Clinical Trial: A Novel High-dose 1 g Mesalamine Suppository (Salofalk) Once Daily Is as Efficacious as a 500-mg Suppository Thrice Daily in Active Ulcerative Proctitis

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Background: Mesalamine suppositories are first-line therapy in active ulcerative proctitis; the standard regime still recommends multiple doses per day. The primary objective of this study was to show the noninferiority of once-daily administration of a novel 1 g mesalamine suppository versus thrice-daily administration of the 0.5 g mesalamine suppository.

Methods: This was a single-blind (investigator-blinded), randomized, multicenter, comparative, Phase III clinical trial. Patients with mild to moderately active ulcerative proctitis inserted either one mesalamine 1 g suppository at bedtime or one mesalamine 0.5 g suppository thrice daily over a 6-week period. The primary endpoint was rate of remission (Disease Activity Index below 4).

Results: In all, 354 patients were evaluable for safety and per-protocol analysis. The new regimen demonstrated noninferiority: The percentage of patients with remission was 87.9% for the once-daily 1 g mesalamine suppository and 90.7% for the thrice-daily 0.5 g mesalamine suppository. Each regimen resulted in prompt cessation of clinical symptoms (e.g., median time to $\leq$3 stools per day (all without blood): 5 days in the 1 g mesalamine once-daily and 7 days in the 0.5 g mesalamine thrice-daily group). Patients preferred applying suppositories once a day.

Conclusions: In active ulcerative proctitis the once-daily administration of a 1 g mesalamine suppository is as effective and safe, yet considerably more convenient, than the standard thrice-daily administration of a 0.5 g mesalamine suppository.

(Inflamm Bowel Dis 2010;16:1947–1956)

Key Words: mesalamine, N-acetyltransferase, once-daily, proctitis, suppository, distal ulcerative colitis

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) of the colon. It is characterized by bloody diarrhea, tenesmus, and abdominal cramps. Some patients suffer from bowel symptoms accompanied by extraintestinal and systemic manifestations such as arthropathy, pyoderma gangrenosum, erythema nodosum, keratitis, uveitis, fever, and anemia. Inflammation of the colon can be detected in the rectum alone or extending continuously upwards into the sigmoid colon, part of or the entire colon, and as so-called backwash ileitis even into the terminal ileum.

Received for publication January 19, 2010; Accepted January 19, 2010.

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Funded in full by Dr. Falk Pharma GmbH, Freiburg, Germany.

The coauthors not listed below have declared no conflict of interest: Tilo Andus, Manfred Stolte, and Michael Vieth have served as speakers and consultants for Dr. Falk Pharma, Freiburg, Germany. Ingolf Cascorbi has received research funding from Dr. Falk Pharma, Freiburg, Germany. Tatyana D. Zvyagintseva has served as a speaker, a consultant, and an advisory board member for Dr. Falk Pharma, and has received research funding from Kharkov Medical Academy of Postgraduated Education. Andrey E. Dorofeyev has served as a speaker, a consultant, and an advisory board member for Dr. Falk Pharma, and has received research funding from Donetsk National Medical University. Karin Dilger, Ralf Mohrbacher, and Roland Greinwald are employees of Dr. Falk Pharma, Freiburg, Germany.

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DOI 10.1002/ibd.21258

Published online 22 March 2010 in Wiley Online Library (wileyonlinelibrary.com).

Local and systemic administration of aminosalicylates such as mesalamine are the treatment of choice in mild to moderate UC.[1–6] Mesalamine's mechanism of action is not yet fully understood; the latest findings implicate peroxisome proliferator-activated receptor gamma and intestinal bacteria as pharmacological targets.[7,8] Rectal administration of mesalamine is the first-line treatment of choice in mild-moderate proctitis, proctosigmoiditis, and left-sided colitis.[9–11] Local treatment is particularly beneficial, since local concentrations of the active drug are high, while systemic absorption is low. Although there is an increasing appreciation of transport processes as determinants of drug disposition, the role of intestinal drug transporters for absorption of mesalamine, e.g., P-glycoprotein, a product of the multidrug resistance 1 (*MDR1*) gene, is not yet elucidated.[12] The cytosolic N-acetyltransferases (NAT1 and NAT2) expressed in the liver but locally in the intestinal mucosa as well are responsible for the biotransformation of mesalamine to the pharmacologically inactive metabolite N-acetylmesalamine.[13] Thus, both efficacy and tolerability are optimized by local administration of mesalamine.

Suppositories, enemas, and foam preparations are widely used for the treatment of distal UC. While suppositories are effective only for proctitis, enemas and foam preparations cover the entire left colon. The major problem with local treatment is compliance/adherence.[14] Most patients find it easier to take a tablet than insert a suppository or clysma.[15,16] To optimize adherence, one administration per day would be an advantage compared to two or three applications every day. An early study by Gionchetti et al. revealed the superiority of 1 g mesalamine versus 2 $\times$ 0.5 g per day.[17] Therefore, a new mesalamine suppository containing 1 g of mesalamine was developed.

We chose the dose of 1 g because an earlier study had shown a dose of 1 g/d to be just as effective as 1.5 g/d.[18] We compared this new mesalamine suppository given once daily in the evening with the standard regimen of 3 $\times$ 0.5 g per day for efficacy, side effects, and patient satisfaction.

MATERIALS AND METHODS

Study Design

This was a single-blind (investigator-blinded), randomized, multicenter, comparative, Phase III clinical trial in patients suffering from mild to moderately active ulcerative proctitis. The study was planned according to a three-stage group sequential adaptive design with optional sample-size adjustments to be done at two interim analyses. The first interim analysis was to take place after 2 $\times$ 85 per-protocol (PP) evaluable patients had finished the trial. The projected total sample size was 380 patients. The study was conducted in 35 centers in four countries: Israel (10 centers), Germany (5), Russia (13), and Ukraine (7), with two arms (parallel group design) comparing two different rectal mesalamine suppository formulations. In order to ensure blindness of the investigator, the distribution and return of study medication as well as all checks of patient diaries were performed by a third person not involved in any assessment at the center. Treatment lasted for 6 weeks (42 days), with control visits scheduled at 2 and 4 weeks after the start of treatment. An independent data monitoring committee reviewed unblinded data at the interim analyses and provided its recommendations to modify, put on hold, or stop the trial for a center or entirely to the sponsor and coordinating investigator (T.A.), who then took appropriate action. The study was conducted in accordance with good clinical practice, the Declaration of Helsinki, and all applicable national laws, and was approved by independent ethics committees at each of the centers prior to starting the study. The EudraCT number is 2004-005018-35.

Patients

Men and women aged 18–75 years with established or newly-diagnosed active ulcerative proctitis (maximal 15 cm of rectum) confirmed by endoscopy, histology, negative stool cultures, and 3 $<$ Disease Activity Index (DAI) $<$ 11 were included.

Excluded were patients with Crohn's disease, with proctitis of a different origin, prior bowel resection leading to diarrhea, and/or pouch formation, toxic megacolon, hemorrhagic diathesis, present or past colorectal cancer, or serious other secondary disease(s). The use of steroids or cycloferon within 1 month, immunosuppressants or anti-TNF-α within 3 months prior to inclusion was also prohibited. Patients who had relapsed during daily maintenance of $>$0.5 g rectal or $>$2 g oral mesalamine, or corresponding doses of rectal or oral sulfasalazine, as well as those with transaminases or alkaline phosphatase levels $\geq$2 $\times$ upper limit of normal or serum creatinine $>$1.5 mg/dL were excluded as well.

The use of nonsteroidal antiinflammatory drugs (NSAIDs) for $>$6 weeks, as well as antibiotics (metronidazole, ciprofloxacin), drugs containing psyllium, *E. coli* Nissle 1917, or loperamide was forbidden during the trial. All oral or rectal treatments for UC had to have ceased prior to study inclusion. Female patients had to have a negative pregnancy test at baseline. All patients gave written informed consent prior to participating in this study.

Study Medications

The test product was the novel 1 g mesalamine suppository (Salofalk 1 g suppository); the reference product was the 0.5 g mesalamine suppository (Salofalk 500 mg suppository). The novel 1 g mesalamine suppository is

characterized by a slow rate of systemic absorption (time to peak concentration about 7 hours) and a long mean terminal elimination half-life of 8 hours. Both drugs were manufactured by Dr. Falk Pharma (Freiburg, Germany). One 1 g mesalamine suppository was administered once daily (OD) at bedtime, the 0.5 g mesalamine suppositories three times daily (TID; morning, noon, and bedtime).

Procedures

At baseline all patients underwent a physical examination and their demographics and medical history were recorded. Vital signs and routine laboratory values were assessed at each visit. The DAI according to Sutherland et al.[19] was assessed at baseline and the final visit. Furthermore, efficacy was assessed with the following scores/scales: the Endoscopic Index (EI)[20] assessed by the same investigator at baseline and the final visit, the Histological Index (HI) according to Riley et al.[21] assessed from biopsies taken at baseline and the end of treatment, and Physicians' Global Assessment (PGA) of efficacy[22] assessed at week 6. The patients' acceptance of and preference for a study drug was evaluated at the final examination or upon the patient's withdrawal. Concomitant medications and adverse events (AEs) were documented at every visit. The patients had to return unused study medication at every visit.

Patient Diaries

The patients recorded the number of stools, presence and degree of rectal bleeding, abdominal pain and cramps, suffering from tenesmus, mucus in or on the stools, general well-being, and regular use of study medications on a daily basis in a diary.

Primary Objective and Efficacy Variable

The primary objective of this study was to show the noninferiority of once-daily administration of the novel 1 g mesalamine suppository versus thrice-daily administration of the 0.5 g mesalamine suppository, examining the proportion of patients (PP analysis set) with clinical remission defined as DAI <4 at the final visit (with last observation carried forward, LOCF), considering a noninferiority margin of 15% (one-sided $\alpha = 0.025$). Exploratory subgroup analyses of the primary endpoint were already fixed in the protocol and included analyses by gender, disease duration ($\leq$5 years versus > 5 years), baseline severity (DAI $\leq$6 versus DAI >6), and smoking history.

Secondary Efficacy Variables

Secondary efficacy endpoints (intention-to-treat, ITT, analysis set) included clinical improvement ($\geq$1 point decrease in DAI from baseline to final visit (LOCF)); mucosal healing ($DAI_{mucosal}$ subscore according to the FDA recommendations $\leq$1 at final visit (LOCF)); endoscopic remission (EI <4 at final visit (LOCF)); histological remission (remission according to the assessment of the pathologist at final visit (LOCF)); time to first resolution of symptoms ($\leq$3 stools per day (all without blood)); therapeutic success (PGA assessed as "complete relief" or "marked improvement") and therapeutic benefit (PGA at least assessed as "slight improvement") at final visit; and acceptance and preference for the study drug.

Treatment Compliance

Treatment compliance was calculated as the proportion of suppositories taken (difference between the number of suppositories issued and returned) compared to the prescribed number of suppositories.

Safety Variables

The frequency of AEs, clinically relevant changes in any laboratory parameters, and vital signs were assessed for the safety population.

Pharmacogenetics

The patients were genotyped for polymorphisms of *MDR1* (2677G>T/A and 3435C>T), as well as of the cytosolic N-acetyltransferases *NAT1* (190C>T, 559C>T, 560G>A, 640T>G, 752T>G, 1088T>A, and 1095C>A) and *NAT2* (191G>A, 282C>T, 341C>T, 481C>T, 590G>A, 803A>G, and 857G>A).

Single nucleotide polymorphisms were determined by polymerase chain reaction (PCR) / restriction fragment length polymorphism (RFLP) and sequencing, and addressed haplotype combinations as published previously.[23,24] Patients were stratified for statistical analysis according to the literature[25–27] to distinguish between putatively rapid or slow NAT1 or NAT2 acetylator phenotypes and high or low active *MDR1* haplotype combinations, respectively.

Statistical Analysis

Efficacy analyses were performed according to the ITT principle as well as on patients without major protocol deviations (PP population). The safety analysis set included all patients treated who had at least one follow-up value for safety variables to be analyzed.

The primary objective of the study was to demonstrate the noninferiority of 1 g mesalamine OD compared to 0.5 g mesalamine TID with respect to the rate of patients with clinical remission at the final visit (considering a noninferiority margin of 15%).

The study was conducted using a three-stage adaptive group sequential test design of O'Brien and Fleming.[28] For (one-sided) $\alpha = 0.025$ and information rates of 0.50, 0.75, and 1, the resulting boundary *P*-values were given by *P*1

TABLE 1. Demographics and Patients' Baseline Characteristics (ITT Population)

		1 g Mesalamine OD ($n = 200$)	0.5 g Mesalamine TID ($n = 203$)
Sex			
Male	*n* (%)	85 (42.5%)	93 (45.8%)
Female	*n* (%)	115 (57.5%)	110 (54.2%)
Ethnic origin	Caucasian: *n* (%)	200 (100.0%)	203 (100.0%)
Age [years]	Mean (SD)	41.4 (13.2)	42.7 (13.9)
Weight [kg]	Mean (SD)	70.3 (15.1)	70.0 (13.9)
Smoking habits			
Nonsmoker	*n* (%)	155 (77.5%)	161 (79.3%)
Exsmoker	*n* (%)	25 (12.5%)	27 (13.3%)
Smoker	*n* (%)	20 (10.0%)	15 (7.4%)
Duration of the disease [years]	Median (range)	2.2 (0.0 – 36.7)	3.8 (0.0 – 31.9)
Patients with extraintestinal disease symptoms	*n* (%)	32 (16.0%)	29 (14.3%)
Course of the disease			
New diagnosis*	*n* (%)	42 (21.0%)	34 (16.7%)
Continuous	*n* (%)	16 (8.0%)	8 (3.9%)
Recurrent	*n* (%)	142 (71.0%)	161 (79.3%)
Number of previous acute episodes			
Based on all patients	Mean (SD)	3.4 (5.7) [$n = 198$]	4.8 (7.0) [$n = 201$]
Based on patients with a recurrent course of the disease only	Mean (SD)	4.8 (6.2) [$n = 140$]	6.0 (7.4) [$n = 159$]
Duration of last remission phase [months]	Median (range)	6.0 (0.00 – 112.0) [$n = 142$]	7.0 (0.00 – 226.0) [$n = 161$]
Duration of current acute episode [months]	Median (range)	1.0 (0.0 – 158.0)	1.0 (0.0 – 110.0)
Patients with previous bowel operations	*n* (%)	11 (5.5%)	7 (3.4%)
Disease Activity Index (DAI)	Mean (SD)	6.2 (1.6) [$n = 200$]	6.2 (1.5) [$n = 201$]
Number of stools [per week]	Mean (SD)	23.1 (15.8) [$n = 200$]	22.7 (13.3) [$n = 201$]
Number of bloody stools [per week]	Mean (SD)	15.9 (15.1) [$n = 200$]	14.9 (11.1) [$n = 201$]
Endoscopic Index (EI)	Mean (SD)	6.8 (2.0)	6.6 (2.0)

*New diagnosis is defined as "duration of disease <6 months" and "course of the ulcerative proctitis" = continuous.

$= 0.00210$, $P2 = 0.00971$, and $P3 = 0.02148$, with critical values 2.863, 2.337, and 2.024, respectively.

The sample size calculation yielded a total of $2 \times 172 = 344$ patients.[29] To prevent a loss of power due to exclusion of protocol deviators from the PP analysis set (≈10%) a total of 380 patients were planned to be enrolled.

For confirmatory testing of H_0 at the interim and final analyses, we used the inverse-normal method of combining the *P*-values of the one-sided shifted asymptotic χ^2-test for comparing two rates and maximum likelihood estimation for the unknown parameters according to Farrington and Manning.[30] All other group comparisons were of an exploratory nature.

Where appropriate, missing values at the final or withdrawal visit were imputed by the last measurement obtained during treatment (LOCF).

Differences in change in DAI, EI, and HI between putatively rapid or slow NAT1 or NAT2 acetylator phenotypes or high or low active *MDR1* haplotype combinations were tested within and between study arms using the Mann–Whitney test.

RESULTS

Patients

A total of 408 patients were allocated to randomized treatment (201 to 1 g mesalamine OD and 207 to 0.5 g mesalamine TID). In all, 403 patients were treated and had at least one follow-up value for safety analysis. Thus, 403 patients were evaluated in the safety and ITT population (200 in the 1 g mesalamine OD and 203 in the 0.5 g mesalamine TID group).

There were no relevant differences between treatment groups regarding demographic variables (Table 1). We observed no relevant difference in anamnestic characteristics at baseline, the exceptions being: longer disease duration, a higher number of previous acute episodes, and a slightly higher proportion of patients with a recurrent acute

ulcerative proctitis in the 0.5 g mesalamine TID group, as well as a slightly higher proportion of patients with a new diagnosis of acute ulcerative proctitis and continuous disease in the 1 g mesalamine OD group (Table 1). The anamnestic characteristics in the PP analysis set were almost identical to those in the ITT analysis set.

Protocol Violations

A total of 54 patients (1 g mesalamine OD: 19; 0.5 g mesalamine TID: 35) were excluded from the PP analysis set due to major protocol deviations, noncompliance or premature study termination caused by reasons unrelated to the study medication. The PP population thus consisted of 354 patients. The criteria used for exclusion from the PP dataset were stated in the Statistical Analysis Plan before breaking the blind. Especially the number of patients showing a major protocol deviation was clearly higher in the 0.5 g mesalamine TID (23 patients) than in the 1 g mesalamine OD group (14 patients).

Primary Efficacy Evaluation

Clinical Remission at Study End (LOCF) - Based on DAI

At the first interim analysis, performed after 145 PP-evaluable patients had completed the study, the shifted asymptotic χ^2-test for comparing two remission rates (1 g mesalamine OD: 82.2%; 0.5 g mesalamine TID: 88.9%) yielded a one-sided observed *P*-value of 0.0819 for the PP analysis set (noninferiority margin: 15%). This *P*-value exceeded the boundary *P*-value of 0.0021. The null hypothesis could thus not be rejected, the study was continued, and the number of patients to be evaluable for PP analysis at the second stage was increased to 120.

At the second interim analysis, performed after another 125 PP-evaluable patients had completed the study, the shifted asymptotic χ^2-test for comparing two remission rates (stage 1: 1 g mesalamine OD: 83.8%; 0.5 g mesalamine TID: 88.7% and stage 2: 1 g mesalamine OD: 89.4%; 0.5 g mesalamine TID: 91.5%) yielded an inverse normal of 2.692 for the PP analysis set (noninferiority margin: 15%). The inverse normal exceeded the critical value of 2.337. The null hypothesis was rejected, noninferiority of 1 g mesalamine OD versus 0.5 g mesalamine TID considering a noninferiority margin of 15% was proven in the confirmatory sense and recruitment was stopped.

Since recruitment continued during the second interim analysis, another 93 patients had been enrolled when the results of the interim analysis became available. We continued to observe these patients, and the final analysis included a total of 354 PP-evaluable patients. At the final analysis the shifted asymptotic χ^2-test comparing two remission rates (overall remission rates: 1 g mesalamine OD: 87.9%; 0.5 g mesalamine TID: 90.7%) yielded a one-sided overall *P*-value of 0.00027 for the PP analysis set (noninferiority margin: 15%). This *P*-value was clearly lower than the global α (0.025). According to the group sequential design, the second interim analysis yielded our confirmatory result. The result of the final analysis was interpreted only in the exploratory sense, yet it demonstrated the robustness of the result.

TABLE 2. Clinical Remission Rates (DAI) by Baseline Covariates (ITT Population)

	Number (%) of Patients in Clinical Remission (DAI <4) at the Final/Withdrawal Visit	
	1 g Mesalamine OD ($n = 200$)	0.5 g Mesalamine TID ($n = 203$)
All	168 (84.0%)	172 (84.7%)
Smoking status		
Nonsmoker	130/155 (83.9%)	140/161 (87.0%)
Exsmoker	21/25 (84.0%)	21/27 (77.8%)
Smoker	17/20 (85.0%)	11/15 (73.3%)
Duration		
$\leq$ 5 years	112/134 (83.6%)	108/123 (87.8%)
$>$ 5 years	56/66 (84.8%)	64/80 (80.0%)
Gender		
Male	68/85 (80.0%)	73/93 (78.5%)
Female	100/115 (87.0%)	99/110 (90.0%)
Severity (DAI at baseline)		
$\leq$ 6 points (mild)	106/118 (89.8%)	99/114 (86.8%)
$>$ 6 points (moderate, severe)	62/82 (75.6%)	72/87 (82.8%)
Extraintestinal symptoms		
Absence	145/168 (86.3%)	152/174 (87.4%)
Presence	23/32 (71.9%)	20/29 (59.0%)

DAI, Disease Activity Index.

Influence of Covariates on Clinical Remission

The predefined exploratory subgroup analyses of the primary endpoint are illustrated for the ITT population in Table 2. Overall, clinical remission rates were higher in females than in males, in patients with mild active ulcerative proctitis (represented by a DAI $\leq$6 points at baseline) than in patients with moderate or severe active ulcerative proctitis (DAI $>$6 points at baseline), and in patients without than in patients with extraintestinal disease symptoms.

Secondary Efficacy Evaluation

DAI, EI, HI, PGA, and Time to First Resolution of Symptoms (ITT Population)

Remission and improvement rates based on DAI, EI, HI, and mucosal healing rates based on the $DAI_{mucosal}$ subscore

TABLE 3. Secondary Efficacy Endpoints (ITT Population)

			1 g Mesalamine OD ($n = 200$)	0.5 g Mesalamine TID ($n = 203$)
DAI*	Clinical improvement[a]	n (%)	186 (93.5%) $n = 199$	184 (92.0%) $n = 200$
	Mucosal healing[b]	n (%)	172 (86.0%) $n = 200$	175 (86.2%) $n = 203$
EI*	Endoscopic remission[c]	n (%)	153 (80.1%) $n = 191$	164 (85.4%) $n = 192$
HI	Histological remission[d]	n (%)	83 (55.3%) $n = 150$	91 (67.9%) $n = 134$
PGA*	Therapeutic success	n (%)	168 (84.0%) $n = 200$	173 (85.2%) $n = 203$
	Therapeutic benefit	n (%)	192 (96.0%) $n = 200$	196 (96.6%) $n = 203$
Time to first resolution of symptoms*,[e]		days; median [95%-CI]	5.0 [4.0, 6.0] $n = 200$	7.0 [5.0, 8.0] $n = 203$

*No significant difference between treatments.
[a]Decrease in DAI by ≥1 point from baseline; DAI >3 at baseline.
[b]$DAI_{mucosal}$ subscore according to the FDA recommendations ≤1, i.e., "intact mucosa with preserved or distorted vessels" or "erythema, decreased vascular pattern, granularity, no mucosal hemorrhage."
[c]EI <4.
[d]Remission according to the assessment of the pathologist.
[e]Defined as no more than three stools per day, all without blood.
DAI, Disease Activity Index; EI, Endoscopic Index; HI, Histological Index; PGA, Physician's global assessment; CI, confidence interval.

according to the FDA recommendations, PGA, as well as time to first resolution of symptoms are presented in Table 3.

Except for a higher rate of patients with histological remission in the 0.5 g mesalamine TID than in the 1 g mesalamine OD group, DAI, and EI did not show any relevant differences between treatment groups. Also, the apparent difference in PGA and in median time to first resolution of symptoms were not statistically significant.

Acceptance of and Preference for the Study Drug (ITT Population)

Patients rated the study drug administration better and reported less interference with their daily routine in the 1 g mesalamine OD than the 0.5 g mesalamine TID group (Table 4). The vast majority of patients preferred applying 1 suppository/day in the evening rather than 3 suppositories/day (morning, noon, and bedtime) (Table 4).

TABLE 4. Acceptance of and Preference for the Study Drug (ITT Population)

	Number (%) of Patients with a Certain Assessment of Acceptance and Preference		
	1 g Mesalamine OD ($n = 200$)	0.5 g Mesalamine TID ($n = 203$)	χ^2-test* P-value
Administration of the study drug			0.0043
Easy	179 (89.5%)	158 (77.8%)	
Not too difficult	17 (8.5%)	40 (19.7%)	
Difficult	2 (1.0%)	1 (0.5%)	
No remark	2 (1.0%)	4 (2.0%)	
Interference with daily routine			< 0.0001
Considerably	17 (8.5%)	24 (11.8%)	
Not too much	45 (22.5%)	89 (43.8%)	
Almost not	136 (68.0%)	86 (42.4%)	
No remark	2 (1.0%)	4 (2.0%)	
Preference of intake frequency			0.0010
Preference for OD intake	185 (92.5%)	163 (80.3%)	
Preference for TID intake	1 (0.5%)	10 (4.9%)	
No preference	12 (6.0%)	26 (12.8%)	
No remark	2 (1.0%)	4 (2.0%)	

*1 g mesalamine OD – 0.5 g mesalamine TID.

TABLE 5. Effect of *MDR1*, *NAT1*, and *NAT2* Genotypes on DAI, EI, and HI in Each Study Arm

	Mean (SD) Change from Baseline to Final Visit/Final Examination (LOCF) in:		
	DAI	EI	HI
1.0 g mesalamine OD			
MDR1 2677TT/3435TT[a]	−4.7 (2.2) $n = 37$	−4.9 (2.5) $n = 37$	−1.5 (1.2) $n = 36$
MDR1 2677GG/3435CC[b]	−4.9 (1.7) $n = 33$	−5.3 (2.2) $n = 33$	−0.8 (1.2)* $n = 31$
NAT1 slow acetylators	−5.0 (1.8) $n = 105$	−5.4 (2.3) $n = 105$	−1.1 (1.1) $n = 102$
NAT1 rapid acetylators	−4.5 (0.7) $n = 2$	−6.0 (1.4) $n = 2$	−1.0 (1.4) $n = 2$
NAT2 slow acetylators	−4.9 (2.1) $n = 101$	−5.2 (2.6) $n = 101$	−1.0 (1.2) $n = 97$
NAT2 rapid acetylators	−4.9 (1.6) $n = 10$	−4.9 (2.6) $n = 10$	−1.4 (0.8) $n = 10$
0.5 g mesalamine TID			
MDR1 2677TT/3435TT[a]	−5.0 (1.7) $n = 29$	−6.0 (2.1) $n = 29$	−0.9 (1.2) $n = 28$
MDR1 2677GG/3435CC[b]	−4.0 (2.2) $n = 23$	−5.0 (3.4) $n = 23$	−1.0 (1.4) $n = 22$
NAT1 slow acetylators	−4.6 (1.9) $n = 104$	−5.0 (2.4) $n = 104$	−1.0 (1.3) $n = 103$
NAT1 rapid acetylators	−6.0 (0.0) $n = 4$	−7.0 (2.8) $n = 4$	−2.5 (0.6)** $n = 4$
NAT2 slow acetylators	−4.7 (1.9) $n = 92$	−5.0 (2.4) $n = 92$	−1.0 (1.2) $n = 91$
NAT2 rapid acetylators	−4.4 (2.1) $n = 7$	−5.9 (3.7) $n = 7$	−1.4 (2.4) $n = 5$

[a]Putatively low activity.
[b]Putatively high activity.
DAI, disease activity index; EI, endoscopic index; HI, histological index; *MDR1*, multidrug resistance gene 1; NAT1, NAT2; N-acetyltransferases.
*$P < 0.05$ vs. *MDR1* 2677TT/3435TT.
**$P < 0.05$ vs. NAT1 slow acetylators.

Treatment Compliance

In all, 99.5% of the patients in the 1 g mesalamine OD and 98.5% of the patients in the 0.5 g mesalamine TID group were considered compliant since they took at least 80% of the prescribed number of suppositories.

Genotyping

Genotyping was performed in 315 patients of the PP population. The allelic frequency distribution of the single nucleotide polymorphisms investigated in this study population did not differ from our reference population, nor did we observe any significant deviations from the Hardy–Weinberg equilibrium. Mean (SD) changes in DAI, EI, and HI in putatively lowly active (2677TT/3435TT) and highly active (2677GG/3435CC) *MDR1* diplotypes, in NAT1 slow and rapid acetylators, as well as in NAT2 slow and rapid acetylators are compared in Table 5. We found no significant differences except 1) the higher histological response (change in HI) for NAT1 rapid acetylators compared to NAT1 slow acetylators in the 0.5 g mesalamine TID group only, and 2) the lower histological response in patients with putatively high activity of P-glycoprotein compared to those with low activity in the 1 g mesalamine OD group only.

Adverse Events

A total of 48 AEs were reported in 38 patients (19.0%) in the 1 g mesalamine OD group, and 67 AEs occurred in 43 patients (21.2%) in the 0.5 g mesalamine TID group. The number (%) of patients experiencing those AEs considered at least possibly drug-related (ADRs) were 5 (2.5%) in the 1 g mesalamine OD and 7 (3.4%) in the 0.5 g mesalamine TID group.

The most frequently reported AEs by preferred term were headache, nasopharyngitis, and colitis ulcerative. Preferred terms that occurred in at least two patients are presented in Table 6.

All patients experienced AEs of mild (1 g mesalamine OD: 14.5%; 0.5 g mesalamine TID: 16.3%) or moderate (1 g mesalamine OD: 4.5%; 0.5 g mesalamine TID: 6.9%) intensity. No patient experienced a severe AE.

A total of two AEs in two patients were rated as serious (SAE) due to both having required hospitalization. One patient in the 1 g mesalamine OD group experienced a subclavian artery embolism; one in the 0.5 g mesalamine TID experienced anxiety. None of these SAEs was assessed as having been study drug-related. No patient died during the course of this study.

Three patients taking 0.5 g mesalamine TID were withdrawn from the study due to AEs. Two patients were withdrawn due to AEs with possible relationship to the study drug (flatulence, pruritus, defecation urgency, constipation); one patient was withdrawn due to elevated liver values at baseline.

TABLE 6. Patients with at Least One AE by Preferred Term (Safety Population, Only Preferred Terms that Occurred in at Least Two Patients)

Preferred Term (MedDRA)	Number (%) of Patients with at Least One AE	
	1 g Mesalamine OD ($n = 200$)	0.5 g Mesalamine TID ($n = 203$)
Headache	5 (2.5%)	11 (5.4%)
Nasopharyngitis	5 (2.5%)	6 (3.0%)
Colitis ulcerative	3 (1.5%)	5 (2.5%)
Lipase increased	4 (2.0%)	3 (1.5%)
Constipation	3 (1.5%)	1 (0.5%)
ALAT increased	1 (0.5%)	2 (1.0%)
Influenza like illness	1 (0.5%)	2 (1.0%)
Leukopenia	2 (1.0%)	1 (0.5%)
Arthralgia	2 (1.0%)	—
ASAT increased	1 (0.5%)	1 (0.5%)
Platelet count decreased	1 (0.5%)	1 (0.5%)
Pruritus	—	2 (1.0%)

ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase.

DISCUSSION

We compared the efficacy and tolerability of a new 1 g suppository versus 3 × 0.5 g mesalamine suppositories in a randomized, single-blinded clinical trial conducted to demonstrate the noninferiority of the 1 g suppository versus 3 × 0.5 g mesalamine suppositories in inducing clinical remission in patients with mild to moderately active ulcerative proctitis.

In the final analysis of all our 403 patients, we observed clinical remission rates based on the DAI in the PP analysis of 87.9% in the 1 g once-daily group and 90.7% in the 0.5 g TID group ($P = 0.00027$ for noninferiority). The clinical remission rates in the ITT analysis were 84.0% versus 84.7% ($P < 0.00008$), respectively. Thus, noninferiority was proven to be statistically highly significant in both analyses.

This conclusion was strongly supported by the analysis of several secondary endpoints (clinical improvement, EI, HI, PGA score). Most revealed no significant differences between the treatment groups. Histological assessment showed higher remission rates in the 0.5 g mesalamine TID (67.9%) than the 1 g mesalamine OD group (55.3%).

This trial's results provide further evidence of the efficacy of the appropriate daily dose of rectal mesalamine given as a suppository. About 90% of all patients went into remission, with resolution of symptoms starting within 5 days. Given the high and rapid responses observed in this trial, we conclude that a daily dose of 1 g rectal 5-aminosalicylate (5-ASA) is appropriate for treating mild-to-moderate active proctitis.

This is supported by the high endoscopic remission rates (80%–85%) we observed. These convincing efficacy data confirm the role of rectal aminosalicylate therapy as a first-choice strategy for inducing remission in active distal UC, and this therapy has been recommended in several guidelines.[1–6]

Rectal mesalamine suppositories even induced mucosal healing in a substantial proportion of patients assessed histologically (histological remission: 55%–68%) with mild-to-moderate active proctitis. This result is confirmed by endoscopy, whereby 86% of the patients presented no mucosal hemorrhage at the final visit. As mucosal healing is a predictor for reducing the risk of colorectal cancer in UC,[31] this might go some way to explain the beneficial role of 5-ASA as a chemopreventive agent in UC.[32]

Both suppository preparations induced a rapid resolution of clinical symptoms apparently superior to oral mesalamine preparations. These results were similar or even better than those of earlier studies with 1 g 5-ASA suppositories.[17,33–36] This finding confirms that a rectal mesalamine suppository is the treatment of choice when the extent of UC is limited to the rectum. Moreover, as mesalamine plasma levels following rectal administration are lower than after oral intake,[37] rectal administration provides an even better benefit-to-risk ratio for the treatment of distal UC.

We found rectal 5-ASA administered as a suppository to be safe in this large, short-term trial, and our findings are fully compatible with published reports,[17,33–36,38,39] as are the type and frequency of AEs.

The main reason for developing this new 1 g suppository was our assumption that once-a-day administration would interfere less with daily routine than applying suppositories three times a day, and that this would improve patient satisfaction and adherence to the therapy.[35,36] This trial effectively confirmed that assumption: 90% of the patients considered it easy to apply one suppository a day, whereas only 78% of the patients regarded TID application to be easy. Therefore, 86% of the patients preferred the 1 g suppository once daily, whereas just 3% preferred the TID administration of 0.5 g suppositories.

Our results are even better in terms of patient acceptance than those of earlier studies demonstrating good tolerance every day in 77% and 54% of patients treated with slow-release 5-ASA suppositories (Pentasa 1 g/day) and 5-ASA suppositories (Rowasa 0.5 g, two times a day), respectively.[35] In addition to the OD administration schedule, the pharmaceutical formulation may account for the differences in patient satisfaction with various 5-ASA suppositories.

This study was not designed to answer the question concerning the effect of this new form of treatment on

long-term adherence, but chances are good that its simplicity will raise compliance and long-term efficacy.

Genetic variants of *MDR1* (gene product P-glycoprotein) may be associated with altered transport activity in the intestinal mucosa, whereas *NAT1* and *NAT2* polymorphisms are associated with the phenotype of a slow and rapid acetylator. Previous studies have provided evidence that both phase-II enzymes are also expressed in the intestinal mucosa.[40] We observed no relevant effect of putatively important *MDR1*, *NAT1*, and *NAT2* gene polymorphisms on clinical and endoscopic response (DAI, EI) to rectal mesalamine in active ulcerative proctitis. Interestingly, in the 0.5 g mesalamine TID group but not in the 1 g mesalamine OD group, the very few NAT1 rapid acetylators reached better histological response (HI) than the NAT1 slow acetylators. Comparison of histological response in NAT1 rapid acetylators between the two different dosing schedules did not show a significant difference. Interpretation of our pharmacogenetic data is limited due to the very small number of NAT1 rapid acetylators ($n = 2$, 1 g mesalamine OD; $n = 4$, 0.5 g mesalamine TID). Moreover, there was a preliminary indication that high activity of the intestinal drug efflux pump, P-glycoprotein, might limit histological response following the 1 g mesalamine suppository OD. However, that histological observation was not reflected in the accompanying EI or DAI results.

In conclusion, our evidence demonstrates that the novel 1 g mesalamine suppository given once a day in the evening is highly effective and well-tolerated. This new preparation may well enhance patients' compliance with topical therapy.

ACKNOWLEDGMENTS

The authors thank all patients and investigators for their participation and contribution to the study. We thank R. Eisebitt for statistical expertise and I. Ottersbach (both ClinResearch, Cologne, Germany) for assistance in conducting the clinical trial.

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APPENDIX

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