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Randomised clinical trial: a comparative dose-finding study of three arms of dual release mesalazine for maintaining remission in ulcerative colitis

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[1]Members of the International Salofalk OD Study Group are listed in the Appendix.

SUMMARY

Background
Comparative data regarding different regimens of oral mesalazine (mesalamine) for maintaining remission in ulcerative colitis are limited.

Aim
To evaluate whether 3.0 g mesalazine once-daily (OD) is superior to the standard treatment of 0.5 g mesalazine three times daily (t.d.s.) and to prove the therapeutic equivalence of OD vs. t.d.s. dosing of total 1.5 g mesalazine for remission maintenance in patients with ulcerative colitis.

Methods
A 1-year, multicentre, double-blind, double-dummy study was undertaken in patients with endoscopically and histologically confirmed ulcerative colitis in remission. Patients were randomised to oral mesalazine 3.0 g OD, 1.5 g OD or 0.5 g t.d.s. The primary efficacy endpoint was the proportion of patients still in clinical remission at the final visit, with clinical relapse being defined as CAI score >4 and an increase of ≥3 from baseline.

Results
The primary efficacy endpoint occurred in 162/217 3.0 g OD patients (75%), 129/212 1.5 g OD patients (61%) and 150/218 0.5 g t.d.s. patients (69%) in the intention-to-treat population, and in 152/177 (86%), 121/182 (67%) and 144/185 (78%) in the per protocol population respectively; 3.0 g OD was superior to both low-dose regimens for the primary endpoint (i.e. $P < 0.001$, 3.0 g OD vs. 1.5 g OD; $P = 0.024$, 3.0 g OD vs. 0.5 g t.d.s.; superiority test, per protocol population). Safety analysis, including comprehensive renal monitoring, revealed no concern in any treatment group.

Conclusion
Mesalazine 3.0 g once daily was the most effective dose for maintenance of remission in ulcerative colitis of the three regimens assessed, with no penalty in terms of safety.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic disorder of the colon characterised by periods of active disease followed by asymptomatic periods (remission). Maintaining remission by prevention of relapses is a well-established objective for chronic medical management of UC, with the aminosalicylates [sulphasalazine, mesalazine (mesalamine), olsalazine and balsalazide] being widely regarded as the gold standard for maintenance therapy. Mesalazine, a newer aminosalicylate, is superior to placebo for maintenance therapy,[1] and because of a better safety profile, has largely superseded sulphasalazine to become the most commonly prescribed aminosalicylate. Nevertheless, a number of questions regarding the optimal use of mesalazine for maintenance of remission remain unresolved.

Data are mixed regarding a possible efficacy benefit of increased daily dosage,[2–4] and recent reviews have concluded that there may be no clear dose-response relationship or any incremental benefit of doses above 1.5 g/day for maintenance of UC remission.[5, 6] Studies of compliance with delayed-release mesalazine in inflammatory bowel diseases revealed three-times daily (t.d.s.) dosing to be an independent predictor of noncompliance.[7] Multiple daily dosing may thus limit the rate of sustained remission with mesalazine in patients with UC.[8]

Several formulations of mesalazine are available. Salofalk granules (Dr Falk Pharma GmbH, Freiburg, Germany) differ from other mesalazine formulations by combining both delayed- and extended-release mechanisms. First, mesalazine release is delayed until pH ≥6.0 due to an enteric, acid-resistant film coating, such that absorption in the upper gastrointestinal tract is prevented. Second, because of inner polymer matrix the mesalazine release is prolonged throughout the entire colon.[9]

We report here the results of a one-year, multicentre, randomised, double-blind, double-dummy study in which we evaluated the efficacy and safety of mesalazine (Salofalk granules) using three different dosing regimens (3.0 g OD, 1.5 g OD or 0.5 g t.d.s.) for maintenance of remission in UC patients.

METHODS

Protocol

This was a 1-year, randomised, double-blind, double-dummy, parallel-group, multicentre, phase III study conducted at 65 gastroenterology centres in 13 countries (see Appendix). The study started in May 2005 and completed in April 2007. The study was performed in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki and was approved in each participating country by a central Independent Ethics Committee and/or local Independent Ethics Committees. Written informed consent was obtained from each patient. The study was registered at ClinicalTrials.gov (NCT00746447).

Participants

Male and female patients aged between 18 and 75 years were eligible to take part in the study if (i) they had an endoscopically and histologically confirmed diagnosis of UC with mucosal inflammation extending at least 15 cm beyond the anal margin during the last active episode, (ii) the last active episode had ended within the 3 months prior to study entry and (iii) they were in remission as defined by Clinical Activity Index (CAI) ≤4,[10] and Endoscopical Index (EI) ≤3.[10] Patients with Crohn's disease, toxic megacolon, impaired renal function, serious comorbidity, use of immunosuppressants within 3 months prior to study entry or use of glucocorticosteroids within 1 month prior to study entry were excluded.

Assignment

Randomisation was performed centrally in blocks of three by means of a computer-generated randomisation list. The randomisation list was sealed and held by biostatistical staff of ClinResearch GmbH who were not involved in the study conduct.

Masking

Mesalazine 3.0 g OD was administered as two sachets each containing 1.5 g mesalazine in the morning and one sachet containing 0.5 g placebo at noon and in the evening; 1.5 g OD was administered as two sachets each containing 0.75 g mesalazine and 0.75 g placebo in the morning and one sachet containing 0.5 g placebo at noon and in the evening; and 0.5 g t.d.s. was administered as two sachets each containing 0.25 g mesalazine and 1.25 g placebo in the morning and one sachet containing 0.5 g mesalazine both at noon and in the evening.

Concomitant medication

The following medications were not allowed during the study: steroids, antibiotics, immunosuppressants, non-steroidal anti-inflammatory drugs, other aminosalicylate

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treatments, loperamide, psyllium-containing drugs or *de novo* treatment with probiotics.

Study objective and endpoints

The objective was to evaluate whether 3.0 g mesalazine OD is superior to the standard treatment of 0.5 g mesalazine t.d.s. and to prove the therapeutic equivalence of OD vs. t.d.s. dosing of total 1.5 g mesalazine for remission maintenance in patients with UC. The primary efficacy endpoint was the proportion of patients still in clinical remission at the final visit, with clinical relapse being defined as CAI score >4 and an increase of ≥3 from baseline. Secondary efficacy endpoints included the proportion of patients in clinical remission at month 12 among the subpopulation with signs of mucosal inflammation at baseline endoscopy, i.e. patients with an EI score >1 at baseline (EI ≤1 represents 'normal mucosa or at maximum faded/disturbed vascular pattern; no friability'), endoscopic remission at month 12 based on the EI, and the change from baseline to month 12 in the number of stools and the number of bloody stools per week. Safety endpoints included the occurrence of adverse events and altered laboratory parameters with a focus on renal monitoring. In addition, trough levels of mesalazine and N-acetyl-mesalazine in plasma were monitored in a subgroup of patients. At the end of the treatment period, patients were asked if they preferred OD or t.d.s. dosing, although all patients were required to follow t.d.s. dosing because of the double-dummy study design.

Evaluation

Study visits took place on day 0 (baseline) and at weeks 4, 12, 24, 36 and 52 (final visit). If patients discontinued the study prematurely, a full final visit was performed if possible. Patients were given a paper diary containing eight items to be completed throughout the study. Clinical signs of UC (e.g. number of stools per day and number of bloody stools per day) and safety and tolerability were assessed at each visit. Endoscopy was performed at the baseline and final visits.

Plasma concentrations of mesalazine and N-acetyl-mesalazine were measured by validated liquid chromatography tandem mass spectrometry.[11] Lower limits of quantification were 10 ng/mL in plasma for both analyses. The within-day and between-day coefficients of variation were below 10%; accuracy of the assay in plasma was in the range 98–105%.

Compliance with study medication was recorded by checking the study medication returned at each study visit and by monitoring the patient diaries. Patients were considered to be compliant if the ratio of the number of administered sachets to the scheduled number of sachets was >75%.

Analysis

The sample size calculation was based on a non-inferiority comparison of the 1.5 g OD group vs. the 0.5 g t.d.s. group. For one-sided $\alpha = 0.025$ with a non-inferiority margin of 15% and assuming that the absolute and assumed proportion of patients with clinical remission at the final visit would be 60% in both groups, a population of 166 patients per group in the per protocol (PP) population was estimated to have 80% power to detect non-inferiority. Assuming that 17% of patients in the intention-to-treat (ITT) population would be excluded from the PP population (the primary analysis population), the planned sample size was 200 patients per treatment group. This sample size also provided 83% power to detect superiority for 3.0 g OD vs. any of the lower dose groups.

Confirmatory testing was performed for the primary efficacy endpoint comparison of the 1.5 g OD and 0.5 g t.d.s. groups, using the asymptotic Chi-squared test. All other comparisons were exploratory. The primary analysis was performed on the PP population and repeated for the ITT population. In addition, superiority of mesalazine 3.0 g OD vs. 0.5 g t.d.s. and 1.5 g OD, respectively, was assessed on the primary efficacy endpoint of clinical remission at the final visit in the ITT population and repeated for the PP population.

For the primary efficacy endpoint, patients who discontinued the study prematurely were calculated as non-responders. For secondary efficacy variables the last observation carried forward (LOCF) approach was used.

The ITT and safety population comprised all randomised patients who received at least one dose of study medication. The PP population was defined as a subset of ITT excluding all patients with major protocol violations as well as patients who were noncompliant with the study medication.

Quantitative variables are described using mean ± standard deviation (s.d.) and/or median (range) as appropriate. Qualitative variables are described by frequency. Where appropriate, 95% confidence intervals (CIs) are provided for differences between treatment groups for secondary efficacy variables. For comparison of baseline and end of treatment values of renal and pharmacokinetic parameters, a two-sided Wilcoxon sign rank test for one sample was used. Kruskal–Wallis test

was used for comparing pharmacokinetic parameters between the three different treatment groups. The level of significance was set at $P < 0.05$.

Biometric analyses were undertaken using the SAS statistical software package (version 9.1.3, SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient disposition

In total, 648 patients were randomised (3.0 g OD: 218; 1.5 g OD t.d.s.: 212; 0.5 g t.d.s.: 218). Thereof, 204 patients (94%), 207 patients (98%) and 211 patients (97%) of the 3.0 g OD group, the 1.5 g OD group and the 0.5 g t.d.s. group, respectively, were compliant. One patient, randomised to the 3.0 g OD group, did not receive any study medication and was excluded from all analyses. Thus, the ITT and safety populations comprised 647 patients, of whom 496 (77%) completed the study (Figure 1). One hundred and four patients were excluded from the PP population, which consisted of 544 patients. The most frequent protocol deviations that led to exclusion from the PP population were intake of study medication for less than 4 weeks ($n = 27$), last acute episode of UC not ending within 3 months prior to study entry ($n = 14$), CAI not ≤4 at study entry ($n = 13$) and >21 days without study medication before the final or withdrawal examination ($n = 12$). The reasons for exclusion from the PP population did not differ significantly between treatment groups. The number of patients completing the study in each group are shown in Figure 1. History of the patients of the three groups showed some slight differences, demonstrating long-standing disease (>5 years) and a shorter interval of remission prior to entry to the study to occur more often in the 1.5 g OD group. Altogether, the three treatment groups showed no significant differences for demographic and anamnestic characteristics at baseline and previous treatment (Table 1).

Treatment compliance

Treatment compliance (i.e. ratio of administered sachets to scheduled sachets >75%) was reported in 204 patients (94%), 207 patients (98%) and 211 patients (97%) of the 3.0 g OD group, the 1.5 g OD group and the 0.5 g t.d.s. group, respectively.

Efficacy

The primary efficacy endpoint, clinical remission at the final visit, occurred in 162/217 3.0 g OD patients (75%), 129/212 1.5 g OD patients (61%) and 150/218 0.5 g t.d.s. patients (69%) (ITT population). Similar results were observed in the PP population, with clinical remission in 152/177 patients (86%), 121/182 patients (67%) and 144/185 patients (78%), respectively. In both analysis sets, 3.0 g OD achieved the highest remission rates. Superiority testing showed a significantly higher rate of the primary efficacy endpoint in the 3.0 g OD group vs. the 1.5 g OD group in both the ITT population and the PP population. The 3.0 g OD regimen was also superior

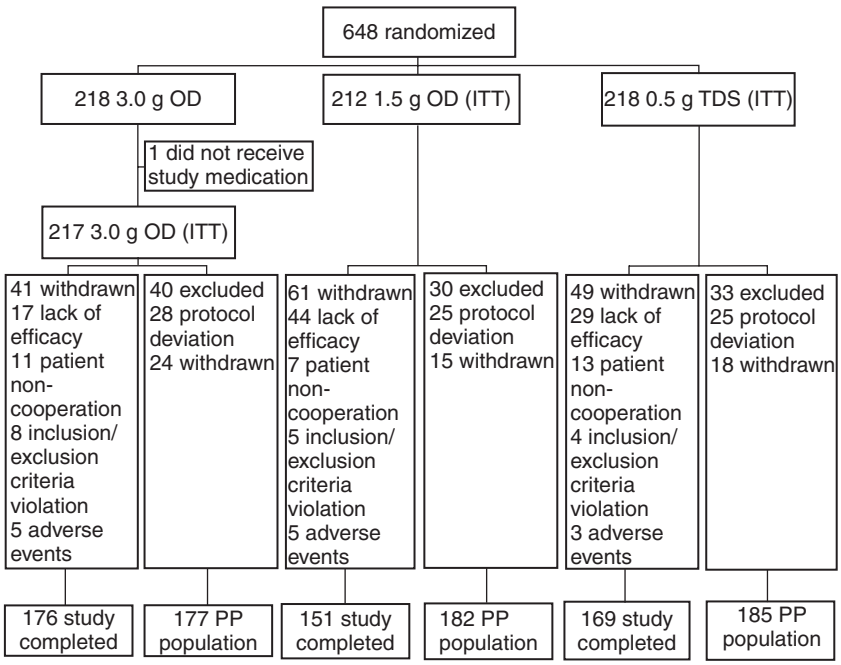

Figure 1 | Patient disposition. ITT, intention-to-treat; PP, per protocol.

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Table 1 | Demographics and anamnestic characteristics at baseline (ITT population)

	3.0 g OD (*N* = 217)	1.5 g OD (*N* = 212)	0.5 g t.d.s. (*N* = 218)
Male gender, *n* (%)	107 (49)	104 (49)	108 (50)
Age (years), mean ± s.d.	45.2 ± 14.0	45.5 ± 14.2	43.6 ± 14.0
Body mass index (kg/m^2), mean ± s.d.	25.2 ± 3.9	25.2 ± 4.2	25.2 ± 4.0
Caucasian, *n* (%)	217 (100)	210 (99)	218 (100)
Smoker, *n* (%)	23 (11)	12 (6)	19 (9)
Disease duration (years), median (range)	3.6 (0.1–43.8)	4.2 (0.2–36.6)	3.9 (0.2–42.4)
Disease duration ≥5 years, *n* (%)	87 (40)	100 (47)	90 (41)
Daily stool frequency, mean ± s.d.	1.6 ± 0.9	1.5 ± 0.7	1.6 ± 1.0
Number of previous episodes, mean ± s.d.			
Total	4.7 ± 5.5 (*n* = 216)	5.2 ± 5.4 (*n* = 211)	5.1 ± 7.5 (*n* = 215)
Last year	1.3 ± 0.7 (*n* = 210)	1.3 ± 0.7 (*n* = 206)	1.3 ± 0.6 (*n* = 215)
Duration of last acute episode (days), mean [95% CI]	96 [74; 117]	80 [71; 89]	113 [78; 147]
Time from start of current remission phase until day 0 (days), mean [95% CI]	57 [37; 78]	43 [35; 51]	67 [36; 97]
Last acute treatment, *n* (%)*			
Oral mesalazine	161 (74)	164 (77)	171 (78)
Rectal mesalazine	58 (27)	61 (29)	49 (23)
Oral sulphasalazine	42 (19)	45 (21)	40 (18)
Oral steroids	19 (9)	13 (6)	22 (10)
Rectal steroids	5 (2)	6 (3)	7 (3)
Intravenous steroids	–	1 (1)	2 (1)
Oral budesonide	1 (1)	1 (1)	5 (2)
Rectal budesonide	1 (1)	2 (1)	1 (1)
Immunosuppressants	1 (1)	–	–
Clinical Activity Index (CAI), mean ± s.d.	1.2 ± 1.5	1.2 ± 1.5	1.2 ± 1.4
Endoscopical Index (EI), mean ± s.d.	1.6 ± 1.2	1.7 ± 1.2	1.6 ± 1.1
EI, *n* (%)			
EI ≤1†	119 (55)	109 (51)	120 (55)
EI >1	98 (45)	103 (49)	98 (45)

* Multiple entries per patient were possible.

† EI ≤1 represents normal mucosa or at maximum faded/disturbed vascular pattern; no friability.

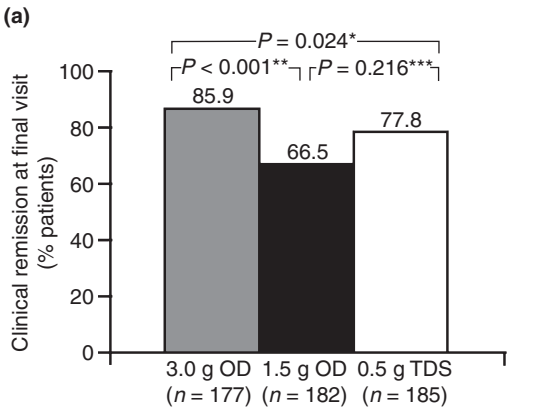

Figure 2 | Primary efficacy endpoint (proportion of patients in clinical remission at final visit, with relapse defined as CAI >4 and ≥3 increase from baseline) according to treatment group for (a) intention-to-treat (ITT) population, *superiority test, 95% CI for difference [−0.026; 0.143]; **superiority test, 95% CI for difference [0.050; 0.225]; ***non-inferiority test, 95% CI for difference [−0.169; 0.011]; and (b) per protocol [PP] population, *superiority test, 95% CI for difference [0.001; 0.160]; **superiority test, 95% CI for difference [0.107; 0.279]; ***non-inferiority test, 95% CI for difference [−0.204, −0.022].

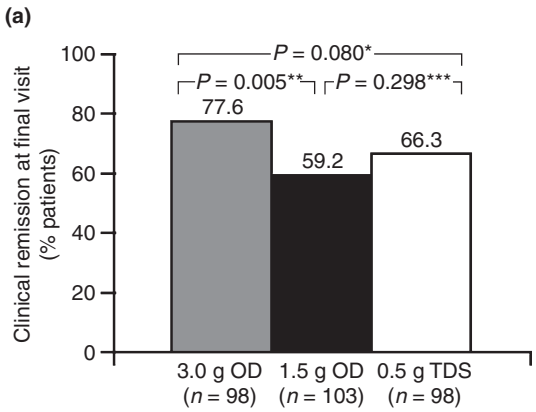

Figure 3 | *Post hoc* analysis of the primary efficacy endpoint (proportion of patients in clinical remission at final visit, with relapse defined as CAI >4 and ≥3 increase from baseline) according to treatment group in the subpopulation of patients with (a) signs of mucosal inflammation (EI >1) at baseline [intention-to-treat (ITT) population] *superiority test, 95% CI for difference [−0.013; 0.237]; **superiority test, 95% CI for difference [0.057; 0.309]; *** superiority test, 95% CI for difference [−0.204; 0.062] and (b) no signs of mucosal inflammation (EI ≤1, i.e. deep endoscopic remission) at baseline (ITT) *superiority test, 95% CI for difference [−0.100; 0.129]; **superiority test, 95% CI for difference [−0.023; 0.220]; ***superiority test, 95% CI for difference [−0.206; 0.038].

to the 0.5 g t.d.s. group in the PP population, and slightly exceeded the significance in the ITT population. Non-inferiority of 1.5 g OD vs. 0.5 g t.d.s. was not achieved at the predefined 15% non-inferiority margin. Similar results were observed in the ITT population. For details see Figure 2.

When the primary efficacy endpoint was analysed *post hoc* in the subpopulation of patients with signs of mucosal inflammation at baseline endoscopy, i.e. having an EI score of >1 at baseline, mesalazine 1.5 g OD was found to be statistically not different to 0.5 g t.d.s.; 3.0 g OD was superior to both low-dose treatment groups (Figure 3a). Interestingly, 3.0 g OD did not gave an additional clinical benefit in patients being in deep endoscopic remission (i.e. EI ≤1) at baseline (Figure 3b), suggesting that a low-dose treatment with mesalazine is sufficient in these patients.

Approximately 70% of patients were still in endoscopic remission (EI ≤3) at 12 months (LOCF method), with no significant differences between treatment groups (Figure 4). Consistent with this, equal proportions of patients were in deep endoscopic remission (EI ≤1) at 12 months (LOCF method), with no significant differences between treatment groups [3.0 g OD group:

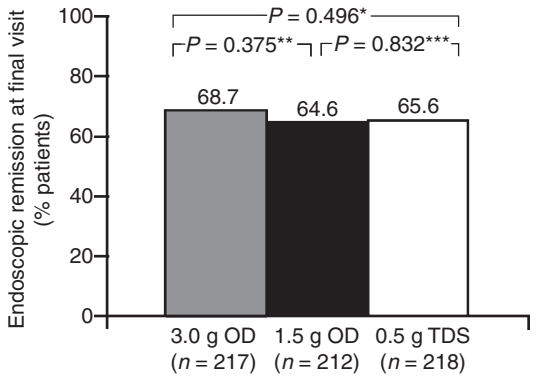

Figure 4 | Endoscopic remission (EI ≤3) at final visit (LOCF method) according to treatment group. *superiority test, 95% CI for difference [−0.058; 0.119]; **superiority test, 95% CI for difference [−0.049; 0.130]; ***superiority test, 95% CI for difference [−0.100; 0.080].

115/217 (53%), 1.5 g OD group: 108/212 (51%), 0.5 g t.d.s. group: 115/218 (53%)].

The 3.0 g OD cohort showed the smallest increase in the number of stools per week [mean ± s.d.: 3.0 g OD 1.1 ± 9.8, 1.5 OD 4.4 ± 14.6 (P = 0.005 vs. 3.0 g OD), 0.5 g t.d.s. 2.2 ± 12.9 (P = NS)] and the smallest increase in the number of bloody stools per week [mean ± s.d.: 3.0 g OD 1.7 ± 6.9, 1.5 g OD 5.8 ± 13.1 (P < 0.001 vs. 3.0 g OD), 0.5 g t.d.s. 3.7 ± 12.7 (P = 0.043 vs. 3.0 g OD)].

The majority of all patients (519/647, 80%) clearly favoured an OD schedule, whereas only 22/647 patients (3%) preferred a t.d.s. schedule; 86/647 patients (13%) had no preference and 20/647 patients (3%) did not comment. There were no differences seen between the treatment groups.

Safety and tolerability

In total, 146 adverse events (AEs) occurred in 89 patients (41%) in the 3.0 g OD group, 154 AEs in 117 patients (55%) in the 1.5 g OD group and 156 AEs in 105 patients (48%) in the 0.5 g t.d.s. group. The most frequent types of AEs were gastrointestinal disorders, including deterioration of UC. Serious AEs were reported in eight patients (4%) in the 3.0 g OD group, seven patients (3%) in the 1.5 g OD group and six patients (3%) in the 0.5 g t.d.s. group, none of which was assessed as related to study medication. Cystatin C, the most sensitive parameter to detect early impairment of renal function,[12] increased above normal in one patient each in the 1.5 g OD and 0.5 g t.d.s. groups, but in no patient in the 3.0 g OD group. Results of renal monitoring are summarised in Table 2.

Monitoring of trough concentrations of mesalazine and its main metabolite, N-acetyl-mesalazine, did not suggest any systemic drug accumulation over the 1 year treatment (see Table 3). None of the statistical comparisons of trough levels within or between treatment groups showed a significant difference.

DISCUSSION

This three-arm study with novel dual release mesalazine is the first trial to evaluate a high-dose OD vs. a low-dose OD and vs. a standard low-dose t.d.s. regimen of oral mesalazine for the prevention of clinical relapse in UC patients in remission using a randomised, double-blind and double-dummy design. An excellent rate of clinical remission maintenance was achieved in the 3.0 g OD group (75%) using Salofalk granules. However, the study failed to demonstrate non-inferiority for 1.5 g OD mesalazine compared with a standard 0.5 g t.d.s. regimen in terms of maintaining remission. We recognise that it

Table 2 | Renal parameters at baseline and final visit (mean ± s.d.)

	Normal range	3.0 g OD (n = 216)		1.5 g OD (n = 211)		0.5 g t.d.s. (n = 217)	
		Baseline	Final visit	Baseline	Final visit	Baseline	Final visit
Creatinine clearance (mL/min/1.73 m^2)	>90	104 ± 29	107 ± 28**	100 ± 25	102 ± 26*	105 ± 27	107 ± 29**
Cystatin C (μg/mL)	<1.44	0.74 ± 0.13	0.79 ± 0.15**	0.73 ± 0.12	0.79 ± 0.15 **	0.73 ± 0.13	0.79 ± 0.16**
α_1-microglobulin (mg/g urine creatinine)	≤16.0	5.8 ± 5.6	5.4 ± 6.3	5.1 ± 4.8	5.4 ± 6.5	4.9 ± 4.9	4.7 ± 6.2
β-N-acetyl-D-glucosaminidase (U/g urine creatinine)	≤5.0	3.5 ± 1.8	3.3 ± 2.2	2.9 ± 1.5	2.9 ± 1.6	3.1 ± 2.5	2.9 ± 2.0*

* P < 0.05 vs. baseline; ** P < 0.001 vs. baseline (Wilcoxon).

would have been ideal to have included a treatment arm in which 1.0 g mesalazine was administered t.d.s., but inclusion of a fourth patient group was felt to be impractical.

The difference in clinical remission rate was most evident in patients with slight inflammation on endoscopy at baseline. Patients with signs of mucosal inflammation despite clinical remission have been shown to experience a higher rate of clinical relapse than those with complete mucosal healing,[13] a finding that was confirmed in our study. In a *post hoc* analysis, we observed that in patients with slightly inflamed mucosa at baseline (i.e. EI 2-3), 3.0 g OD continued to maintain a high rate of clinical remission (72%) while the lower-dose regimens were less effective. This interesting result suggests that status of mucosa might be a prognostic factor for drug response. Endoscopic monitoring of patients with clinically quiescent disease seems to be worthwhile.

To date, three published randomised trials have compared OD vs. twice-daily dosing of the same amount of oral mesalazine for maintenance of clinical remission in UC patients.[13–15] Whereas one study demonstrated significant superiority of OD dosing,[14] another study showed numerically better results for divided daily dosing,[13] while the third study showed exactly the same numbers in both groups.[15]

A direct comparison of clinical remission rates between our study and the three previous studies investigating mesalazine OD regimens for maintenance of remission of UC,[13–15] is not reliable because of overt differences in study design, endpoints, galenical formulations and dosing. Obviously, an open-label,[13] or single-blinded design[14, 15] is subject to bias towards overestimating a treatment effect in the OD treatment group compared with a double-blind, double-dummy design such as that used in our study, where patients in the OD groups had to administer trial medication three times daily (active in the morning, placebo at noon and in the evening) for blinding purposes. Whereas the open-label study concluded that mesalazine 2.4 g/day administered as a single or divided dose demonstrated a good safety profile, was well tolerated and was effective as maintenance treatment, the single-blind study concluded that oral mesalazine 2.0 g OD had better remission rates, acceptability, and self-reported adherence to therapy compared with patients given oral mesalazine 1.0 g twice daily.[13, 14]

Furthermore, it should be borne in mind that the full potential of a mesalazine OD maintenance regimen compared with a divided dose regimen will have been missed because all treatment groups adhered nearly perfectly to the treatment over 1 year. Such high adherence rates are typical for a well-controlled clinical trial setting, but do not reflect the real-life situation, where lack of adherence is found in about 50% of patients over 1 year,[16] and is clearly one of the driving factors for treatment failure with mesalazine. Thus even if a t.d.s. dose regimen would be slightly (8%) superior in maintaining remission compared with an OD regimen at the same daily mesalazine dose as suggested in our study, better adherence to the simpler OD regimen might compensate for the small disadvantage in clinical practice and might be the preferred long-term strategy. The efficacy of granulated mesalazine 1.5 g given once a day has previously been demonstrated in a large phase III randomised, double-blind, placebo-controlled study involving 305 patients with inactive UC, in which 79% of patients receiving 1.5 g OD stayed relapse-free for 6 months compared with only 58% given placebo.[17]

Our study failed to demonstrate non-inferiority of 1.5 g OD compared with a standard 0.5 g t.d.s. regimen in maintaining remission. The two patient populations may be different because of the relapse risk. A shorter interval between end of the preceding acute episode and study entry in the 1.5 g OD group might have promoted a higher risk of early relapse. Similarly, the 1.5 g OD group had the highest number of patients with long-standing disease (47% vs. 41% in the 0.5 g t.d.s. group), indicating that these patients were less likely to achieve remission.

Table 3 | Trough levels of mesalazine and N-acetyl-mesalazine in plasma [mean (95% CI)]

	3.0 g OD (*n* = 10)		1.5 g OD (*n* = 8)		0.5 g t.d.s. (*n* = 9)	
	Week 2	Week 52	Week 2	Week 52	Week 2	Week 52
Mesalazine [ng/mL]	646 [0–1295]	797 [68–1526]	224 [28–421]	197 [54–341]	215 [34–395]	326 [0–731]
N-acetyl-mesalazine [ng/mL]	1122 [396–1847]	1280 [290–2270]	732 [361–1103]	663 [270–1057]	981 [466–1496]	844 [176–1512]

Blood samples were drawn in the morning prior administration of the study medication. All comparisons within treatments (Mann–Whitney) and between treatments (Kruskal–Wallis) were not statistically significant.

Once daily administration of mesalazine (3.0 g or 1.5 g) was as safe as the standard 0.5 g t.d.s. regimen. The favourable long-term safety of the three tested regimens is substantiated by the results of renal and trough level monitoring. Nephrotoxicity, in particular tubular toxicity, might be of concern during long-term treatment with high doses of mesalazine.[18] The shortcomings of serum creatinine as a marker of renal function are well recognised and therefore estimation of glomerular filtration rate and quantification of serum cystatin C and urinary protein excretion were also performed. α1-microglobulin is one of the most common indicators of tubular proteinuria and β-NAG was demonstrated to give an early indication of direct damage of tubular cells.[19] We did not detect tubular toxicity in any of the study patients. However, because of the slight increase in cystatin C in each treatment group, it remains prudent to monitor renal function every 3 months during long-term administration of mesalazine. Our results are in accordance with a new systematic review showing that the incidence of nephrotoxicity in inflammatory bowel disease patients receiving mesalazine appears to be less than 1%, with reactions being idiosyncratic rather than dose-related.[20]

The favourable long-term safety of the three tested regimens is substantiated by the results of drug monitoring. Trough levels of mesalazine and its metabolite in plasma during 1 year of treatment are in agreement with our corresponding pharmacokinetic trial demonstrating lack of systemic drug accumulation of OD mesalazine (3.0 g or 1.5 g) over time.[21]

In conclusion, while all three of the assessed mesalazine regimens are effective, mesalazine 3.0 g OD offers the highest rate of remission maintenance in UC without a penalty in terms of safety or tolerance. Thus, 3.0 g OD is an appropriate dose for the maintenance of remission in UC, particularly in patients with signs of inflammatory activity or in whom endoscopic evidence is not available.

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REFERENCES

1. Sutherland LR, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2006; **2**: CD000544.
2. Fockens P, Mulder CJ, Tytgat GN, *et al.* Comparison of the efficacy and safety of 1.5 compared with 3.0 g oral slow-release mesalazine (Pentasa) in the maintenance treatment of ulcerative colitis. Dutch Pentasa Study Group. *Eur J Gastroenterol Hepatol* 1995; **7**: 1025–30.
3. Hanauer SB, Sninsky C, Robinson M, *et al.* An oral preparation of mesalazine as long-term maintenance therapy for ulcerative colitis. A randomized placebo-controlled trial. *Ann Intern Med* 1996; **124**: 204–11.
4. Paoluzi OA, Iacopini F, Pica R, *et al.* Comparison of two different daily dosages (2.4 vs. 1.2 g) of oral mesalazine in maintenance of remission in ulcerative colitis patients: 1-year follow-up study. *Aliment Pharmacol Ther* 2005; **21**: 1111–9.
5. Bergman R, Parkes M. Systematic review: the use of mesalazine in inflammatory bowel disease. *Aliment Pharmacol Ther* 2006; **23**: 841–55.
6. Hanauer SB. Review article: high-dose aminosalicylates to induce and maintain remissions in ulcerative colitis. *Aliment Pharmacol Ther* 2006; **24**: 37–40.
7. Shale MJ, Riley SA. Studies of compliance with delayed-release mesalazine therapy in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2003; **18**: 191–8.
8. Cohen RD. Review article: evolutionary advances in the delivery of aminosalicylates for the treatment of ulcerative colitis. *Aliment Pharmacol Ther* 2006; **24**: 465–74.
9. Brunner M, Greinwald R, Kletter K, *et al.* Gastrointestinal transit and release of 5-aminosalicylic acid from (15)Sm-labelled mesalazine pellets vs. tablets in

male healthy volunteers. *Aliment Pharmacol Ther* 2003; **17**: 1163–9.
10. Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. *BMJ* 1989; **298**: 82–6.
11. Dilger K, Trenk D, Rössle M, *et al.* A clinical trial on absorption and N-Acetylation of oral and rectal mesalazine. *Eur J Clin Invest* 2007; **37**: 558–65.
12. Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. *Am J Kidney Dis* 2002; **40**: 221–6.
13. Kamm MA, Lichtenstein GR, Sandborn WJ, *et al.* Randomised trial of once- or twice-daily MMX™ mesalazine for maintenance of remission in ulcerative colitis. *Gut* 2008; **57**: 893–902.
14. Dignass AU, Bokemeyer B, Ad AH, *et al.* Mesalamine once daily is more effective than twice daily in patients with quiescent ulcerative colitis. *Clin Gastroenterol Hepatol* 2009; **7**: 762–9.
15. Sandborn WJ, Korzenik J, Lashner B, *et al.* Once-daily dosing of delayed-release oral mesalamine (400-mg tablet) is as effective as twice-daily dosing for maintenance of remission of ulcerative colitis. *Gastroenterology* 2010; **138**: 1286–96.
16. Kane SV, Accortt NA, Magowan S, *et al.* Predictors of persistence with 5-aminosalicylic acid therapy for ulcerative colitis. *Aliment Pharmacol Ther* 2009; **29**: 855–62.
17. Lichtenstein GR, Gordon GL, Zakko S, *et al.* Clinical trial: once-daily mesalamine granules for maintenance of remission of ulcerative colitis – a 6-month placebo-controlled trial. *Aliment Pharmacol Ther* 2010; **32**: 990–9.
18. Patel H, Barr A, Jeejeebhoy KN. Renal effects of long-term treatment with 5-aminosalicylic acid. *Can J Gastroenterol* 2009; **23**: 170–6.
19. Hofmann W, Regenbogen C, Edel H, *et al.* Diagnostic strategies in urinalysis. *Kidney Int Suppl* 1994; **47**: S111–4.
20. Gisbert JP, Gonzalez-Lama Y, Mate J. 5-Aminosalicylates and renal function in inflammatory bowel disease: a systematic review. *Inflamm Bowel Dis* 2007; **13**: 629–38.
21. Dilger K, Baumgärtner P, Thomann T. Once-daily oral mesalazine (1.5 g/day or 3.0 g/day) does not accumulate in plasma during repeated dosing-results from a clinical trial. *Gut* 2007; **56**(Suppl. III): A150.

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