The Optimal Dose of 5-Aminosalicylic Acid in Active Ulcerative Colitis: A Dose-Finding Study With Newly Developed Mesalamine

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Background & Aims: **5-Aminosalicylate is the gold standard for inducing remission in patients with mildly to moderately active ulcerative colitis. The optimal dose is as yet not defined. Despite some recent developments, the ideal formulation for 5-aminosalicylic acid is still awaited. A new pellet preparation was designed combining slow and delayed release properties. Aims of the study were to find the optimal dose and to test efficacy and safety of a new 5-aminosalicylic acid formulation.** ***Methods:*** **Three hundred twenty-one patients were included in a double-blind multicenter trial. Inclusion criteria were active ulcerative colitis (Clinical Activity Index [CAI] and Endoscopic Index [EI] according to Rachmilewitz, CAI 6–12; EI ≥4). Three different doses of 5-aminosalicylic acid (0.5 g 3 times a day, 1.0 g 3 times a day, and 1.5 g 3 times a day) were studied for 8 weeks.** ***Results:*** **Clinical remission rate (CAI ≤4) was highest in the 1.0 g 3 times a day group (66 %), 50% in the 0.5 g 3 times a day group, and 55% in the 1.5 g 3 times a day group. Hierarchical testing showed no significance, indicating a lack of dose response across the 3 mesalamine doses. In addition, times to first clinical response were similar: 26.5 days (1.0 g 3 times a day), 27.5 days (0.5 g 3 times a day), and 21.5 days (1.5 g 3 times a day). Endoscopic improvement was better with 1.0 g mesalamine 3 times a day than with 0.5 g 3 times a day, but overall endoscopic and histologic improvement was not different between treatment groups. Baseline activity, duration, and localization of ulcerative colitis did have some influence on the therapeutic activity, but there was no significant interaction with the dose of the study drug. Safety, with special focus on kidney function, was excellent in all 3 groups.** ***Conclusions:*** **There is no significant dose response between mesalamine 1.5 g/day, 3.0 g/day, and 4.5 g/day. The optimal dose to induce remission of ulcerative colitis is 0.5 g 5-aminosalicylic acid 3 times a day. Patients failing with this dose may benefit from an increase of the dose up to 1.0 g 3 times a day, but should also be considered for alternative treatment. A newly developed pellet formulation of 5-aminosalicylic acid has promising efficacy and excellent safety.**

Aminosalicylates are the gold standard for the treatment of patients with mildly to moderately active ulcerative colitis (UC). Initially, sulfasalazine (SASP) was the only available formulation by which the therapeutically active 5-aminosalicylic acid (mesalamine) could be delivered down to the inflamed colon. Unfortunately, the second component of sulfasalazine, sulfapyridine, acting as carrier system for mesalamine, was found to exert a reasonable number of adverse side effects. As a consequence, alternative mesalamine delivery systems were developed.[1] In a recent meta-analysis[2] a significant superiority of the new mesalamine preparations in inducing clinical improvement was observed in comparison with SASP. In addition, the new mesalamine preparations proved to be significantly more tolerable than SASP.[2]

Although the therapeutic effectiveness of the new mesalamine preparations is clear, the optimal dose is as yet not defined. A meta-analysis comparing 3 dose ranges of mesalamine with placebo was in support of high dose treatment,[3] whereas a comparison between mesalamine and SASP could not confirm this dose response effect.[2]

Abbreviations used in this paper: SASP, sulfasalazine; IBD, inflammatory bowel disease; UC, ulcerative colitis; CAI, clinical activity index; EI, endoscopic activity index; HI, histologic activity index; SD, standard deviation.

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Summarizing presently available knowledge, Riley stated ". . . the value of increasing the oral dose of 5-ASA much in excess of 3 g daily is not clear."[4]

Although the new mesalamine preparations have some advantages, they are still not ideally formulated. Mesalamine release from olsalazine and balsalazide relies on successful bacterial action, and Eudragit-coated mesalamine depends on the appropriate intestinal pH.[1] Moreover, gastric emptying of acid-resistant mesalamine varies markedly when administered to fasting or fed healthy subjects,[5] and it is related to nutritive density of meals and eating habits.[6] When several meals are eaten, because of their size, undissolved Eudragit-coated mesalamine tablets may accumulate within the stomach and then be emptied as a whole at night, with the resultant risk of dose dumping.[7]

To overcome this potential disadvantage of the tablets, a new mesalamine pellet formulation was developed with a particle size of approximately 1 mm, allowing transit through the stomach in conjunction with food intake.

Therefore, the study presented here is aimed to answer 2 questions: (1) Which is the optimal dose of mesalamine for the induction of remission in active UC and (2) how effective and tolerable is a newly developed mesalamine pellet preparation?

Patients and Methods

This was a randomized, double-blind trial comparing the efficacy and safety of 3 different doses of newly developed mesalamine-containing pellets for 8 weeks in patients with mildly to moderately active UC. The study was conducted in 60 hospitals and private practice settings in Austria, Germany, Hungary, and Israel (see list of participating investigators at the end of this article).

Patient Selection and Randomization

Patients were included in the study if they were aged between 18 and 70 years and had a mild to moderate (clinical activity index [CAI], 6–12; endoscopic index [EI] $\geq$4) attack of UC with at least 1 previous episode or persistently bloody diarrhea at least 14 days preceding start of the study. Exclusion criteria were as follows: confirmation of pathogens in the initial microbiologic stool examination; proctitis with an extent of the inflammation less than 15 cm; pretreatment with oral/rectal steroids on more than 3 days in the week before the baseline evaluation or immunosuppressants in the last 4 weeks before, or permanent oral therapy with mesalamine more than 2 g/day in the 2 weeks preceding start of the trial; known intolerance to salicylates.

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

Study Medication

Patients were treated with 3 different doses of mesalamine-containing pellets (Dr. Falk Pharma GmbH, Freiburg, Germany): 0.5 g 3 times a day, 1.0 g 3 times a day, and 1.5 g 3 times a day. These mesalamine pellets are a new formulation aimed to combine delayed and sustained release characteristics. Mesalamine together with a polymer providing sustained release forms the core of a pellet with a total size less than 2 mm. The pellet core is coated with Eudragit-L, an acrylic-based resin stable at low pH values, but dissolving at a pH $>$6.0. This formulation is designed to start release of mesalamine in the terminal ileum after dissolution of the eudragit-L coat, but because of the properties of the matrix polymer within the core, more mesalamine will be transferred to the distal parts of the intestine.

The pellets were dispensed by sachets containing mesalamine pellets or a mixture of mesalamine and placebo pellets. The pellets with active drug and placebo pellets were identical in outward appearance. To ensure blindness, the sachets of the 3 different dose groups contained the same number and volume of pellets. In the sachets with the highest dose all pellets consisted of the active drug. In the sachets with lower doses only a part of the pellets consisted of the active drug, whereas the other part was made up with placebo pellets. The pellets were dispensed by means of a metering device that had to be turned until a "click" was heard, and the device was slightly arrested. The medication had to be taken 3 times a day 1 hour before meals. No concomitant medication to treat UC was allowed throughout the trial. Instructions for the usage and handling of the study medication written in the local language were supplied to the patients.

Evaluation

Clinic visits of the patients were required on entry to the study and after 2, 4, 6, and 8 weeks of treatment.

Primary Efficacy Variables

At the beginning of the study and for each office visit, a CAI according to Rachmilewitz et al.[8] was used to assess the therapeutic effect of the treatment. The index was calculated as the sum of the total scores of 7 variables: the number of stools, percentage of bloody stools, abdominal pain, and general well-being in the last 7 days; temperature due to colitis; presence of extraintestinal manifestations, and laboratory findings (erythrocyte sedimentation rate, hemoglobin). Primary aim of the study was to compare the 3 treatment groups as to the number of patients who entered into a clinical remission (CAI $\leq$4).

Secondary Efficacy Variables

At entry and at end of the study, patients underwent a colonoscopy including biopsies. Endoscopic remission was assessed by using a 5-point index[8]: granularity; vascular pattern, vulnerability (contact injury), and integrity of the mucosa. An EI of $<$4 was defined as endoscopic remission, with a reduction of the EI by at least 1 point defined as endoscopic improve-

ment. All biopsy specimens were examined and assessed by a single pathologist with a 4-point scale according to Riley et al.[9] Histologic improvement was defined as reduction of the histologic activity index (HI) by at least 1 point.

Additional secondary efficacy variables were clinical improvement (CAI decreased by at least 3 points), calculation of the life quality index (LQI) according to Turnbull et al.,[10] and physician's global assessment.

Safety and Acceptability Evaluation

Laboratory assessments including erythrocyte sedimentation rate, C-reactive protein, blood count, liver enzymes, amylase, creatinine, electrolytes, and total protein were obtained at inclusion into the study and at days 14, 28, 42, and 56. Urine strip test and sediment were obtained as well. In German patients, urinary dipeptidyl-aminopeptidase IV (DPP-IV), alkaline phosphatase (AP), and β-*N*-acetyl-D-glucosamidase (β-NAG) were measured too.

Tolerability of the study medication was assessed by a 4-point scale (very good, good, fair, poor) and the compliance by weighing of the returned sachets.

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

Statistical Methods

The primary objective of the study was to assess whether an 8-week treatment with 1.5 g mesalamine pellets 3 times a day was more effective than 0.5 g mesalamine pellets 3 times a day in inducing clinical remission as measured by CAI. The remission rates were compared by using Fisher exact test (one-sided, $\alpha = 0.05$). In case of a significant result, according to a hierarchical test procedure, 1.0 g mesalamine 3 times a day should be compared with 0.5 g mesalamine 3 times a day in a second step, thus avoiding α-adjustment for multiple testing.[11]

With a 1-tailed test at the 5% significance level and a power of 80% and assuming an absolute difference of remission rates of 18%, 105 patients were needed in each treatment group.

The comparison of clinical remission rates as stratified by various subgroups was assessed in a logistic regression model. In addition, Kaplan-Meier curves were plotted. If no CAI or other measure was documented at the individual study end, the last observation carried forward method was applied. Statistical analysis of endoscopic and histologic improvement rates was performed by 2-tailed Fisher exact test adjusted for multiple comparisons (Bonferroni).

Baseline comparability was assessed by Kruskal-Wallis tests for duration of the disease, duration of the current episode, and CAI at baseline, whereas Fisher exact test was applied for localization of UC and the baseline CAI category (≤8 vs. >8).

Two types of analysis were performed, an intention-to-treat analysis (ITT) and a per protocol analysis (PP). All randomized patients, with the exception of those who were incorrectly diagnosed (n = 4) and 1 patient twice included in the study, constituted the ITT population. The PP population comprised all patients who did not violate the protocol in a relevant way.

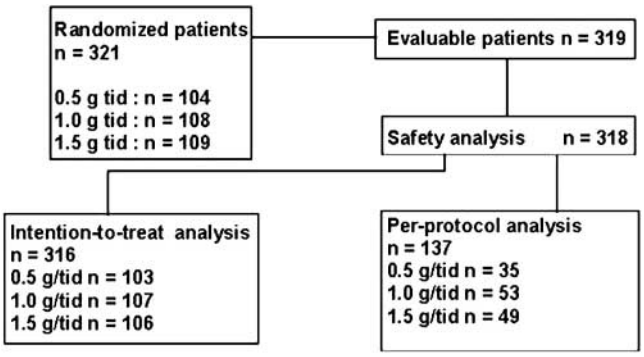

Figure 1. Flow chart of patients included and analyzed.

Statistical tests were executed by using the SAS 6.12 (SAS Institute Inc, Cary, NC) and stat X act 3.0 (Cytel Statistical Software, Cambridge, MA).

Ethical Guidelines

The study was conducted according to the Helsinki Declaration (Hong Kong, 1989) and adhered to good clinical practice guidelines. The study was approved by the Ethikkommission der Ärztekammer Nordrhein, Germany, and the local Ethics committees in all participating countries. All patients gave written informed consent.

Results

Figure 1 depicts the number of patients included and analyzed. Patients were well matched for demographic data and pretreatment clinical characteristics (Table 1). A majority of the patients (64%–69%) had experienced treatment for UC before the study, most often with oral mesalamine (37%–45%). There were no differences in prior treatment between the groups. In the 1.5 g/day group, 70 patients completed the 8-week study period, 86 patients in the 3.0 g/day group, and 85 patients in the 4.5 g/day group; the most frequent reason for premature termination was inefficiency of treatment (23%, 17%, and 13%, respectively).

Clinical Activity

The number of patients achieving clinical remission was highest in the 1.0 g 3 times a day group (66%), whereas the 1.5 g 3 times a day group was only slightly more effective (55%) than the 0.5 g 3 times a day group (50%). The difference between 4.5 g/day and 1.5 g/day was not statistically significant ($P = 0.318$). Thus, the hierarchical test procedure stopped at this stage. Explorative statistical testing showed $P = 0.014$ for the difference between 3.0 g/day and 1.5 g/day (Figure 2). Table 2 lists in detail remission rates for all participating countries.

Table 1. Patient Characteristics at Inclusion (Intention-to-Treat Population)

Treatment group characteristic	500 mg tid	1000 mg tid	1500 mg tid
Number	103	107	106
Men	54 (52%)	56 (52%)	54 (51%)
Median age (yr, range)	39.0 (20–69)	40.0 (18–75)	41.5 (19–69)
Duration of disease (yr, mean) (SD)	7.2 (8.1)	7.7 (7.4)	7.5 (7.8)
Duration of current attack (days, mean) (SD)	49.0 (40.2)	47.2 (58.0)	42.6 (43.3)
Extent of disease (n)			
Proctosigmoiditis	59 (57%)	40 (37%)	47 (44%)
Left-sided	27 (26%)	44 (41%)	35 (33%)
Subtotal/total	16 (16%)	22 (21%)	24 (23%)
Not defined	1 (1%)	1 (1%)	0
Nonsmoker (n)	72 (70%)	65 (61%)	61 (58%)
CAI, mean (SD)	7.8 (1.6)	8.2 (1.7)	8.2 (1.6)
EI, mean (SD)	7.8 (2.0)	8.2 (2.0)	8.0 (2.0)
HI, mean (SD)	2.8 (0.7)	2.7 (0.8)	2.8 (0.7)
LQI, mean (SD)	21.1 (5.7)	21.5 (5.5)	20.5 (5.5)
Pretreatment (n)			
Oral mesalamine	44 (43%)	48 (45%)	39 (37%)
Rectal mesalamine	22 (21%)	17 (16%)	19 (18%)
Sulfasalazine	18 (17%)	16 (15%)	18 (17%)
Systemic steroids	10 (10%)	10 (9%)	7 (7%)
Topical steroids	15 (15%)	14 (13%)	16 (15%)
Miscellaneous	8 (8%)	9 (9%)	6 (6%)

tid, 3 times a day; SD, standard deviation.

Although the observed response rates were generally higher in Israel and Hungary than in Germany, the 3.0 g/day group had the highest number of remissions, and 4.5 g/day was slightly better than 1.5 g/day in all 3 countries. The analysis of the different results adjusted by the factor country in a logistic model showed no significance for a country effect ($P = 0.38$). Thus, the therapeutic effect was not significantly different between Germany, Israel, and Hungary.

Kaplan-Meier analysis including all patients (Figure 3) depicts the probability of not entering into remission against the time on treatment. No significant difference between the 3 groups was observed with the log-rank test. In addition, the time to the first response was calculated for only those patients achieving remission (no censored data) as the interval between the first intake of study medication and the time when CAI was ≤4 for the first time. Accordingly, mean time to first response was 27.5 days in the 1.5 g/day group, 26.5 days in the 3.0 g/day group, and 21.5 days in the 4.5 g/day group. Median times were 26.5, 17.0, and 15.0 days, respectively.

Table 2. Number of Patients Achieving Remission (Intention-to-Treat Analysis)

	500 mg tid		1000 mg tid		1500 mg tid	
Country	n	Remission (%)	n	Remission (%)	n	Remission (%)
Germany	47	22 (47)	54	34 (63)	54	28 (52)
Israel	29	16 (55)	26	19 (73)	26	16 (62)
Hungary	27	14 (52)	27	18 (67)	26	14 (54)

NOTE. Austria enrolled only 8 patients in one center; therefore, the results were pooled with those of the German sites.
$P = 0.014$ vs. 1.5 g/day, comparison of the overall remission rates between 1000 mg tid (66%) and 500 mg tid (50%).

The difference in the mean CAI from baseline to end of study was 3.3 in the 1.5 g/day group, 4.5 in the 3.0 g/day group, and 3.9 in the 4.5 g/day group. The proportion of patients who experienced clinical improvement (ie, final CAI ≤4 or at least 3 points lower than at baseline) was highest (75%) in the 3.0 g/day group in comparison to 66% in the 4.5 g/day group and 64% in the 1.5 g/day group, respectively (Figure 4).

Subgroup Analyses

The remission rates calculated for different subgroups are summarized in Table 3. The respective results concerning dose relationship are very similar to total remission rates. No significant interaction between the

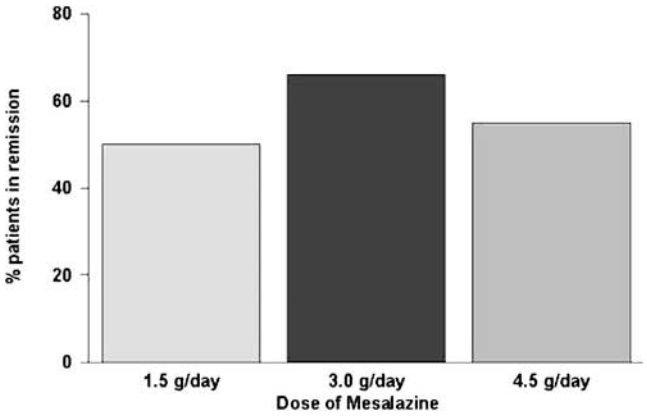

Figure 2. Proportion of patients achieving clinical remission.

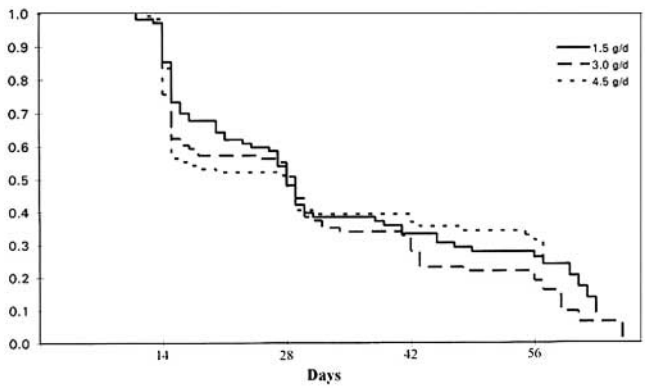

Figure 3. Probability not to go into clinical remission.

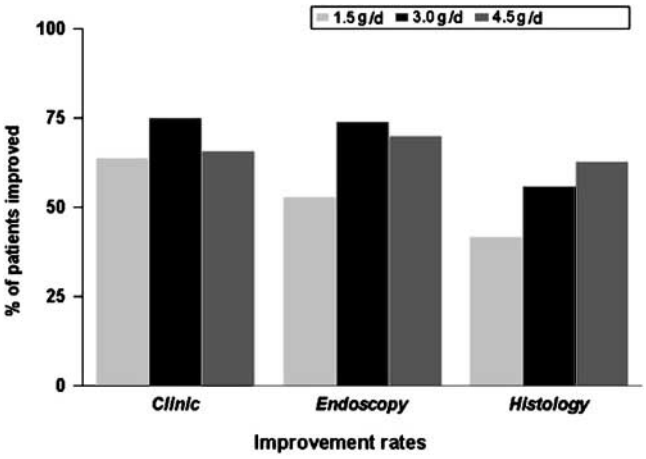

Figure 4. Proportion of patients with clinical, endoscopic, and histologic improvement.

dose and any of the subgroup factors was detected. However, severity and duration of the disease significantly affected the outcome. Patients with milder disease at entrance of the study (CAI ≤8) had higher (P = 0.016, adjusted for treatment group) remission rates (overall remission rate, 62 %) than patients with CAI >8 (49%). Better remission rates (P = 0.019, adjusted for treatment group) were also observed in patients with longer (>5 years) history of the disease (overall remission rate 64% vs 51% in patients with a disease ≤5 years). Although no statistically significant influence was observed by the localization of the disease (P = 0.083), it is of interest to note the high remission rates in the group of patients with proctosigmoiditis (54%, 85%, 53% under 1.5 g/day, 3.0 g/day, and 4.5 g/day, respectively), pointing to strong therapeutic efficacy of the new mesalamine preparation in very distal colitis.

Endoscopic and Histologic Activity

Results on endoscopic and histologic improvement are depicted in Figure 4. Again, patients with 3.0 g/day showed a higher rate of endoscopic improvement (84%) than with 1.5 g/day (53%; $P \leq 0.0001$) and with 4.5 g/day (70%; P = 0.10).

In general, numbers of histologic improvement rates were lower. Patients in the group with 4.5 g/day showed the best results (63%) in comparison to the other groups, 1.5 g/day (42%; P = 0.051) and 3.0 g/day (56%; P = 1.00).

Quality of Life, Global Assessment, Acceptability of the Study Medication

Life quality index improved in all 3 treatment groups, in the 1.5 g/day group from 21.1 ± 5.6 to 24.4 ± 6.9 (Δ = 3.2), in the 3.0 g/day group from 21.5 ± 5.5 to 25.7 ± 7.4 (Δ = 4.2), and in the 4.5 g/day group from 20.6 ± 5.5 to 24.9 ± 7.1 (Δ = 4.3).

Relief of symptoms or marked improvement was assessed by the attending physician in the 1.5 g/day group for 40% of the patients and in the 3.0 g/day and 4.5 g/day groups for 58% and 54%, respectively. Worsening was demonstrated in 22%, 15%, and 14% of the patients, respectively. The patients had been asked for an assessment of the new pellets in comparison with previously used mesalamine tablets. Patients from all 3 study groups who had previous experience with mesalamine

Table 3. Response Rate in Subgroups (Intention-to-Treat Population)

	Treatment group		
	500 mg tid	1000 mg tid	1500 mg tid
Initial CAI			
≤8	38 (57%, n = 67)	47 (72%, n = 65)	36 (58%, n = 62)
>8	14 (39%, n = 36)	24 (57%, n = 42)	22 (50%, n = 44)
Duration of UC			
≤5 y	24 (46%, n = 52)	29 (58%, n = 50)	28 (48%, n = 58)
>5 y	28 (55%, n = 51)	42 (74%, n = 57)	30 (63%, n = 48)
Localization			
Proctosigmoiditis	32 (54%, n = 59)	34 (85%, n = 40)	25 (53%, n = 47)
Left-sided	12 (44%, n = 27)	25 (57%, n = 44)	20 (57%, n = 35)
Subtotal	8 (50%, n = 16)	12 (55%, n = 22)	13 (54%, n = 24)
Extraintestinal manifestations			
Present	5 (63%, n = 8)	8 (53%, n = 15)	4 (29%, n = 14)
Absent	47 (49%, n = 95)	63 (68%, n = 92)	54 (59%, n = 92)
Smoking status			
Smoker	11 (85%, n = 13)	6 (60%, n = 10)	6 (50%, n = 12)
Ex-smoker	7 (39%, n = 18)	25 (78%, n = 32)	16 (48%, n = 33)
Nonsmoker	34 (47%, n = 72)	40 (62%, n = 65)	36 (59%, n = 61)

tid, 3 times a day.

medication rated the pellets as better than tablets 44%, no difference 29%, and worse 28%.

Per Protocol Analysis

The number of patients included in the per protocol analysis and the reasons for exclusion are given in Figure 1. Results of the per protocol analysis were similar to those of the ITT analysis. The proportion of patients achieving remission was 63% in the 1.5 g/day group, 81% in the 3.0 g/day group, and 63% in the 4.5 g/day group. Again, the difference between 4.5 g/day and 1.5 g/day was not significant ($P = 0.57$). Explorative statistics showed differences between the 3.0 g/day group and the 1.5 g/day group ($P = 0.049$) as well as between the 3.0 g/day group and the 4.5 g/day group ($P = 0.049$).

Safety Analyses

Overall, no unexpected adverse events occurred during the study. No deaths, but 14 serious adverse events in 12 patients were reported, most often hospitalization because of deterioration of UC (7 patients: 4 with 1.5 g/day, 2 with 3.0 g/day, and 1 patient with 4.5 g/day). Other serious adverse events were elective non-intestinal operation (2 patients), elevated liver enzymes, pancreatitis, deafness, hemolytic anemia, and pneumonia (each 1 patient).

Discontinuation of the study medication because of adverse events occurred in 27 patients, 11 in the 1.5 g/day group, 7 in the 3.0 g/day group, and 9 in the 4.5 g/day group. The most frequent reason was deterioration of UC or UC-related symptoms (19 patients).

The number of patients reporting at least 1 adverse event was 64 of 102 (63%) in the 1.5 g/day group, 66 of 108 (61%) in the 3.0 g/day group, and 63 of 108 (58%) in the 4.5 g/day group. The most frequent adverse event was headache, 24%, 23%, and 21%, respectively.

Laboratory tests also showed no unexpected findings. An elevation of liver enzymes that was found clinically relevant by the attending physician was observed in 10 patients (1 patient in the 1.5 g/day group, 3 patients in the 3.0 g/day group, and 6 patients in the 4.5 g/day group). Despite these pathologic findings, study medication was continued in 7 of 10 patients.

Special attention was paid to kidney function tests. Measurement of serum urea and serum creatinine levels showed no relevant pathologic alterations. Significant changes of the renal tubular marker enzymes β-NAG and DPP-IV as measured in the urine of the German patients at entrance and at end of the study were not observed, and there was no statistically significant difference between the 3 treatment groups (Table 4).

Table 4. Urinary Marker Enzymes at Start and End of Study Medication

Dose of mesalamine (mg 3 times a day)	Time (n, patients)	β-NAG (U/g creatinine)	DPP-IV (U/g creatinine)
500	Start (46)	3.9 ± 4.5	7.6 ± 9.2
	End (46)	3.5 ± 3.5	8.3 ± 10.3
1000	Start (49)	3.6 ± 1.7	9.3 ± 10.9
	End (53)	3.3 ± 1.7	6.6 ± 5.7
1500	Start (52)	4.0 ± 4.1	6.8 ± 5.6
	End (55)	3.7 ± 2.7	10.5 ± 22.5

Values are given as mean ± standard deviation.

The global tolerability of the study medication was rated by the patients as very good or good in 82% (1.5 g/day group), 88% (3.0 g/day group), and 75% (4.5 g/day group).

Discussion

Compared to placebo, mesalamine is superior in inducing remission of UC. This effectiveness holds true for different dosage subgroups (<2 g/day, 2–2.9 g/day, ≥3 g/day), although there is a trend toward a dose-dependent relationship.[2] An initial dose between 1.5 g/day and 2 g/day mesalamine is widely used in clinical practice. According to clinical requirements, the dose is increased up to 4.5 g/day and more.

The present study does not demonstrate either a dose response between 3 different doses of mesalamine or superiority of high dose treatment. A dose of 1.0 g/day seems to be particularly efficacious, but an increase of the dose to 1.5 g 3 times a day showed no better results to either the lowest dose (0.5 g 3 times a day) or the middle dose (1.0 g/day). Others reported significantly better therapeutic efficacy of mesalamine at high doses, 4.8 g/day compared to 1.6 g/day,[12] and of 4 g/day compared to 2 g/day,[13] which was in contrast to results showing no differences between the clinical effects of mesalamine 1 g/day, 2 g/day, and 4 g/day, respectively,[14] and between 0.8 g/day versus 2.4 g/day.[15] A small 3 arm study (1.2 g/day, 2.4 g/day, 3.6 g/day) comprising only mildly active UC showed a significantly inferior remission rate of the low dose group.[16] Altogether, from these data the optimal dose of mesalamine for active UC remains still to be defined.

Indeed, the present study cannot prove therapeutic superiority of high dose mesalamine. This may indicate a ceiling effect when the dose becomes increased beyond a certain amount. The only existing trial in moderately active UC with 3 different doses[14] demonstrated numeric, but not significant superiority of mesalamine 4 g/day (59% treatment success) over 1 g/day (45% treatment success), but similar effects with 2 g/day (57%

treatment success). A dose of 4 g/day was better than 2 g/day.[13] As yet the therapeutic effectiveness of 3 g/day of mesalamine has not been compared to other dosages. The effects of 3 g/day mesalamine were similar to 3 g/day olsalazine, which contains a higher amount of mesalamine, in inducing endoscopic remission.[17]

It has been argued that studies in groups of unselected patients can miss benefits of high dose therapy in some patients at a certain risk.[9] Therefore, we performed subgroup analyses in patients with initially high CAI, longstanding and extensive disease, and with extraintestinal manifestations. Again, no significant dose relationship was found. Also in these groups of at-risk patients, an increased dose of 4.5 g/day had no better clinical benefits. With the exception of endoscopic improvement, which was better with 3.0 g/day than with 1.5 g/day, no other significant differences were observed between the treatment groups with respect to endoscopic and histologic changes.

Mesalamine exerts its pharmacologic effects topically. It has been suggested that the response to mesalamine may be related to adequate mucosal concentrations of the drug.[18] A given oral dose showed high interindividual variability in mucosal concentrations,[19] and increasing the oral dose did not correspond to an increase of mesalamine in the mucosa.[20] When mesalamine is delivered to the intestines, it gets presystemically acetylated to therapeutically inactive N-acetyl-aminosalicylic acid, mainly by a colonic mucosal enzyme.[21] This N-acetyltransferase reaction takes place under substrate saturation conditions.

Testing mucosal acetylation of different concentrations of mesalamine showed optimal reaction.[21] Thus, intestinal metabolism may give some explanation for the clinically observed dose ceiling effect.

The newly developed pellet formulation of mesalamine tested here has been compared to Eudragit-L–coated mesalamine showing similar efficacy.[22] Considering the data from the literature,[3] the rates of inducing remission seem at least to be promising. In clinical practice, therapeutic success depends heavily on compliance. So far, it is of interest to note the superior acceptability of the pellets as rated by the patients.

The study medication showed a favorable safety profile. Unexpected adverse events could not be observed. Of note, the number and severity of the reported side effects did not differ between the 3 treatment groups. In light of an ongoing discussion of putative harmful effects on kidney function, especially with higher doses,[4,23] renal function was meticulously assessed. Besides the usual methods, some more sensitive tests were performed to screen for kidney dysfunction during the study. No unexpected alterations were found. Thus, at least in the short term, high doses of mesalamine can be administered without increased risk of harmful effects on kidney function.

In conclusion, this study cannot demonstrate a dose response of mesalamine in inducing remission of UC between 0.5 g 3 times a day (1.5 g/day), 1.0 g 3 times a day (3.0 g/day), and 1.5 g 3 times a day (4.5 g/day). Thus, the lowest effective dose (0.5 g 3 times a day) is recommended. Patients failing with this dose may benefit from an increase to 1.0 g 3 times a day, but doses beyond this amount do not seem to be of any value and should lead to a change in treatment strategy. The newly developed pellet formulation of mesalamine seems to have promising efficacy, very good acceptability by patients, and a favorable safety profile.

Appendix

The International Salofalk Pellets Study Group had the following members:

Participating Investigators from Austria: Regional Hospital, Graz: G. Brandstätter.

Participating Investigators from Germany: University Hospital, Regensburg: T. Andus; Private Practice, Heidelberg: H.P. Beckenbach; Hospitals Dr. Schreiber, Munich: R. Burlefinger; Private Practice, Munich: A. Dettmer; Private Practice, Aschaffenburg: W. Dillmann; Charité, Humbold-University, Berlin: Y. Dörffel; University Hospital Homburg/Saar: K.W. Ecker; Private Practice, Weinheim: D. Gragert; Poliklinik München: M. Gross; University Hospital, Hamburg: S. Howaldt; City Hospital, Bielefeld-Rosenhöhe: U. Junge; Private Practice, Berlin: H.-J. Kramm; Krankenhaus Merheim, Köln: B. Krakamp; Evangelisches Krankenhaus, Köln: W. Kruis; Private Practice, Mannheim: B. Küppers; Charite, Humbold-University, Berlin: H. Lochs; Klinikum Innenstadt der Universität, München: K. Loeschke; Private Practice, Amberg: E. Meier; Private Practice, Saarbrücken: H. Mlitz; Private Practice, Schwarzenbek: M. Mucha; Marienhospital, Osnabrück: M.-K. Müller; Private Practice, Flensburg: J. Pankow; Krankenhaus Tabea, Hamburg: A. Raedler; University Hospital, Göttingen: G. Ramadori; University Hospital, Ulm: M. Reinshagen; University Hospital Würzburg: W. Scheppach; Städt. Krankenhaus Neuperlach, München: W. Schmitt; Private Practice, Regensburg: E. Schütz; Private Practice, Wolmirstedt: M. Schumacher; Hospital Stralsund, Stralsund: J. Spengler; University Hospital, Frankfurt/Main: J. Stein; Private Practice, Mannheim: R. Vogt; University Hospital Großhadern, München: C. von Ritter; University Hospital, Mainz: R. Wanitschke; Private Practice, Hannover: M. Wöltje; St. Michael-Krankenhaus, Völklingen: D. Wördehoff.

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