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Christopher Probert, Axel Dignass, Stefan Lindgren, Marco Oudkerk Pool, Philippe Marteau

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Combined oral and rectal mesalazine for the treatment of mild-to-moderately active ulcerative colitis: Rapid symptom resolution and improvements in quality of life

Christopher S.J. Probert[a,*], Axel U. Dignass[b], Stefan Lindgren[c,d], Marco Oudkerk Pool[e], Philippe Marteau[f,g]

[a] Department of Gastroenterology, University of Liverpool, Liverpool, UK
[b] Department of Gastroenterology, Hepatology and Oncology, Agaplesion Markus Hospital, Frankfurt, Germany
[c] Department of Clinical Sciences Malmö, Lund University, Malmö, Sweden
[d] Department of Gastroenterology, University Hospital Skane, Malmö, Sweden
[e] Flevo Ziekenhuis, Hospitaalweg 1, Almere, The Netherlands
[f] Department of Hepato-gastroenterology, AP-HP, Lariboisière Hospital, Paris, France
[g] Denis Diderot Paris 7 University, Paris, France

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Abstract

Background and aims: Mesalazine (5-aminosalicylic acid) is the standard first-line therapy for mild-to-moderate ulcerative colitis. In the PINCE study, remission rates were significantly greater with combined oral/enema vs. oral/placebo treatment at 8 weeks (64% vs. 43%, respectively; $p = 0.030$). In this analysis, we explored early response, mucosal healing rates, cessation of rectal bleeding, and quality of life in PINCE.

Methods: Patients with extensive mild-to-moderately active ulcerative colitis received 8 weeks of oral mesalazine 4 g/day, plus 4 weeks of daily active (1 g mesalazine) or placebo enema. Early response was assessed using the abbreviated ulcerative colitis disease activity index. Mucosal healing was assessed by disease activity index endoscopic mucosal appearance score. Cessation of bleeding (patient diaries), quality of life (EQ-5D), and patient acceptability (questionnaire) were also assessed.

Results: Combined mesalazine oral/enema treatment achieved a significantly higher rate of improvement in abbreviated ulcerative colitis disease activity index (score decrease ≥ 2) within 2 weeks, compared with oral-only treatment ($p = 0.032$). Bleeding ceased significantly more quickly with combination vs. oral therapy ($p = 0.003$). More patients showed mucosal healing (disease activity index endoscopic mucosal appearance score 0/1) with combination vs. oral

* Corresponding author at: Department of Gastroenterology, Institute of Translational Medicine, University of Liverpool, Crown Street, Liverpool L69 3GE, UK. Tel.: +44 151 7946822; fax: +44 151 7946825.
E-mail address: Chris.Probert@liverpool.ac.uk (C.S.J. Probert).

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therapy, which was significantly different between groups at week 4 ($p = 0.052$). Both groups showed quality of life improvements, with a significant benefit for combination vs. oral therapy at week 4 in multiple domains. Most patients reported finding the treatment acceptable.
Conclusions: Rapid cessation of symptoms was seen with combination therapy, which is particularly important to patients and may improve quality of life.

1. Introduction

Mesalazine (5-aminosalicylic acid [5-ASA]) is recommended for the treatment of most forms of mild-to-moderately active ulcerative colitis (UC) in guidelines from the European Crohn's and Colitis Organisation,[1] reflecting the status of mesalazine as the current standard of care for both the induction and maintenance of remission in mild-to-moderate UC. Nevertheless, there is scope to further optimize drug delivery and dosing schedules, which may improve patient adherence.[2]

Mesalazine has been shown to be effective when used as either an oral therapy,[3–8] a rectal therapy administered as a suspension (enema), suppository, gel or foam,[9–18] or when oral and rectal formulations are used in combination.[15,19–23] A dose-related effect has been shown for oral mesalazine such that doses ≥2 g/day show superior efficacy compared with lower doses,[24] and 2.4–4.0 g daily oral therapy is generally used to induce remission.[22] Clinical response rates of 60–70% and clinical remission rates of 40–70% have been reported in various 6–8 week studies.[25] However, both the oral and the rectal routes of administration are limited in their sites of mesalazine delivery. Oral therapy alone may not be sufficient to achieve therapeutic response in the distal sites of the large bowel, while mesalazine suppositories and rectal suspensions do not have any effect above the rectosigmoid junction and splenic flexure, respectively.[22] Thus, combination therapy may show benefits over either route used in isolation.

The PINCE study was a European, multicenter, randomized trial, comparing therapy with combined mesalazine (PENTASA®; Ferring Pharmaceuticals, Denmark) oral (4 g/day) plus rectal suspension (1 g/day), and mesalazine (PENTASA) oral (4 g/day) plus placebo suspension in patients with extensive mild-to-moderately active UC. Remission rates, based on clinical and endoscopic criteria, were higher in the mesalazine combination therapy group than in the oral therapy group at weeks 4 and 8, significantly so at week 8 (combination, 64% vs. oral 43%, $p = 0.030$).[22]

UC treatment has several important goals in addition to remission.[25] Mucosal healing is an important outcome, and may prevent or reduce the risk of colorectal cancer.[26] Other important outcomes from the patient's perspective include the rapid cessation of distressing symptoms such as rectal bleeding, an important clinical endpoint in many trials of UC therapy. In the PINCE study, of those patients with rectal bleeding at baseline, 73% in the mesalazine combination therapy group, compared with 38% in the oral therapy group achieved cessation of rectal bleeding over the 8-week study.[22] Rectal bleeding, abdominal pain, and other symptoms of the condition can also have a significant impact on patient quality of life (QoL).[2] In the present secondary analysis of the PINCE study, we examined mucosal healing, early (week 2) clinical efficacy, time to cessation of rectal bleeding in patients with different types of bleeding at baseline (traces, frank, or mainly blood), and QoL in patients receiving combined or oral-only treatment.

2. Materials and methods

2.1. Patients

Patients were recruited between January 2002 and July 2003 in six European countries (France, UK, Spain, Germany, The Netherlands, and Sweden). The study was approved by local institutional review boards and ethics committees. Male and female patients >18 years of age were eligible to participate if they had previously established extensive UC with mild-to-moderate exacerbation, and a UC disease activity index (UCDAI) score of ≥3 and ≤8.[4] All patients gave written, informed consent prior to study entry. Exclusion criteria included: infectious colitis; oral maintenance treatment with total daily doses >3 g of sulfasalazine, mesalazine, or 4-ASA within 30 days prior to study entry; any immunosuppressive agents during the 30 days prior to study enrollment; chronic use of nonsteroidal anti-inflammatory drugs (oral and/or rectal routes) in the 7 days prior to inclusion (chronic use defined as drug intake for a minimum of 7 consecutive days); intake of corticosteroids (oral and/or rectal routes) within 7 days prior to enrollment; severe renal/hepatic impairment, malignant disease, allergy to salicylates, alcoholism, or drug addiction, or any other disease or condition that might interfere with study assessments, as judged by the investigator; participation in another clinical study in the previous 30 days; women of child bearing potential who were not using an effective method of contraception; or pregnancy and lactation.

2.2. Study design

This was a double-blind, multinational, randomized, parallel group, placebo-controlled, 8-week clinical study in outpatients with a previously established diagnosis of extensive mild-to-moderately active UC (macroscopic inflammation beyond the splenic flexure during a full colonoscopy).[22] Patients were randomized to receive either mesalazine (PENTASA) enema (1 g/day [OD] in 100 ml at bedtime) or placebo enema for a period of 4 weeks. Patients in both arms also received oral mesalazine (PENTASA; 2 g/twice daily [BD], granules swallowed with water or juice) for 8 weeks.

Patients, enrolled following a medical evaluation of the initial clinical and endoscopic severity of their UC, were

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evaluated at randomization (day 1), and at 4 weeks (±2 days) and 8 weeks (±2 days) using the UCDAI score, which is based on clinical signs and endoscopic evaluation of the distal colon during rectosigmoidoscopy.[4] Remission was defined as a UCDAI score <2, and improvement was defined as a decrease in UCDAI score of ≥2 points from baseline. Abbreviated UCDAI (no sigmoidoscopy) was assessed at week 2 (±1 day). Patients were asked to complete diaries daily with their number of stools and assessment of rectal bleeding. Time to cessation of rectal bleeding was evaluated based on the diary records.

2.3. Endpoints and post-hoc analyses

All endpoints were defined prior to study start. The primary endpoint was remission rate at 4 weeks based on the UCDAI score. Secondary endpoints included: remission rates at 8 weeks; improvement rates at 4 and 8 weeks (UCDAI); improvement rates at 2, 4, and 8 weeks (abbreviated UCDAI); time to cessation of rectal bleeding; and patient QoL. Patient QoL was assessed using the EQ-5D questionnaire at baseline and at 2, 4, and 8 weeks.[27] This QoL scale includes five domains covering mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each question has three response categories: no problem; some problem; and inability or extreme problems. Acceptability of using an oral/enema combination therapy was assessed at week 8; patients were asked if they would like to take a combination therapy in case of relapse. Post-hoc analyses were carried out to assess differences in mucosal healing between the two treatments, and to extend the abbreviated UCDAI analysis at week 2.

2.4. Statistical methods

Differences in the proportion of patients between groups were analyzed by two-sided Chi-square test. For changes from baseline, median change was analyzed with the two-sided Wilcoxon test, while mean change was analyzed with the F-statistic for analysis of variance. Time to cessation of rectal bleeding (date of cessation minus date of first intake) was analyzed using nonparametric Kaplan–Meier methodology. Differences between groups were analyzed using a two-sided log-rank test. The significance of the median change from baseline in mucosal score was based on nonparametric testing of distributions in the intent-to-treat (ITT) population.

3. Results

In total, 127 patients at 43 centers in six countries were randomized to receive 2 g oral mesalazine (PENTASA) BD plus either 1 g mesalazine (PENTASA) enema (n = 71) or placebo enema (n = 56) OD. As reported previously,[22] baseline demographics were well balanced between groups. Of the 116 ITT patients, 63 were in the active enema group and 53 in the placebo enema group. Of these, 71 patients (42 and 29, respectively) constituted the per-protocol population (i.e. no protocol violations).

3.1. Remission and improvement: early response

After only 2 weeks, the rates of remission (abbreviated UCDAI < 2) were 33% for the combination therapy group compared with 30% for the oral therapy group.[28] Furthermore, improvement (abbreviated UCDAI decrease ≥ 2) was seen in >30% of patients in both arms. Improvement rates compared with baseline (abbreviated UCDAI decrease ≥ 2) were significantly higher in the combination therapy group than the oral therapy group at week 2 (65% vs. 45%; p = 0.032; Table 1), week 4 (89% vs. 62%; p = 0.001), and week 8 (86% vs. 68%; p = 0.026). Results of the logistic regression analyses for the ITT population confirmed that patients receiving combination therapy were more likely to have improvement than patients receiving oral therapy at week 4 (odds ratio 6.560; p = 0.002) and week 8 (odds ratio 3.578; p = 0.027). A median change of −2 in abbreviated UCDAI at week 2 was seen in the combination therapy group compared with −1 in the oral therapy group (Table 1); a difference that was statistically significant (p = 0.030). Remission rates (UCDAI < 2) in the ITT population were numerically higher in the combination therapy group compared with the oral therapy group at week 4 (44% vs. 34%), and significantly higher at week 8 (64% vs. 43%; p = 0.030).

3.2. Mucosal healing

Mucosal healing was evident in both treatment groups (Table 2), and there was a trend for more patients to achieve mucosal healing with combined vs. oral therapy. In the combination therapy group, 95% of patients had a mucosal score (disease activity index endoscopic mucosal appearance score) of 0 or 1 at week 4 compared with 83% of patients in the oral therapy group (ITT population, p = 0.052). The mean change from baseline in mucosal score was −1.09 (combination therapy group) vs. −0.60 (oral therapy group; p = 0.006) at week 4 and −1.10 (combination therapy group) vs. −0.66 (oral therapy group; p = 0.024) at week 8.

3.3. Rectal bleeding

The time to the cessation of rectal bleeding in patients with baseline rectal bleeding and with cessation of rectal bleeding

Table 1 Change under treatment in abbreviated UCDAI at 2 weeks (ITT population).

Abbreviated UCDAI at 2 weeks	Mesalazine oral + active enema (n = 63)	Mesalazine oral + placebo enema (n = 53)
Median change from baseline (p = 0.030, Wilcoxon test; two-sided)	−2.00	−1.00
Mean change from baseline (p = 0.053, F-statistic for analysis of variance)	−2.44	−1.64
Percent improved (95% confidence interval) (p = 0.032, chi-square test)	65 (53–77)	45 (32–59)

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Table 2 Mucosal healing from baseline to week 8 with mesalazine oral plus active enema (combination therapy) and mesalazine oral plus placebo enema (oral therapy) in the PINCE study (ITT population, observed cases).

Time point	Mucosal score [a]	Mesalazine oral + active enema, % (n)	Mesalazine oral + placebo enema, % (n)
Baseline[†]	0	0 (0)	0 (0)
	1	32 (20)	43 (23)
	0 or 1	32 (20)	43 (23)
	2 or 3	68 (43)	57 (30)
	p value [‡]	0.196	
Week 4[¶]	0	37 (21)	23 (11)
	1	58 (33)	60 (28)
	0 or 1	95 (54)	83 (39)
	2 or 3	5 (3)	17 (8)
	p value [‡]	0.052	
Week 8[§]	0	50 (29)	38 (18)
	1	36 (21)	38 (18)
	0 or 1	86 (50)	77 (36)
	2 or 3	14 (8)	23 (11)
	p value [‡]	0.203	

For the combination vs. oral therapy groups, respectively: [†]*n* = 63 and *n* = 53; [¶]*n* = 57 and *n* = 47; [§]*n* = 58 and *n* = 47.

[a] Disease activity index endoscopic mucosal appearance score: 0 = normal; 1 = erythema, reduced capillary network, mild friability, minimal granularity; 2 = friability, marked erythema, no vascularization, erosions, pus; 3 = ulceration, spontaneous bleeding, pus.

[‡] *p* value based on chi-square test of the difference between treatment arms in the proportion of patients with a score of 0/1 or 2/3.

during the study is shown in Table 3. For patients whose bleeding ceased, the mean duration of rectal bleeding was 21.0 days (standard deviation [SD] 18.4) in the combination treatment group compared with 24.4 days (SD 21.0) in the oral therapy group. Bleeding stopped within 7 days of the start of the study for 35% of patients in the combination therapy group and 25% of those in the oral therapy group.

Kaplan–Meier methodology showed that the time to cease rectal bleeding was significantly shorter for patients in the combination therapy group compared with oral therapy, with a median of 28 days vs. >56 days, respectively (log-rank *p* value 0.003, Fig. 1). The time taken to cease rectal bleeding in all patients with frank blood at baseline (irrespective of achieving cessation of rectal bleeding during the study) was also shorter in patients treated with the combination vs. oral therapy (median 21 days vs. >56 days, respectively; log-rank *p* value 0.003).

Table 3 Cessation of rectal bleeding among patients with rectal bleeding at baseline and with cessation of rectal bleeding during the study (ITT population).

Mesalazine treatment	Baseline score	Mean time to cessation, days (range)
Oral + active enema	All patients	21.0 (0–53)
	Traces of blood	18.4 (0–51)
	Frank blood	20.5 (0–53)
	Mainly blood	31.5 (1–46)
Oral + placebo enema	All patients	24.4 (1–63)
	Traces of blood	21.3 (1–51)
	Frank blood	18.9 (3–49)
	Mainly blood	54.5 (46–63)

3.4. Quality of life and treatment acceptability

The proportion of patients who reported 'some problem' in any domain fell in both treatment groups from baseline to week 8 with no major differences between the treatment groups (Table 4). However, results show a trend for more rapid effects in the combination therapy group in several domains. In the mobility domain, the proportion of patients with 'some problems' at week 4 in the combination therapy group decreased to a greater extent than that in the oral therapy group; this was a small but significant improvement ($p = 0.049$). Also at week 4, there was a significant improvement in the 'usual activity' domain ($p = 0.034$), a trend towards improved pain/discomfort ($p = 0.053$), and a significant improvement in anxiety/depression ($p = 0.049$) in the combination therapy group compared with the oral therapy group.

Of 114 patients asked if they were prepared to take a combination therapy in the future, 51 patients (84%) from the combination therapy group and 45 patients (85%) from the oral therapy group responded positively.

4. Discussion

The PINCE study showed that adding a mesalazine enema to an oral mesalazine regimen provides additional benefit for patients with extensive mild-to-moderately active UC defined by involvement beyond the splenic flexure.[22] Although the PINCE trial did not reach its primary endpoint of showing a higher remission rate at 4 weeks for the combination therapy group, secondary endpoints were met, including remission at 8 weeks.[22] As enema therapy was given only until week 4, this result may indicate a delayed treatment effect. In the present analyses, we demonstrate several earlier efficacy benefits for the combination therapy compared with the oral therapy alone. These comprise 2-week UC improvement based on decreased abbreviated UCDAI score, increased mucosal healing from 4 weeks onwards, reduced time to cessation of rectal bleeding, and improved QoL in several domains.

At just 2 weeks after starting treatment, 26% more patients had achieved an improvement from baseline (≥2 decrease in abbreviated UCDAI) with combination vs. oral therapy alone ($p = 0.032$), emphasizing the rapidity of response achieved with combination therapy in this patient population. Data from PINCE also show a trend for more patients to go on to achieve endoscopic remission with combination therapy compared with oral therapy, with 50% and 38% of patients, respectively, achieving a mucosal score of 0 at week 8, vs. 0% at baseline (Table 2). Indeed, the effect on mucosal score was significantly greater for the combination therapy from 4 weeks onwards. This reflects the extensive UC in the study population: the patients in PINCE

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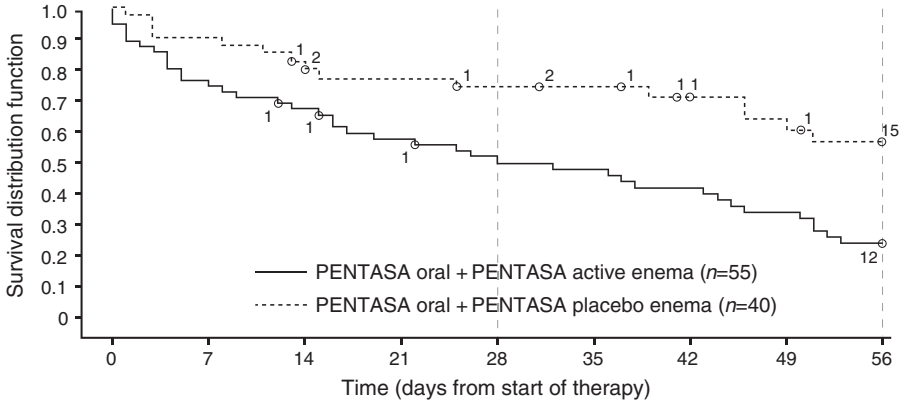

Figure 1 Time to cessation of rectal bleeding in all patients with rectal bleeding at baseline in the PINCE study. Note: All patients without cessation of rectal bleeding until day 56 or until premature withdrawal are censored. Circles mark censored patients with number of patients censored. Data includes patients who had prematurely withdrawn, i.e., for whom no information is available.

Table 4 QoL assessments at baseline, week 2, week 4, and week 8 in the PINCE study. The *p* values indicate a difference in the rate of improvement from baseline (week 0) to week 4 for the combination therapy group compared with the oral therapy group.

QoL measurement	Mesalazine treatment	Week	Total, n	No problems, *n* (%)	Some problems, *n* (%)	Inability or extreme problems, *n* (%)
Mobility	Oral + active enema	0	62	54 (87)	8 (13)	0 (0)
		2	61	57 (93)	4 (7)	0 (0)
		4	58	57 (98)	1 (2) *	0 (0)
		8	57	55 (97)	2 (4)	0 (0)
	Oral + placebo enema	0	53	49 (93)	4 (8)	0 (0)
		2	53	47 (89)	5 (9)	1 (2)
		4	49	45 (92)	4 (8) *	0 (0)
		8	40	39 (98)	1 (3)	0 (0)
Usual activity	Oral + active enema	0	62	44 (71)	18 (29)	0 (0)
		2	61	44 (72)	17 (28)	0 (0)
		4	58	51 (88)	7 (12) **	0 (0)
		8	57	53 (93)	4 (7)	0 (0)
	Oral + placebo enema	0	53	28 (53)	25 (47)	0 (0)
		2	53	38 (72)	15 (28)	0 (0)
		4	49	34 (69)	15 (31) **	0 (0)
		8	40	35 (88)	5 (13)	0 (0)
Pain/discomfort	Oral + active enema	0	62	17 (27)	44 (71)	1 (2)
		2	61	36 (59)	24 (39)	1 (2)
		4	58	46 (79)	11 (19) †	1 (2)
		8	57	47 (83)	9 (16)	1 (2)
	Oral + placebo enema	0	53	17 (32)	34 (64)	2 (4)
		2	53	30 (57)	23 (43)	0 (0)
		4	49	32 (65)	17 (35) †	0 (0)
		8	40	34 (85)	6 (15)	0 (0)
Anxiety/depression	Oral + active enema	0	62	42 (68)	18 (29)	2 (3)
		2	60	45 (75)	15 (25)	0 (0)
		4	58	49 (85)	9 (16) ***	0 (0)
		8	57	48 (84)	9 (16)	0 (0)
	Oral + placebo enema	0	53	24 (45)	29 (55)	0 (0)
		2	53	35 (66)	17 (32)	1 (2)
		4	49	31 (63)	17 (35) ***	1 (2)
		8	40	28 (70)	11 (28)	1 (3)

* $p = 0.049$.
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*** $p = 0.049$.
† $p = 0.053$.

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had more extensive disease than in many other studies; the results with the combination therapy may therefore indicate greater efficacy in such patients. As the majority of clinical symptoms in extensive UC probably relate to disease activity in the distal part of the colon, treatments that target the distal colon are more likely to show rapid cessation of symptoms, leading to subsequent clinical remission.[29] Combination therapy has previously been shown to be significantly better at stopping rectal bleeding than rectal suspension or oral therapy alone, with a mean time to cessation of bleeding of 11.9, 24.8, and 25.5 days, respectively.[15] Furthermore, a recent analysis found that this differential effect on rectal bleeding may occur from as early as day 8 of treatment onwards, with clinical remission at week 3 also significantly more frequent in those who received combination vs. oral therapy.[30] These data are consistent with the 2-week improvement seen in the present study, suggesting that earlier cessation of rectal bleeding may translate into earlier mucosal healing in patients with extensive mild-to-moderately active UC. Oral formulations that enable delivery throughout the whole colon are likely to best complement a combination therapy regimen.

The rapid cessation of symptoms, seen at 2 weeks in the PINCE study seem to have a profound effect on QoL and may promote an increase in patient adherence to medication. In the wide treatment of UC, it is important to acknowledge that while more than 90% of patients in clinical studies are compliant, only 40% of patients in everyday life take their prescribed therapy.[31] It is encouraging that the majority of patients in the combination therapy group stated that they would be willing to take combination rectal suspension and oral therapy in the future.

For extensive mild-to-moderately active UC, data from the PINCE study suggest that combination therapy could be more effective than either oral or topical treatment used in isolation. While some level of dose proportionality has been observed with mesalazine treatment,[24] it seems unlikely that the results seen here are simply a result of a short-term increase in dosage. This is particularly true for patients with extensive disease, for whom an increase in dosage of a topical therapy alone is unlikely to outweigh the challenges of successful oral drug delivery to the distal colon and topical administration above the rectosigmoid junction and splenic flexure. However, it is also worth considering that in contrast to treatment for induction of remission, doses in the maintenance setting are often substantially less.[25,32] Consideration of dose proportionality at this low end of the dose spectrum may indeed yield benefits in the long-term management of patients with UC and may be a suitable topic for further investigation.

Overall, our results provide further evidence that combination therapy improves the rate of mucosal healing and reduces the time taken to cease rectal bleeding compared with oral mesalazine alone. The rapid cessation of symptoms is of particular importance to patients, as a shorter time period from initiation of treatment to noticeable alleviation of symptoms has a direct impact on their QoL. The data also strengthen current guideline recommendations, which advocate the first-line use of combination therapy for patients with extensive, mild-to-moderately active UC.[1] Although it is common practice to introduce oral steroids at an early stage in the hope of a rapid response,[33] our data indicate that rapid improvements in UC symptoms can also be achieved by adding a mesalazine enema to an oral mesalazine regimen.

Statement of authorship

CSJ Probert was involved in the conception and design of the study; the acquisition, analysis and interpretation of data; drafting and revising the manuscript; and providing final approval of the version to be submitted.

S Lindgren was involved in the conception and design of the study; the interpretation of data; drafting and revising the manuscript; and providing final approval of the version to be submitted.

A Dignass was involved in the conception and design of the study; the acquisition, analysis and interpretation of data; drafting and revising the manuscript; and providing final approval of the version to be submitted.

P Marteau was involved in the conception and design of the study; the acquisition, analysis and interpretation of data; drafting and revising the manuscript; and providing final approval of the version to be submitted.

M Oudkerk Pool was involved in the acquisition of data; and drafting and revising the manuscript; and providing final approval of the version to be submitted.

Ethics

This study was conducted in accordance with the Declaration of Helsinki, in compliance with the approved protocol, good clinical practice (GCP) and applicable regulatory requirements. The investigator obtained written consent from each patient after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards, and any other aspects of the study that were relevant to the patient's decision to participate.

Conflict of interest disclosures

CSJ Probert: lectures and/or hospitality supported by the following companies: Abbott, Falk Foundation, Ferring, Procter and Gamble, Schering Plough, Shire, and UCB. Study grants from the following companies: Procter and Gamble, Schering Plough, and Shire. Paid consultant for the following companies: Abbott, Falk, Ferring, Schering Plough, Shire, Tillotts, UCB, and Warner Chilcott.

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