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Budesonide foam versus budesonide enema in active ulcerative proctitis and proctosigmoiditis

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SUMMARY

Background
Rectal budesonide is an effective treatment of active ulcerative proctitis or proctosigmoiditis.

Aim
To compare the therapeutic efficacy, tolerability and safety, and patient's preference of budesonide foam vs. budesonide enema.

Methods
Patients with active ulcerative proctitis or proctosigmoiditis (clinical activity index >4 and endoscopic index ≥4) were eligible for this double-blind, double-dummy, randomized, multicentre study. They received 2 mg/25 mL budesonide foam and placebo enema ($n = 265$), or 2 mg/100 mL budesonide enema and placebo foam ($n = 268$) for 4 weeks. Primary endpoint was clinical remission (clinical activity index ≤4) at the final/withdrawal visit (per protocol).

Results
A total of 541 patients were randomized – 533 were evaluable for intention-to-treat analysis and 449 for per protocol analysis. Clinical remission rates (per protocol) were 60% for budesonide foam and 66% for budesonide enema ($P = 0.02362$ for non-inferiority of foam vs. enema within a predefined non-inferiority margin of 15%). Both formulations were safe and no drug-related serious adverse events were observed. Because of better tolerability and easier application most patients preferred foam (84%).

Conclusion
Budesonide foam is as effective as budesonide enema in the treatment of active ulcerative proctitis or proctosigmoiditis. Both budesonide formulations are safe, and most patients prefer foam.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease of unknown aetiology and pathogenesis. Distal UC is managed by topical administration of 5-aminosalicylic acid (5-ASA) or corticosteroids as suppositories, enemas or rectal foams. Several trials have demonstrated the efficacy and safety of rectal budesonide administered as an enema in active distal UC.[1–11] However, many patients have problems with retaining liquid enemas. To overcome this problem, a rectal foam was developed. A small volume of the foam (25 mL per puff) together with its high viscosity, might favour the retention and subsequently the patient's acceptance when compared with the administration of a high-volume (100 mL) liquid enema.

Two pilot trials [12, 13] have demonstrated that budesonide foam led to a statistically significant improvement of clinical symptoms in patients with active distal UC. A recent randomized, open, parallel-group, active-controlled, multicentre clinical trial including 251 patients has shown similar efficacy and safety of budesonide foam compared with hydrocortisone acetate foam in patients with active ulcerative proctosigmoiditis.[14]

The objectives of the present study were to compare the efficacy of a daily dose of 2 mg rectal budesonide administered either as foam or as enema in patients with active ulcerative proctitis or proctosigmoiditis, to study the safety and tolerability of the two formulations, and to evaluate patients' preference regarding acceptance and handling of the study drugs.

PATIENTS AND METHODS

Study design

This was a double-blind, double-dummy, randomized, multicentre, comparative study (phase III). Patients were enrolled in 52 centres: 14 in Germany, 10 in Hungary, 10 in Israel, 10 in Lithuania, four in Latvia, two in Estonia and two in the Netherlands. Patients were enrolled from February 2001 to March 2003. The study was conducted in accordance with good clinical practice and the Declaration of Helsinki, and approved by independent ethics committees for each of the centres.

Patients

Patients between 18 and 70 years of age were eligible for the study if they had active ulcerative proctitis or proctosigmoiditis confirmed by endoscopy, histology and a negative stool culture. A clinical disease activity (CAI) according to Rachmilewitz[15] of >4, and an endoscopic index (EI)[15] of ≥4 were mandatory. Exclusion criteria were: uncertain diagnosis of UC, symptoms of disease present for <2 weeks, macroscopic lesions proximal to the sigma (>40 cm *ab ano*), Crohn's disease, prior bowel operation, use of oral/rectal steroids within 1 month prior to baseline, use of immunosuppressants within 3 months prior to baseline, and long-term nonsteroidal antiinflammatory drug (NSAID) treatment. 5-ASA-containing or -releasing drugs had to be withdrawn at baseline at the latest. Rectal administration of any other medication was forbidden. All patients had to sign an informed consent form prior to entering the study.

Medication

Patients were randomized to receive either budesonide 2 mg foam (Budenofalk®; Dr. Falk Pharma GmbH, Freiburg, Germany) and placebo enema (group I), or budesonide 2 mg enema (Entocort®; Astra Zeneca, Wedel, Germany) and placebo foam (group II). Both groups were stratified for the sequence of study drug application, i.e. sequence E: enema in the morning, foam in the evening; sequence F: foam in the morning, enema in the evening.

Assessment

Patients were assessed at the beginning of the study and 2 and 4 weeks later. The baseline visit included case history, physical examination, blood tests, endoscopy (entire colon in case of a new diagnosis, sigmoidoscopy up to the uninflamed colon in cases of established diagnosis), calculation of the CAI,[15] calculation of the EI,[15] assessment of the histological index (HI),[16] calculation of the disease activity index (DAI) according to Sutherland *et al.*,[17] and microbiological stool examinations. The final visit or withdrawal examination included vital signs, blood tests, sigmoidoscopy, calculation of the CAI, calculation of the EI, calculation of the DAI, assessment of the HI, determination of physicians' global assessment, determination of the assessment of tolerability by investigator and patient, and recording of patient's acceptance of the study drugs.

Primary study endpoint was clinical remission defined by a CAI ≤ 4 at the final/withdrawal visit in the per protocol (PP) population. Secondary endpoints

were: change of the CAI, change of the number of stools per day, change of the number of bloody stools per day, clinical improvement based on the CAI, time to first clinical remission, change of the DAI, clinical remission and improvement based on the DAI, endoscopic remission and improvement, histological improvement, therapeutic success and benefit based on physician's global assessment, and patient's acceptance of the study drugs. Safety parameters were: adverse events, laboratory tests, serum cortisol and vital signs.

Statistics

The study was planned using a classical group sequential test design of the O'Brien/Fleming type,[18] with sample size adjustments after the planned interim analyses.[19, 20] For (one-sided) $\alpha = 0.025$, the critical values were given by 4.049, 2.863, 2.337 and 2.024 for the first, second, third and fourth analysis respectively. For specified α and assumed remission rates of 0.55 in both groups the power $(1-\beta)$ was approximately 80%, if the test stages consist of $n_1 = n_2 = n_3 = n_4 = 43$ patients per treatment group, resulting in a calculated sample size of approximately 344 patients. The primary goal of the study was to test the non-inferiority of budesonide foam vs. budesonide enema with a non-inferiority margin of 15% (one-sided $\alpha = 0.025$). For confirmatory hypothesis testing at the interim analyses as well as at the final analysis, the inverse normal method of combining the *P*-values of the shifted asymptotic chi-squared test for comparing two rates and maximum likelihood estimation for the unknown parameters was used (Farrington and Manning, method 3).[21] For estimating treatment effects, the differences between the remission rates and corresponding 97.5% one-sided repeated confidence intervals were provided. The result of the final group-sequential analysis was used for the confirmative proof of one-sided equivalence (non-inferiority) of budesonide foam compared with budesonide enema. The primary analysis of the primary study endpoint was defined to be the PP analysis.

RESULTS

Patients

A total of 541 patients were randomized – 535 could be evaluated for safety, 533 for the intention-to-treat (ITT) analysis, and 449 for the PP analysis (Figure 1).

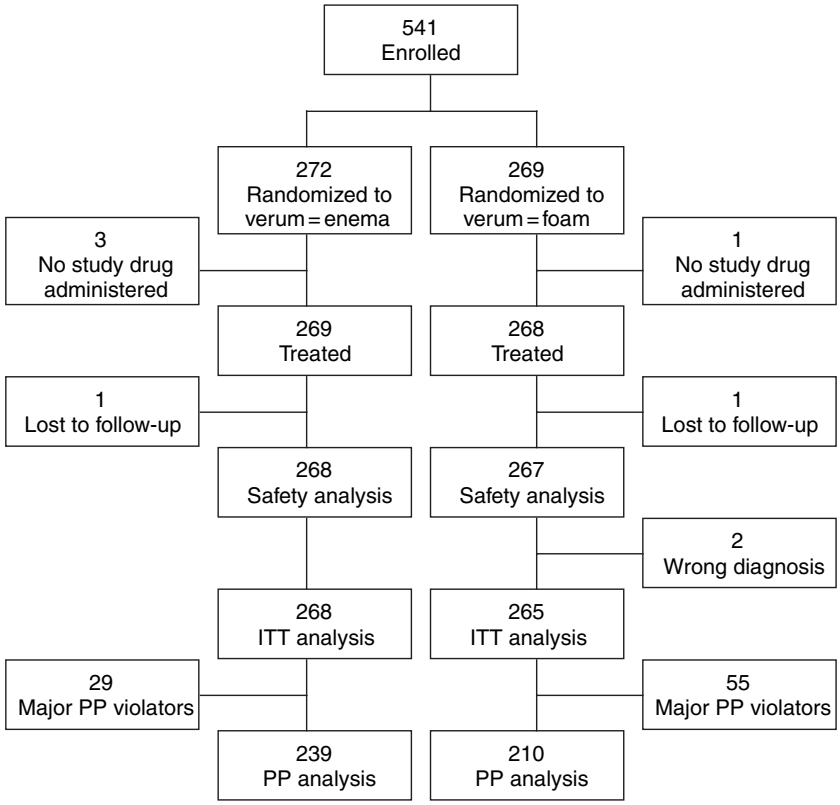

Figure 1. Disposition of patients.

The most frequent reasons for the exclusion from the PP analysis were premature discontinuation of the study ($n = 34$), inadequate compliance ($n = 29$), selection criteria violated ($n = 21$), not allowed concomitant medication ($n = 10$), no valid follow-up CAI ($n = 5$), non-adherence to the time windows ($n = 1$). Table 1 shows that the two treatment groups were well balanced for basic demographic data and disease history. There were no statistically significant differences between groups with regard to baseline CAI scores and location of inflammation.

Primary efficacy evaluation

The clinical remission rates based on the CAI in the PP analysis set were 60% for budesonide foam and 66% for budesonide enema (Figure 2). The primary analysis was defined to be the analysis adjusted for the randomized treatment sequence (PP analysis set). The *P*-value resulting from the four-stage group-sequential test procedure for this analysis was $P = 0.02362$ (one sided) (95% CI: −0.15 to 0.04). Thus, budesonide foam was proven to be not inferior to budesonide enema at the experiment-wise significance level of 0.025 using a non-inferiority margin of 15%. For the unstratified PP analysis (neglecting the treatment sequence) the *P*-value was 0.02123 (95% CI: −0.15 to 0.04). In the ITT analysis set, the remission rates were similar to the ones found in the PP analysis set; 57% for budesonide foam and 65% for budesonide enema, but showed confidence intervals that slightly exceeded the stringent non-inferiority margin: the stratified test that adjusted for the randomized treatment sequence resulted in the 95% CI of −0.17 to 0.003 ($P = 0.07340$), the unstratified test yielded a 95% CI of −0.16 to 0.005 ($P = 0.06691$).

Significant centre effects were not observed, however, there were considerable differences between the geographical clusters. In the PP analysis set, the remission rates in the Baltic states were 72% for budesonide enema and 54% for budesonide foam, whereas the rates in the other clusters (Germany and the Nether-

Table 1. Demographic data and disease history [intention-to-treat (ITT)]

	Budesonide foam ($n = 265$)	Budesonide enema ($n = 268$)	Total ($n = 533$)
Sex, *n* (%)			
Male	117 (44.2)	134 (50.0)	251 (47.1)
Female	148 (55.8)	134 (50.0)	282 (52.9)
Age (years), mean (s.d.)	44.4 (12.9)	43.1 (13.7)	43.8 (13.3)
Weight (kg), mean (s.d.)	71.7 (15.2)	71.2 (14.1) ($n = 267$)	71.5 (14.6) ($n = 532$)
Smoking habits, *n* (%)			
Nonsmoker	188 (70.9)	195 (72.8)	383 (71.9)
Ex-smoker	57 (21.5)	50 (18.7)	107 (20.1)
Smoker	20 (7.5)	23 (8.6)	43 (8.1)
Type of disease, *n* (%)			
New	55 (20.8)	69 (25.7)	124 (23.3)
Established	210 (79.2)	199 (74.3)	409 (76.7)
Course of disease, *n* (%)			
Unknown (initial)	54 (20.4)	69 (25.7)	123 (23.1)
Continuous	11 (4.2)	11 (4.1)	22 (4.1)
Recurrent	200 (75.5)	188 (70.1)	388 (72.8)
Duration of UC (years), median (range)	4.9 (0–39.8)	3.3 (0–36.4)	4.0 (0–39.8)
Time since first diagnosis (years), median (range)	3.5 (0–39.8)	2.3 (0–31.8)	2.6 (0–39.8)
Number of previous episodes, mean (s.d.)	5.6 (6.5) ($n = 205$)	4.9 (5.5) ($n = 194$)	5.3 (6.0) ($n = 399$)
Duration of present acute episode (weeks), median (range)	5.0 (0–837) ($n = 264$)	5.7 (0.3–688)	5.4 (0–837) ($n = 532$)
Length of inflammation (cm), mean (s.d.)	23.6 (10.4)	24.3 (10.7)	24.0 (10.5)
CAI, mean (s.d.)	7.6 (2.0)	7.5 (2.0)	7.5 (2.0)
DAI, mean (s.d.)	7.2 (1.8)	7.3 (2.0)	7.2 (1.9)
Endoscopic Index (EI), mean (s.d.)	7.7 (1.9)	7.7 (1.8)	7.7 (1.9)

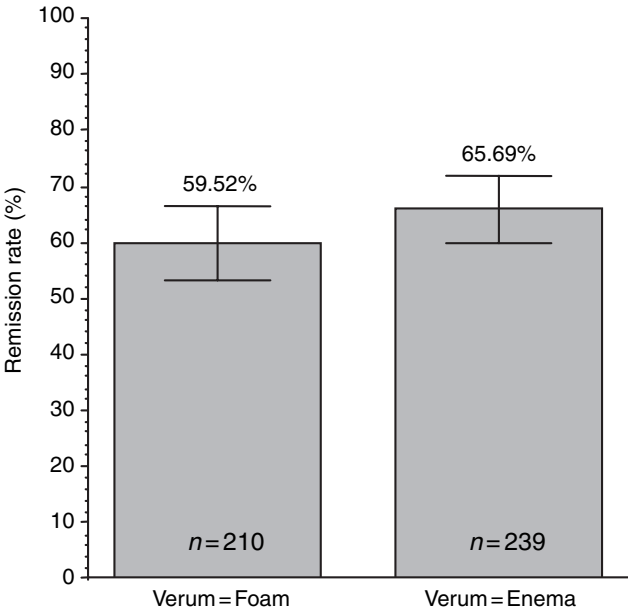

Figure 2. Primary endpoint: rates of clinical remission (CAI) in the per protocol (PP) analysis set.

lands, Hungary, Israel) were 61–64% for both treatment groups.

Influence of covariates on clinical remission

The influence of baseline covariates on the clinical remission rates was analysed descriptively in the ITT analysis set. The data are shown in Table 2. The baseline CAI had a clear influence on the remission rates ($P = 0.0003$; logit model): patients with a low CAI achieved clinical remission more frequently than patients with a high CAI. Localization of the disease did not show an obvious influence on the clinical outcome, indicating that both foam and enema are effective in patients with proctitis as well as in patients with proctosigmoiditis. Non-response to rectal 5-ASA or to oral 5-ASA had no adverse influence on the response to rectal budesonide.

Secondary efficacy evaluation

Most of the secondary efficacy parameters showed the same trend as the primary efficacy parameters (Table 3). The results based on the DAI agreed well with the results based on the CAI. The rates for endoscopic remission were 52% for budesonide foam and 54% for budesonide enema (PP). The rates for histological improvement were 51% for budesonide foam and 57% for budesonide enema (PP). The therapeutic success rates (physician's global assessment) were 58% for budesonide foam and 64% for budesonide enema, and the therapeutic benefit rates were 81% for budesonide foam and 85% for budesonide enema (PP).

Safety and tolerability

In total, 143 adverse events (AEs) occurred in 86 patients (32%) of the budesonide foam group and 133 AEs in 87 patients (33%) of the budesonide enema group. The most frequent AEs were headache, UC deteriorated, nausea and abdominal pain. All other AEs occurred in only a few patients. Almost all adverse events were of mild or moderate intensity. Sixty-three AEs (23% of all AEs) in 46 patients were considered to be certainly, probably/likely, or possibly drug-related, and nine AEs were unassessable/unclassifiable. Seven serious adverse events (SAEs) occurred in six patients {two patients in the budesonide foam group [UC aggravated, angina unstable], and four patients in the budesonide enema group [UC aggravated (2×), renal colic, pneumonia and cerebrovascular accident]}. None of the SAEs was related to study medication. No deaths occurred during the study. No global changes of any of the laboratory parameters occurred. Most abnormalities of laboratory parameters were rated as not clinically significant or related to the underlying disease. Low serum cortisol levels [i.e. <5.4 μg/dL (<150 nmol/L)] in samples taken between 07:00 and 09:00 hours were observed in two patients of the budesonide foam group and in three patients of the budesonide enema group. The change from baseline arithmetic mean in serum cortisol was 1.10 (95% CI: 0.03 to 2.2) for the budesonide foam group, and −0.06 (95% CI: −1.2 to 1.1) for the budesonide enema group. Thus, both study drugs were safe.

Each patient had to administer one enema and one puff of foam per day. Within patient, a significant advantage of the foam over the enema was found in the patient's rating of handling of the device ($P < 0.0001$; Bowker test) (Table 4).

Retention problems, unpleasant feeling, rectal/abdominal pain and flatulence occurred more often with enema than with foam (Table 4). In particular, only 11% of the patients had retention problems after the administration of foam, while 39% of the patients had retention problems with the enema. In addition, only 12% of the patients reported an unpleasant feel-

Table 2. Clinical remission rates (CAI) by baseline covariates [intention-to-treat (ITT)]

	Number (%) of patients in clinical remission (CAI) at visit 3 (LOCF)		Adjusted odds ratio* (95% confidence interval)
	Budesonide foam	Budesonide enema	
Baseline CAI			
≤8	118/199 (59)	137/193 (71)	1.4 (1.01 to 2)
>8	32/66 (49)	35/74 (47)	
Localization			
Proctitis	61/105 (58)	68/99 (69)	1.4 (0.99 to 2)
Proctosigmoiditis	89/160 (56)	105/169 (62)	
Duration of disease			
≤5 years	79/135 (59)	107/159 (67)	1.4 (0.97 to 2)
>5 years	71/130 (55)	66/109 (61)	
Smoking history			
Nonsmoker	101/188 (54)	126/195 (65)	1.4 (0.99 to 2)
Ex-smoker	37/57 (65)	32/50 (64)	
Smoker	12/20 (60)	15/23 (65)	
Extraintestinal manifestations			
absent	146/249 (59)	165/254 (65)	1.4 (0.98 to 2)
present	4/16 (25)	8/14 (57)	
Nonresponse to rectal 5-ASA (present episode)			
No	134/226 (59)	149/229 (65)	1.4 (0.99 to 2)
Yes	16/39 (41)	24/39 (62)	
Nonresponse to oral 5-ASA (present episode)			
No	117/198 (59)	148/218 (68)	1.4 (0.95 to 1.9)
Yes	33/67 (49)	25/50 (50)	

* Odds ratio for treatment groups enema versus foam, adjusted for covariate.
LOCF, last observation carried forwards.

ing during administration of the foam whereas 36% reported this about the enema. Moreover, only 10% of the patients reported to have rectal/abdominal pain during administration of the foam versus 18% of the patients reported such pain during enema administration. Similar numbers were also reported for flatulence during/after the administration of the drug.

The overall preference of the study drug was recorded at the final visit. Altogether 84% of the patients preferred the foam while the enema was only preferred by 6% of the patients and 10% had no preference (Figure 3). When patients with no preference were omitted from the analysis the proportion of those who preferred foam over enema was 93% (95% CI: 91–95%). The *P*-value of the binomial test was <0.0001.

DISCUSSION

This is the first randomized controlled trial that directly compares budesonide foam and budesonide enema in patients with active distal UC. Our results demonstrate that both budesonide formulations are similarly effective and that around 60% of the patients achieve clinical remission with either of the two budesonide formulations. Because of the non-inferiority margin of 15%, 541 patients had to be enrolled. Thus, the reported trial is the thus far biggest trial on the rectal treatment of distal UC.

The study shows that among the covariates only baseline disease activity had a statistically significant effect on the response to rectal budesonide. Patients with a CAI of >8 achieved clinical remission significantly less frequently than those with a CAI ≤ 8. All other covariates analysed showed no statistically significant effect on remission rates. Patients who had previously failed to oral or rectal 5-ASA showed a tendency towards a lower remission rate than those who previously responded to oral or rectal 5-ASA. Nevertheless, remission was obtained with budesonide foam in 49% and 41% and with budesonide enema in 50% and 62% of the non-responders to oral or rectal 5-ASA respectively. These results show that rectal

Table 3. Secondary efficacy evaluation [per protocol (PP)]

	Treatment group		
	Budesonide foam	Budesonide enema	Difference between changes* (95% CI)
Change of CAI, mean	−3.9	−4.1	−0.17 (−0.8 to 0.46)
Change of number of stools per week, mean	−12.7	−13.3	−0.56 (−3.8 to 2.7)
Change of number of bloody stools per week, mean	−14.1	−14.4	−0.29 (−3.7 to 3.1)
Change of DAI, mean	−3.6	−4.0	−0.42 (−0.94 to 0.10)
Time to first clinical remission,† median (95% CI)	9 (7 to 12)	7 (5 to 10)	Hazard ratio 1.1 (0.94 to 1.4)
Clinical improvement rates (CAI), n/N_t (%)	177/210 (84)	205/239 (86)	Difference between proportions* (95% CI) −0.02 (−0.08 to 0.05)
Clinical remission rates (DAI), n/N_t (%)	116/204 (57)	149/234 (64)	−0.07 (−0.16 to 0.02)
Clinical improvement rates (DAI), n/N_t (%)	170/204 (83)	205/233 (88)	−0.05 (−0.11 to 0.02)
Endoscopic remission rates, n/N_t (%)	106/204 (52)	127/234 (54)	−0.02 (−0.12 to 0.07)
Endoscopic improvement rates, n/N_t (%)	151/204 (74)	188/234 (80)	−0.06 (−0.14 to 0.02)
Histological improvement rates, n/N_t (%)	103/202 (51)	130/230 (57)	−0.06 (−0.15 to 0.04)
Therapeutic success rates (PGA), n/N_t (%)	121/210 (58)	152/239 (64)	−0.06 (−0.15 to 0.03)
Therapeutic benefit rates (PGA), n/N_t (%)	170/210 (81)	202/239 (85)	−0.04 (−0.11 to 0.04)

N_t: group total; 95% CI: confidence interval.
* Budesonide foam–budesonide enema.
† Defined as the first day with three or less stools, all without blood.

budesonide is a good treatment option for non-responders to oral or rectal 5-ASA.

The therapeutic equivalence of budesonide foam and budesonide enema as shown in the primary analysis is also supported by the results of the secondary analyses. The mean change of the CAI was nearly identical between foam and enema (−3.9 vs. −4.1) as well as the reduction in the number of bloody stools per week, which is a predominant symptom of distal UC (−14.1 vs. −14.4). Noteworthy is the high rates of endoscopic remissions (52% for budesonide foam, 54% for budesonide enema) and histological improvements (51% for budesonide foam, 57% for budesonide enema) achieved in both study groups. These findings demonstrate the therapeutic efficacy of both rectal budesonide preparations.

The results of the present multicentre study are in good agreement with the results of previous studies using budesonide foam.[12–14] In the study of Bar-Meir *et al.*,[14] budesonide foam was tested in a similar patient population as in the present study. Bar-Meir *et al.* reported a remission rate of 55% based on the DAI.[17] In the present study, the remission rate based on the DAI was 57%. This shows a very good reproducibility of the therapeutic efficacy of budesonide foam in different studies.

A comparison of the results of the present study and published meta-analyses suggests that rectal budesonide is similarly effective as rectal 5-ASA.[22] A clinical remission rate of 60% as found for budesonide foam in this trial compares favourably with the pooled symptomatic remission rates of 53% for rectal 5-ASA. The same is true for the endoscopic improvement rates (budesonide foam: 74%, 5-ASA: 73%). Moreover, the remission and improvement rates observed for budesonide foam in the present study are much higher than those observed for placebo in the meta-analysis (symptomatic remission and improvement rates with placebo: 9% and 34%, respectively; endoscopic remission and improvement rates with placebo: 17% and 38% respectively).[22]

In terms of tolerability and patient's preference, foam showed a clear advantage over enema. The majority of the patients (84%) preferred the foam while only 6% preferred the enema. The small volume of the foam might lead to less problems with retention, less rectal pain, and fewer flatulence after administration of the medication. In a recent study

Table 4. Application problems [intention-to-treat (ITT)]

	% of patients	
	Foam ($n = 483$)	Enema ($n = 483$)
Handling of device		
Easy	89	29
Not too difficult	9	52
Difficult	2	19
Retention problems		
None	89.0	61.1
Slight	9.1	25.1
Moderate	1.2	10.1
Considerable	0.6	2.9
Severe		0.8
Unpleasant feeling		
None	87.6	63.8
Slight	11.2	26.5
Moderate	0.6	6.6
Considerable	0.4	2.5
Severe	0.2	0.6
Rectal/abdominal pain		
None	90.1	82.0
Slight	7.9	12.2
Moderate	1.4	4.3
Considerable	0.6	1.4
Flatulence		
None	90.1	79.7
Slight	7.7	14.1
Moderate	1.7	3.9
Considerable	0.4	1.4
Severe	0.2	0.8

comparing a new mesalazine foam (Claversal® foam, Merckle, Blaubeuren, Germany) with a standard liquid enema in patients with active distal UC,[23] patients applying the foam had a higher number of adverse events with a possible or probable relationship to the study medication than in the enema group. Gastrointestinal symptoms were the most prominent (mainly flatulence), and the authors attributed this probably to an incorrect application of the foam by some patients.

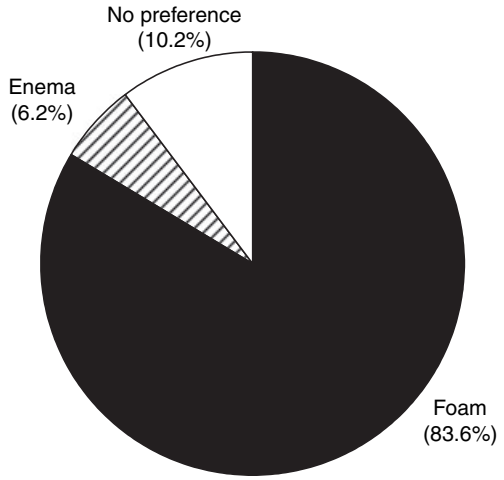

Figure 3. Patients' overall preference.

The different rating of different rectal foams might indicate, that the individual characteristics of each foam application device as well as volume and pressure of the foam might influence tolerability results.

In conclusion, the present study showed that budesonide foam and budesonide enema show a good efficacy in patients with active distal UC. Budesonide foam was proven to be equally effective as budesonide enema. The budesonide foam was well tolerated and the vast majority of the patients preferred the administration of a rectal foam when compared with a rectal enema.

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REFERENCES

1 Danielsson A, Hellers G, Lyrenäs E, *et al.* A controlled randomised trial of budesonide versus prednisolone retention enemas in active distal ulcerative colitis. *Scand J Gastroenterol* 1987; **22**: 987–92.

2 Matzen P, for The Danish Budesonide Study Group. Budesonide enema in distal ulcerative colitis. A randomised dose-response trial with prednisolone enema as positive control. *Scand J Gastroenterol* 1991; **26**: 1225–30.

3 Danielsson A, Löfberg R, Persson T, *et al.* A steroid enema, budesonide, lacking systemic effects for the treatment of distal ulcerative colitis or proctitis. *Scand J Gastroenterol* 1992; **27**: 9–12.

4 Bianchi Porro G, Prantera C, Campieri M, *et al.* Comparative trial of methylprednisolone and budesonide enemas in

active distal ulcerative colitis. *Eur J Gastroenterol Hepatol* 1994; **6**: 125–30.
5 Tarpila S, Turunen U, Seppälä K, *et al*. Budesonide enema in active haemorrhagic proctitis – a controlled trial against hydrocortisone foam enema. *Aliment Pharmacol Ther* 1994; **8**: 591–5.
6 Löfberg R, Ostergaard Thomsen O, Langholz E, *et al*. Budesonide versus prednisolone retention enemas in active distal ulcerative colitis. *Aliment Pharmacol Ther* 1994; **8**: 623–9.
7 Lémann M, Galian A, Rutgeerts P, *et al*. Comparison of budesonide and 5-aminosalicylic acid enemas in active distal ulcerative colitis. *Aliment Pharmacol Ther* 1995; **9**: 557–62.
8 Bayless T, Sninsky C, for the US Budesonide Enema Study Group. Budesonide enema is an effective alternative to hydrocortisone enema in active distal ulcerative colitis. *Gastroenterology* 1995; **108**: A778.
9 Lindgren S, Suhr O, Persson T, Pantzar N. Treatment of active distal ulcerative colitis (UC) and maintenance of remission with Entocort® enema: a randomised controlled dosage study. *Gut* 1997; **41** (Suppl 3): A223.
10 Hanauer SB, Robinson M, Pruitt R, *et al*. Budesonide enema for the treatment of active, distal ulcerative colitis and proctitis: a dose-ranging study. *Gastroenterology* 1998; **115**: 525–32.
11 Ejderhamn J, Browaldh L, Oldaeus G, Saalman R, Stenhammer L. Treatment with glucocorticosteroid enemas in children with ulcerative colitis; a randomised single-blind multicenter comparison between budesonide and prednisolone. *Gut* 1999; **45** (Suppl V): A170.
12 Rufle W, Frühmorgen P, Huber W, Kimmig JM. Budesonid-Schaum als neues Therapieprinzip bei der distalen Colitis ulcerosa im Vergleich mit Mesalazin-Klysmen. Eine offene, kontrollierte, randomisierte und prospektive multizentrische Pilotstudie. *Z Gastroenerol* 2000; **38**: 287–93.
13 Schlottmann K, Bregenzer N, Caesar I, Bretzke G, Elsel W, Ecker K-W and the German Budesonide Study Group. Open randomized, multicenter trial comparing safety and efficacy of budesonide foam with betamethasone enema in patients with active distal ulcerative colitis. *Gastroenterology* 1998; **114**: A1078.
14 Bar-Meir S, Fidder HH, Faszczyk M, *et al*., The International Budesonide Study Group. Budesonide foam vs. hydrocortisone acetate foam in the treatment of active ulcerative proctosigmoiditis. *Dis Col Rect* 2003; **46**: 929–36.
15 Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomized trial. *Br Med J* 1989; **289**: 82–6.
16 Riley SA, Mani V, Goodman MJ, Dutt S, Herd ME. Microscopic activity in ulcerative colitis: what does it mean? *Gut* 1991; **32**: 174–8.
17 Sutherland LR, Martin F, Greer S, *et al*. 5-Aminosalicylic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis, and proctitis. *Gastroenterology* 1987; **92**: 1894–8.
18 O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979; **35**: 549–56.
19 Lehmacher W, Wassmer G. Adaptive sample size calculations in group sequential trials. *Biometrics* 1999; **55**: 1286–90.
20 Wassmer G. *Statistische Testverfahren für gruppensequentielle und adaptive Pläne in klinischen Studien. Theoretische Konzepte und deren praktische Umsetzung mit SAS*. Köln: Verlag Alexander Mönch, 1999.
21 Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. *Statistics in Medicine* 1990; **9**: 1447–54.
22 Marshall JK, Irvine EJ. Rectal corticosteroids versus alternative treatments in ulcerative colitis: a meta-analysis. *Gut* 1997; **40**: 775–81.
23 Malchow H, Gertz B, the Clafoam Study Group. A new mesalazine foam enema (Claversal Foam) compared with a standard liquid enema in patients with active distal ulcerative colitis. *Aliment Pharmacol Ther* 2002; **16**: 415–23.

APPENDIX

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