higher following treatment with olsalazine sodium (66.2%) compared to treatment with mesalazine (60.7%). Clinical activity index scores in patients treated with olsalazine sodium and in those treated with mesalazine were 3.8 ± 3.49 and 3.52 ± 2.90, respectively. The investigator's global assessment of the patient's symptomatic state suggests that olsalazine sodium is clinically and endoscopically as effective as mesalazine. Treatment with olsalazine sodium was rated as 'good' for 78% of patients, 'average' for 13% of patients and 'poor' for 8% of patients. By comparison, treatment with mesalazine was rated as 'good' for 69% of patients, 'average' for 19% of patients, 'poor' for 10% of patients and 'very poor' for 2% of patients.

Safety evaluation

Laboratory assessments. Thirty-one patients had low haemoglobin, an increased leucocyte count and a high ESR, which were caused by their ulcerative colitis. Serum creatinine was elevated in two patients treated with mesalazine. One of these patients had a high level of serum creatinine upon inclusion into the study. Serum alkaline phosphatase and serum gamma-glutamyl transferase were elevated in nine and 23 patients, respectively. There was no indication that serum levels of alkaline phosphatase or serum gamma-glutamyl transferase were influenced by the intake of the study medications.

Adverse events. One or more adverse events was reported in 70 patients; of these patients, 41 were treated with olsalazine sodium and 29 were treated with mesalazine (Table 4). Twenty patients withdrew from the study because of adverse events; 11 of these patients were treated with olsalazine sodium and nine were treated with mesalazine. The two treatment groups did not differ significantly with respect to either the proportion of patients with at least one adverse event or the

Table 4. Adverse events

	Olsalazine	Mesalazine	Total
Total number of adverse events reported	94	69	193
Number of patients reporting one or more adverse event	41	29	70
Number of patients withdrawn due to adverse event	11	9	20
Total number of patients reporting gastrointestinal adverse events	29	19	48
Number of patients complaining of diarrhoea (withdrawals)	11 (1)	6 (2)	17 (3)

proportion of patients who were withdrawn from treatment due to adverse events. A total of 163 adverse events were reported among the randomized patients. Of these, 94 adverse events occurred in patients treated with olsalazine sodium and 69 in those treated with mesalazine. The majority (42%) of these adverse events were associated with disturbances of the gastrointestinal system, such as diarrhoea, bloody stools, vomiting, abdominal discomfort, heartburn, flatulence and nausea. Diarrhoea was reported in 11 (12%) of the patients treated with olsalazine sodium compared with six (7%) who were treated with mesalazine. Premature termination of the treatment because of diarrhoea occurred in one patient with olsalazine sodium compared with two patients who were treated with mesalazine.

Serious adverse events were reported in three patients treated with olsalazine sodium and four treated with mesalazine. Only one of these, a case of pseudo lupus erythematosus syndrome, was possibly associated with the study medication (mesalazine).

DISCUSSION

This is the first controlled trial to compare treatment with olsalazine sodium with that of an enteric-coated mesalazine in patients with active ulcerative colitis. Previously, olsalazine sodium was compared with a Eudragit-S enteric-coated mesalazine in patients with inactive ulcerative colitis.[14] Patients treated with olsalazine sodium for 12 months tended to remain in remission for longer than those who were treated with mesalazine and tended to experience fewer relapses of their disease ($P = 0.024$), particularly if they had left-sided ulcerative colitis.[13]

Statistics of the study were based on a threshold difference of 20% in remission rates between the two treatment groups, which is in line with other trials. According to this protocol, the present study provides evidence that the therapeutic effectiveness of the 5-ASA prodrug olsalazine sodium is no different to a Eudragit-L enteric-coated preparation of 5-ASA (mesalazine) in bringing patients with mild to moderate active ulcerative colitis into endoscopic remission within 12 weeks of treatment.

Regarding therapeutic efficacy with respect to the extent of disease the largest difference between treatment groups was seen in left-sided ulcerative colitis. Although the difference in the number of patients achieving endoscopic remission was 25% in favour of olsalazine sodium, it was not statistically significant. A potential therapeutic superiority of olsalazine sodium over mesalazine in the treatment of left-sided colitis might be explained by the different mechanisms by which they release 5-ASA into the bowels.[1] Whereas mesalazine releases 5-ASA in the more proximal parts of the small intestine, olsalazine sodium releases 5-ASA in the caecum. These different modes of 5-ASA delivery to the inflamed mucosa result in higher concentrations of 5-ASA along the large bowel when provided by olsalazine.[15] In addition to the variable supply of 5-ASA to the bowels distinct pharmacological properties such as the secretory activity of olsalazine may explain different therapeutic effects.

A subgroup analysis of the endoscopic remission rates according to the initial endoscopic grade showed that patients with a moderate attack of ulcerative colitis (endoscopic grade 3) showed lower remission rates than those with a milder attack of ulcerative colitis (endoscopic grade 2) ($P = 0.003$). After randomization, more patients with an endoscopic grade of 3 were included in the olsalazine sodium treatment group than in the mesalazine-treated group. This slight imbalance between the treatment groups, however, did not affect the endoscopic remission rate achieved with olsalazine sodium, which was comparable with that achieved with mesalazine.

The results of both the clinical activity index and the investigator's global assessment further demonstrate that olsalazine sodium is as clinically effective as mesalazine in patients with active mild to moderate ulcerative colitis.

There is some evidence that increasing the dose of mesalazine may confer increased clinical benefits compared with lower doses.[16–18] There is also evidence that relatively high doses of olsalazine sodium have superior therapeutic effects over lower doses.[7] Although the optimum doses of 5-ASA preparations remain open to question, the present study suggests that a dose of 3 g/day of either olsalazine sodium or mesalazine produces good clinical effects without significantly decreasing the tolerability.

The potential for olsalazine sodium and mesalazine to increase the frequency of diarrhoeal adverse events is of considerable concern for those who treat patients with ulcerative colitis. Indeed, in this study, 12% of patients treated with olsalazine sodium and 7% of those treated with mesalazine reported diarrhoea. However, a premature termination of the treatment because of

diarrhoea occurred in only three patients (olsalazine sodium one patient, mesalazine two patients). The dose of olsalazine sodium was gradually increased during the first week of the study and patients were advised to take olsalazine sodium with meals. This recommendation may account for the low number of withdrawals due to diarrhoea, considering the relatively high dose of olsalazine sodium (3 g/day) used. Where no such recommendations have been made, the rate of withdrawal associated with olsalazine sodium has been much higher.[19, 20]

In conclusion, this study demonstrates that the therapeutic efficacy and tolerability of olsalazine sodium, 3 g/day, and mesalazine, 3 g/day, is comparable in inducing endoscopic and clinical remission in patients with mild to moderate active ulcerative colitis within 12 weeks of treatment.

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The investigators participating in the study included (figures in parentheses are the number of patients randomized into the study by the investigator(s)): Dr Jörg-Wolfgang Brandes, Medizinische Klinik I, Städtisches Klinikum, Braunschweig, Germany (30); Dr Stefan Schreiber/Dr Jens Hämling, Universitätsklinik Eppendorf, Martinistrasse 52, 20251 Hamburg, Germany (25); Dr Dieter Theuer, Herbststrasse 15, Heilbronn, Germany (20); Dr Bernd Krakamp, Städtisches Krankenhaus, Cologne, Germany (20); Dr Erich Schütz, Castra Regina Center, Regensburg, Germany (15); Prof. Peter Otto/Dr Andreas Thilo, Krankenhaus Burgwedel, Burgwedel, Germany (10); Prof. Hartwig Lorenz-Mayer, Medizinische Klinik I, Städtisches Krankenhaus, Friedrichshafen, Germany (9); Prof. Wolfgang Kruis, Evangelisches Krankenhaus Kalk, Cologne, Germany (8); Prof. Klaus Ewe/Dr Bärbel Ueberschaer/, I Med. Klinik und Poliklinik Johannes-Gutenberg-Universität, Mainz, Germany (8); Dr Gert Judmaier, Universitätsklinik für Innere Medizin, Innsbruck, Austria (8); Dr Eberhard Schwenke/Dr Gabriele Balke, Altstadt-Krankenhaus, Magdeburg, Germany (5); Prof. Michael Manns/Dr Stephan Bischoff/Dr Jörg Evers, Medizinische Hochschule Hannover, Germany (4); Prof. Enno Hentschel, Hanusch Hospital, Vienna, Austria (4); Prof. Klaus-Ulrich Schentke/Dr Thomas Mehnert, Klinik Innere Medizin, Medizinische Akademie, Dresden, Germany (2); Dr Siegbert Kolb, Bahnhofstrasse 87, Staffelstein, Germany (2); Prof. H Jörg Steinhardt, Kreiskrankenhaus Wangen, Wangen, Germany (1).

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