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West, R.; Russel, M.; Bodelier, A.; Kuijvenhoven, J.; Bruin, K.; Jansen, J.; ... ; Lubbinge, H.

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Lower Risk of Recurrence with a Higher Induction Dose of Mesalazine and Longer Duration of Treatment in Ulcerative Colitis: Results from the Dutch, Non-Interventional, IMPACT Study

Rachel West[1], Maurice Russel[2], Alexander Bodelier[3], Johan Kuijvenhoven[4], Karlien Bruin[5], Jeroen Jansen[6], Andrea van der Meulen[7], Eric Keulen[8], Leonieke Wolters[9], Robert Ouwendijk[10], Geert Bezemer[10], Vassilis Koussoulas[11], Thjon Tang[12], Aart van Dobbenburgh[13], Marianne van Nistelrooy[13], Itta Minderhoud[14], Sigrid Vandebosch[15], Hans Lubbinge[16]

1) Franciscus Gasthuis & Vlietland, Rotterdam;
2) Medisch Spectrum Twente, Enschede;
3) Amphia Ziekenhuis, Breda;
4) Spaarne Gasthuis, Haarlem;
5) Tweesteden Ziekenhuis, Tilburg;
6) Onze Lieve Vrouwe Gasthuis (OLVG), Amsterdam;
7) Leids Universitair Medisch Centrum (LUMC) Leiden;
8) Orbis Medisch Centrum, Sittard/Geleen;
9) Albert Schweitzer Ziekenhuis, Dordrecht;
10) Ikazia Ziekenhuis Rotterdam;
11) Nij Smellinghe Ziekenhuis, Drachten;
12) IJsselland Ziekenhuis, Capelle a/d Ijssel;
13) Gelre Ziekenhuizen, Zutphen;
14) Tergooi Ziekenhuis, Hilversum;
15) Zorgsaam Ziekenhuis, Terneuzen;
16) Tjongerschans Ziekenhuis, Heerenveen, Netherlands

Address for correspondence:
Rachel West
Franciscus Gasthuis & Vlietland, Kleiweg 500, 3045 PM Rotterdam, Netherlands.
R.West@Franciscus.nl

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ABSTRACT

Background & Aims: The dose and duration of mesalazine treatment for ulcerative colitis (UC) is a potentially important determinant of effectiveness, with evidence suggesting that continuing the induction dose for 6-12 months may improve outcomes; however, real-world data are lacking. We assessed mesalazine use in Dutch clinical practice, including how differences in dose and duration affected UC outcomes.

Methods: Adults with mild-to-moderate UC who received oral prolonged-release mesalazine *de novo* or had a dose escalation for an active episode were followed for 12 months in this non-interventional study (ClinicalTrials.gov identifier: NCT02261636). The primary endpoint was time from start of treatment to dose reduction (TDR). Secondary endpoints included recurrence rate, adherence, and work productivity.

Results: In total, 151 patients were enrolled, of whom 108 (71.5%) were newly diagnosed with UC. The majority (120; 79.5%) received a dose of ≥4 g/day. Nearly one-third (48; 31.8%) underwent dose reduction, with mean TDR being 8.3 months. Disease extent and endoscopic appearance did not influence duration of induction therapy, while TDR increased with higher baseline UCDAI scores. TDR was longer in patients without (mean 8.8 months) than with (4.1 months) recurrence, although not significantly (p=0.09). Patients on ≥4 g/day had a significantly lower chance of recurrence versus those on 2-<4 g/day (26.6% vs 62.5%, respectively; p=0.04). Longer treatment duration was associated with significantly reduced recurrence risk [hazard ratio >6 months vs 3-6 months: 0.19 (95%CI: 0.08-0.46); p<0.05], particularly for those on ≥4 g/day [0.15 (0.06-0.40) vs 0.26 (0.01-11.9) for 2-<4 g/day). Patients reported significantly increased work productivity, which was maintained throughout follow-up.

Conclusions: Mesalazine was effective induction therapy, with treatment duration not meaningfully influenced by disease extent and endoscopic appearance at initiation. A higher induction dose of oral mesalazine (≥4 g/day) and longer duration of treatment (>6 months) was associated with a lower recurrence risk.

Key words: ulcerative colitis – time dependent mesalazine – 5-ASA – 5-aminosalicylate – induction.

Abbreviations: AE: adverse event; ECCO: European Crohn's and Colitis Organisation; IBD: inflammatory bowel diseases; TDR: time to dose reduction; UC: ulcerative colitis; UCDAI: Ulcerative Colitis Disease Activity Index; aUCDAI: abbreviated UCDAI; WPAI: Work Productivity and Activity Impairment; 5-ASA: 5-aminosalicylate.

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disorder of the colon and rectum, characterised by flares of active disease with diarrhoea, rectal bleeding, and urgency, alternating with periods of remission [1, 2]. Mesalazine, a 5-aminosalicylic acid (5-ASA) compound, is the current standard of care for induction and maintenance of remission in mild-to-moderate UC, and is given orally, topically, or in combination, depending on disease distribution and severity [3-5]. Clinical guidelines, such as from the European Crohn's and Colitis Organisation (ECCO), typically recommend for mild-to-moderately active UC an oral mesalazine dose of ≥2.4 g/day combined with ≥1 g/day of mesalazine enema [3]. For maintenance of remission, a dose of 2 g/day oral mesalazine is recommended and, if required, 3 g/week rectal treatment [3].

Maintaining the same dose of oral mesalazine to induce remission and keeping the patient on this dose for up to 12 months was reported in a few studies to increase the rate and

duration of remission [6-8]. In a retrospective study of 411 patients with UC, the only significant predictor of remission (defined as Physician's Global Assessment of 'normal') at one year post-induction was using the same mesalazine dose for maintenance and induction treatment [6]. Further studies have indicated that continuing an induction dose of ≥4 g/day may result in more beneficial outcomes than <3 g/day [9], and that higher clinical remission rates with an unchanged maintenance dose are achieved irrespective of endoscopic healing status [8]. Data such as these are reflected in the Dutch inflammatory bowel diseases (IBD) guidelines, which state that the mesalazine dose for UC maintenance therapy should be equal to the induction dose and that it should be continued for at least 6-12 months, after which dose de-escalation can be considered [10]. How these guidelines are being applied in routine clinical practice in the Netherlands and the resultant impact on patient outcomes has not been formally assessed.

The aim of this study was to assess how mesalazine is used as treatment for patients with active mild-to-moderate UC in Dutch clinical practice, at which doses and for how long, and how this affected disease outcomes.

METHODS

This was a Phase 4, non-interventional, observational, prospective study (IMPACT; ClinicalTrials.gov identifier: NCT02261636), conducted between January 2015 and December 2017 in 16 outpatient clinics in the Netherlands. Participants were followed for 1 year across seven study visits (Day 1 and Months 1, 2, 3, 6, 9, and 12), with follow-up information collected as part of routine care or by telephone if a visit did not occur within ±7 days (Supplementary Table I). This study was partially retrospective due to the strategy used for data capture for Visit 1 (baseline) and sometimes Visit 2 (Month 1). At Visit 1, treatment details, demographics and baseline characteristics were recorded, including clinical disease activity [abbreviated Ulcerative Colitis Disease Activity Index (aUCDAI)] and, if available, endoscopic appearance of mucosa (standard UCDAI) [11]. The Work Productivity and Activity Impairment (WPAI) questionnaire [12] was also completed. Follow-up visits captured information on treatment changes, adverse events (AEs), aUCDAI, global patient assessment of UC treatment acceptability ('excellent', 'good', 'moderate', 'bad', or 'unknown'; months 1, 3, 9, and 12), work productivity (WPAI; months 3 and 12), and self-reported adherence [four Yes/No questions and scale 1-10 (low-high); months 2, 6, and 12). At Month 12, treatment was rated ('excellent', 'good', 'moderate', 'bad', 'unknown') for outcome, tolerability (by patients and physicians) and for use and administration, including preferred formulation and dosing frequency (patients only).

This study was not subject to the Medical Research Involving Human Subjects Act (Wet Medisch Wetenschappelijk Onderzoek) and was therefore not submitted to an Independent Ethics Committee. All patients provided informed consent.

Patients (≥18 years) with mild-to-moderate UC extending beyond the rectum (≥10 cm) who received prolonged-release mesalazine (Pentasa®, Ferring Pharmaceuticals, St Prex, Switzerland) compact sachets (1 g, 2 g, 4 g) and/or tablets (500 mg, 1 g), either as *de novo* induction treatment or as a dose escalation for an active episode, were eligible to take part in the study. Patients on locally acting steroids (*e.g.* budesonide), systemic steroids, immunosuppressants (e.g. thiopurines), or biologicals were excluded. All enrolled patients were treated according to standard clinical practice, with treatment decisions made by the treating physician in consultation with the patient.

The primary endpoint was the time from mesalazine treatment start (Day 1) to the first date of dose reduction or study completion [time to dose reduction (TDR)]. Secondary and additional endpoints included: a) association between TDR or cumulative dose until dose reduction and disease severity, disease extension, and extraintestinal manifestations; b) association between recurrence rate of active disease (defined as any of the following after month 3: increase in the mesalazine dose; addition of enema; or initiation/addition of another therapy) and TDR, cumulative dose until dose reduction, duration of treatment, and initial daily dose; c) association between initial dose duration and total aUCDAI score at 12 months; d) association between the mesalazine formulation in combination with dosing frequency and self-reported therapy adherence. All patients were assigned to one of three compliance levels based on the four Yes/No questions in the questionnaire (Yes=0; No=1), and classified as high (0 points), medium (1-2), or low (3-4); e) UC treatment acceptability and global assessment of mesalazine treatment; f) work-related productivity through 12 months/final visit; g) AEs.

All enrolled patients who received at least one dose of oral prolonged-release mesalazine and had at least one follow-up visit were included in the analyses. The original target was 250 patients recruited by 50 of the 600 gastroenterologists in the Netherlands, predicated on there being approximately 1,400 patients with mild-to-moderate UC newly diagnosed (n=1,200) [13] or relapsed and changing mesalazine therapy (n=200) in the Netherlands per annum. This target turned out to be unachievable within a reasonable inclusion period and, after consultation with the Ferring statistical department, was revised to 150 patients, which was deemed sufficient for analysis and representative of the real-world setting. Descriptive statistical analysis was applied to all endpoints, where appropriate. The Log-rank test and Wilcoxon Rank Sum test were used to compare TDR and cumulative dose until dose reduction, respectively, in patients with and without recurrence. Changes in work productivity from baseline were assessed by (non-parametric) analysis of variance (ANOVA). Differences in recurrence rates for those initiated on 2-<4 g/day versus ≥4 g/day mesalazine were assessed by Fisher's exact test.

Four groups of patients were analysed separately based on the duration of induction dose: ≤2 months; >2-3 months; >3-6 months; and >6 months. Time to recurrence was compared between groups by Cox regression, adjusted for imbalanced factors (age, number of previous episodes at inclusion, severity, disease extension, extraintestinal manifestations and UCDAI score on current episode), with results expressed as a hazard ratio (HR) with 95% confidence interval (CI). The Chi-square test was used to compare rectal mesalazine use between patients on induction treatment for ≤6 versus >6 months. A Kruskal-Wallis test, with a Dunn's test for post-hoc analysis, was used to compare differences in aUCDAI total scores at 12 months between the groups.

All statistical assessments were two-sided and evaluated at a significance level of 0.05. No adjustment was made for multiplicity.

RESULTS

Study Population

A total of 151 patients (median age 46 years) were enrolled, the majority with newly diagnosed mild-to-moderate UC (108; 71.5%) (Fig. 1; Table I). Over half the patients (80; 53%) completed the study; the most common reason for discontinuation (37/71; 52.1%) was due to switching treatment. At baseline, patients had a mean total UCDAI score of 5.4. The majority (120; 79.5%) of patients received a mesalazine dose of ≥4 g/day, mostly as a 4 g sachet given once daily (115; 76.2%). Approximately two-thirds (97; 64.2%) did not receive rectal treatment.

Primary Efficacy Endpoint

Nearly one-third of patients (48; 31.8%) had dose reductions before study completion, and the mean TDR was 8.3 months in the Efficacy Analysis Set (n=151).

Secondary and Additional Efficacy Endpoints

Regardless of UC severity (aUCDAI score) at baseline, most subjects (143; 94.7%) received ≥4 g/day of oral mesalazine by month 3. Stratified by aUCDAI score at baseline, mean TDR varied between 5.6-9.2 months, with no clear pattern discernible (Table II). None of the eight patients who received 2-<4 g/day of mesalazine underwent dose reduction. Cumulative dose until dose reduction also showed no clear association with aUCDAI scores at baseline.

Using the full UCDAI, TDR tended to increase with worsening disease severity at baseline, being shortest in patients with a score of 0-2 (mean 3.2 months) and longest in those with a score of 9-12 (8.4 months) (Table II). UCDAI score at baseline did not appear to meaningfully influence the cumulative dose of mesalazine until the dose reduction, although it was highest in those with a score of 9-12 (median 1,112 vs 394-729 g for scores <9).

Table I. Patient demographics and baseline characteristics (n=151)

Female, n (%)	73 (48.3)	
Age (years), median (min, max)	46.0 (18, 83)	
UCDAI - total score[a]		
Mean (standard deviation)	5.4 (2.5)	
Median (min, max)	5 (0, 11)[d]	
aUCDAI - total score[a]		
Mean (standard deviation)	3.8 (2.1)	
Median (min, max)	4 (0, 8)[d]	
Current episode, n (%)		
Newly diagnosed UC	108 (71.5)	
Relapse	43 (28.5)	
Rectal treatment, n (%)		
No	97 (64.2)	
Yes, enema	38 (25.2)	
Yes, suppository	16 (10.6)	
Disease extension, n (%)		
Proctosigmoiditis (≥10cm)	49 (32.5)	
Left-sided UC	61 (40.4)	
Extensive UC	39 (25.8)	
Endoscopy not done[b]	2 (1.3)	
Initial daily dose and formulation of oral mesalazine, n (%)		
2-<4 g	31 (20.5)	
sachet		26 (17.2)
tablets		5 (3.3)
≥4 g	120 (79.5)	
sachet		118 (78.1)
tablets		2 (1.3)
Extraintestinal manifestations[c], n (%)		
Yes	14 (9.3)	
No	136 (90.7)	

UC: ulcerative colitis; UCDAI: Ulcerative Colitis Disease Activity Index; aUCDAI: abbreviated UCDAI; [a]UCDAI score calculated at Visit 1 (baseline); [c]Not recorded for 1 patient; [d]Data for Visit 1 (baseline) were captured retrospectively..

In patients with endoscopy data (149; 98.7%), mucosal appearance was found to be broadly similar for all dose groups (Table III). Dose reduction appeared to occur slightly earlier in those with extensive UC (TDR mean 6.4 months) compared with left-sided UC (mean 8.4 months) and proctosigmoiditis (mean 8.2 months). Similarly, cumulative dose until dose reduction was

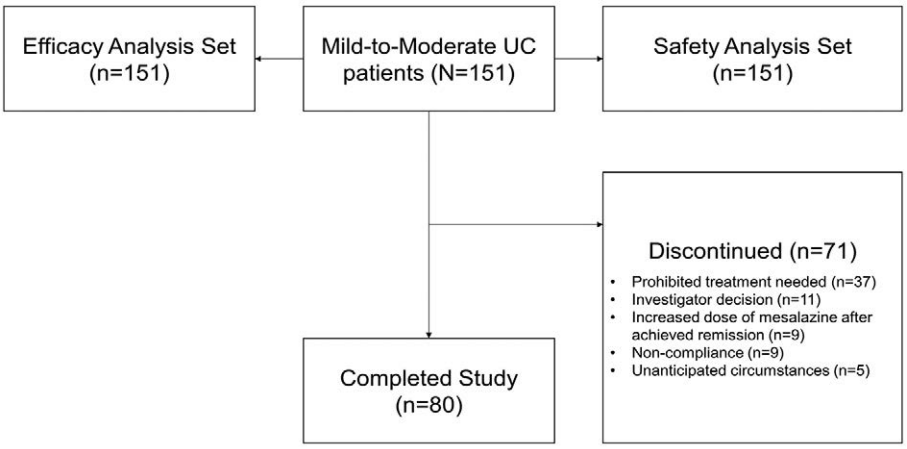

Fig. 1. Flow chart. Efficacy Analysis Set comprised all patients that had fulfilled the inclusion criteria and had at least 1 follow-up visit. Safety Analysis Set included all patients treated with at least one dose of oral prolonged-release mesalazine.

Table II. Disease severity at day 1 (baseline) and TDR/cumulative dose until dose reduction (Efficacy Analysis Set)

	Abbreviated UCDAI Score				UCDAI Score			
	0-2 (n=48)	3-4 (n=51)	5-6 (n=29)	7-8 (n=21)	0-2 (n=18)	3-5 (n=56)	6-8 (n=40)	9-12 (n=19)
TDR[a], mean months	9.2	7.9	5.6	7.8	3.2	8.0	6.6	8.4
Cumulative dose until dose reduction, median g (min, max)	686 (44, 4,048)	624 (56, 4,096)	380 (36, 1,540)	752 (40, 6,016)	729 (44, 2,968)	466 (80, 4,096)	394 (36, 1,540)	1,112 (40, 6,016)

TDR: time to dose reduction; UCDAI: Ulcerative Colitis Disease Activity Index; [a]TDR (months) was measured from the date of first dosing to the first date of dose reduction (event) or the study completion date. The data collected for 6 patients after date of recurrence (*i.e.* withdrawal criteria) was excluded from the efficacy analysis.

lowest for extensive UC [median (min, max) 476 (40, 6,016) g vs 692 (76, 4,048) g for left-sided UC and 632 (36, 2,968) g for proctosigmoiditis]. TDR was similar in those with (mean 8.7 months) and without (8.2 months) extraintestinal manifestations, with the cumulative dose lower in the former [median (min, max) 448 (244, 1,480) g] than the latter [622 (36, 6,016) g].

Forty-three patients (28.5%) experienced a disease recurrence, of whom 18 (41.9%) had a dose reduction. Of the 108 patients without relapse, 30 (27.8%) had a dose reduction. TDR (mean 4.1 vs 8.8 months; p=0.09) and cumulative dose until dose reduction [median (min, max) 492 (76, 1,612) g vs 675 (36, 6,016) g; p=0.36] did not differ significantly between patients with and without recurrence.

Recurrence occurred most often in patients that received the initial dose for >3-6 months (54.1%), with time to recurrence longest in those with >3 months therapy duration (Table III). Adjusted analyses showed that time to recurrence was significantly reduced by an induction therapy duration of >6 versus >3-6 months in newly diagnosed patients (HR=0.23, 95%CI: 0.09-0.56; p<0.05), but not relapsed patients (HR=0.12, 95%CI: 0.01-1.39) (Supplementary file).

Patients on ≥4 g/day had a significantly reduced recurrence rate compared with those initiated on 2-<4 g/day (26.6% vs 62.5%, respectively; p=0.04). Compared to patients on >3-6 months therapy duration, those on mesalazine for >6 months had a significantly reduced risk of recurrence (HR=0.19, 95%CI: 0.08-0.46; p<0.05), which was particularly apparent in those on ≥4 g/day (Fig. 2). A higher proportion of patients on treatment for >6 than ≤6 months received rectal mesalazine therapy, although this difference was not statistically significant (42.9% vs 30.7%, respectively; p=0.12).

The aUCDAI score at 12 months/final visit was significantly higher in patients who received the initial dose for ≤2 than for >6 months (mean 3.2 vs 1.1, respectively; p<0.01) (Table III).

In total, 9 (12.7%) patients discontinued due to non-compliance. No statistically significant differences in high, medium, or low treatment compliance were found between patients receiving a single versus multiple doses per day. High self-reported adherence across all timepoints was reported for patients on once daily (scores ≥8) and twice daily (≥9.5) regimens (Supplementary file).

The majority of patients rated their treatment as 'excellent' or 'good' (month 1: 89.2%; 3: 92.4%; 9: 91.1%; 12: 69.2%) (Supplementary file). Most patients had a good/excellent experience (73%) using prolonged-release mesalazine sachets and tablets. Treatment outcome (61.9%), tolerability (80.2%), and administration (83.3%) were defined predominantly as good/excellent at 12 months, with similar results reported by physicians (Supplementary file). Patients' preferred formulation was granules (66.1%), given once daily (77.7%).

Unemployment was relatively stable at 26-30% throughout the study as was the average hours worked per week (mean ~35 hours across all visits) (Table IV). At month 3, patients reported significantly improved work productivity from baseline, in terms of hours of work lost (p<0.01), impact

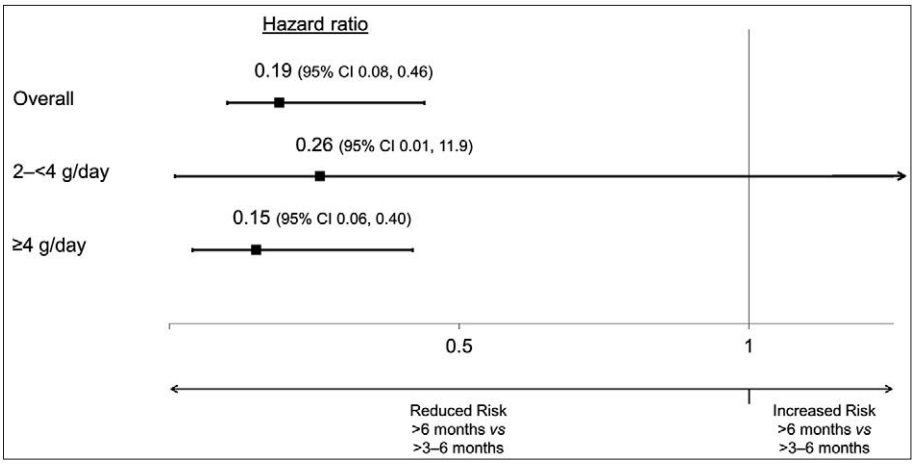

Fig. 2. Time-to-event analysis of recurrence in patients on >6 months versus >3-6 months induction therapy (Efficacy Analysis Set). Cox regression was used to adjust for imbalanced factors and to compare the difference between dose duration groups. CI: Confidence interval.

Table III. Recurrence rates, UCDAI score (12 months) and endoscopic appearance (Visit 1) by duration of induction therapy (Efficacy Analysis Set)

	Dose Duration			
	≤2 Months (n=37)	>2-3 Months (n=14)	>3-6 Months (n=37)	>6 Months (n=63)
Recurrence[a], n (%)	6 (16.2)	5 (35.7)	20 (54.1)	12 (19.1)
Time to recurrence, mean months	8.0	4.5	10.8	10.6
aUCDAI - Total Score at 12 months/final visit Mean (standard deviation)	3.2 (2.9)	1.6 (2.1)	2.2 (2.7)	1.1 (1.7)[b]
Endoscopic appearance of mucosa at day 1[b], n (%)				
0: normal	2 (6.3)	0 (0)	1 (2.9)	3 (5.7)
1: Erythema, decreased vascular pattern, mild friability, minimal granularity	17 (53.1)	9 (69.2)	25 (71.4)	25 (47.2)
2: Friability, marked erythema, absent vascular pattern, erosions, pus	10 (31.3)	4 (30.8)	8 (22.9)	20 (37.7)
3: Ulceration, spontaneous bleeding	3 (9.4)	0 (0)	1 (2.9)	5 (9.4)

[a] Unadjusted for baseline factors; data missing for 18 patients; [b]p<0.01 vs ≤2 months (other comparisons between dose duration groups were not significant); UCDAI: Ulcerative Colitis Disease Activity Index; aUCDAI: abbreviated UCDAI; For the rest of the abbreviations see Tables I and II. See Supplementary Table II for demographics of each dose duration group.

on work productivity (p<0.01), and impact on other daily activities (p<0.01). These improvements were maintained through month 12/final visit, albeit slightly lower [significant for impact on work productivity (p<0.01) and impact on other daily activities (p<0.01)].

Twenty-three patients (15.2%) experienced AEs with a possible relationship with mesalazine. Two (1.3%) of these patients had serious AEs (one patient experienced anorexia, weight loss, headache, and diarrhoea; the other night sweats, snoring, puffy eyes, decreased taste, dry mouth, increased dreaming, and palpitations). Overall, the most reported AEs were headache (4.6%) and diarrhoea (2.6%). In 13 patients (8.6%), an AE resulted in a dose change.

Five patients (3.3%) discontinued due to an AE, four of which were possibly-related to treatment.

DISCUSSION

In this study of Dutch clinical practice, 151 patients with mild-to-moderate UC spent an average of 8.3 months on high dose therapy with prolonged-release mesalazine before dose reduction. Most patients (79.5%) were initiated on ≥4 g/day and those that received this dose had a significantly lower chance of recurrence compared with those on 2-<4 g/day (26.6% vs 62.5%, respectively; p=0.04). Disease activity was also found to be significantly reduced at the end of follow-up (≤12 months) in patients who received the initial dose for >6 than ≤2 months (aUCDAI, mean 1.1 vs 3.2, respectively; p<0.01). Most strikingly, after controlling for confounding factors, patients on ≥4 g/day for >6 months had the lowest risk of recurrence (85% reduced risk vs 3-6 months). In a previous retrospective study, an improvement in remission rate at 1 year of 14.7% for mild and 25.3% for moderate-to-severe UC was reported when the induction dose was maintained rather than reduced [6]. Other groups have also observed that long-term treatment with mesalazine (≥4 g/day) may be more effective than short-term treatment for maintenance of remission [7, 9].

Interestingly, in our study, there was no major influence of endoscopic appearance, presence of extraintestinal manifestations, and disease extent at baseline on the duration of induction treatment and cumulative dose until dose reduction. On one hand, it is perhaps not surprising that these baseline factors did not materially influence the decision on how long to maintain the induction dose, as this would depend on multiple factors, including, importantly, patient response to therapy. On the other hand, it might be reasonable to expect patients with a worse endoscopic appearance at baseline, for example, to be treated longer with a high(er) dose. A higher UCDAI score,

Table IV. Summary of effect of UC on work-related productivity (Efficacy Analysis Set).

Work productivity question	Day 1/Baseline	Month 3	Month 12
Currently employed, n (%)	110/151 (72.8)	76/103 (73.8)	85/122 (69.7)
Mean weekly hours worked (SD)	34.7 (11.8)	35.1 (11.9)[a]	34.4 (12.4)[a]
Median weekly hours worked (range)	36.0 (2-70)	36.0 (10-70)	36.0 (6-70)
Mean hours of work lost due to UC in last week (SD)	5.4 (11.4)	1.4 (5.8)[b]	2.7 (8.1)[a]
Median hours of work lost due to UC in last week (range)	0 (0-44)	0 (0-32)	0 (0-40)
Mean rating of impact of UC on work productivity (SD)	3.6 (3.4)	1.4 (2.6)[b]	2.0 (3.2)[b]
Median rating of impact of UC on work productivity (range)	3.0 (0-10)	0 (0-10)	0 (0-10)
Mean rating of impact of UC on other daily activities (SD)	4.0 (3.4)	1.5 (2.5)[b]	2.4 (3.3)[b]
Median rating of impact of UC on other daily activities (range)	4.0 (0-10)	0 (0-8)	0 (0-10)

[a]Not significant vs Day 1/baseline; [b]p<0.01 vs Day 1/baseline; SD: standard deviation; UC: ulcerative colitis. Scale for work productivity/daily activity 0-10, whereby 0 = UC had no effect on my work productivity/daily activity to 10 = UC completely prevented me from working/carrying out any daily activities. For the rest of the abbreviations see Tables I and II.

rather than aUCDAI score at baseline, however, did seem to increase induction duration. A plausible explanation for this is that the UCDAI was utilised primarily in new patients, whereas the aUCDAI was applied in new and relapsed patients; physicians are generally more likely to keep relapsed patients on a higher dose for a longer time irrespective of disease severity. Related data came from a Japanese study [8], which found that maintaining the induction dose is more likely to maintain clinical remission regardless of endoscopic healing.

There appeared to be clear intent by physicians to maximise (optimise) the dose of oral mesalazine to induce remission. By 3 months after initiation, nearly all patients (94.7%) were on ≥4 g/day. Higher mesalazine doses have been demonstrated to increase remission rates. In a meta-analysis of 48 induction trials, mesalazine >3 g/day was found to be superior to 2-3 g/day at inducing remission (odds ratio for failure to induce remission: 0.78, 95%CI: 0.66-0.93) [13]. Surprisingly, however, nearly two-thirds (64.2%) of patients in our study did not receive rectal treatment, which is contrary to current guidelines [3, 10]. Combined oral and rectal treatment has been shown to be even more effective than high dose (>3 g/day) oral monotherapy at inducing remission (surface under the cumulative ranking [SUCRA] probabilities 0.99 vs 0.82, respectively) [12]. This perhaps indicates that the decision to not prescribe rectal treatment was more about patient acceptability and belief that a high dose (≥4 g/day) of oral mesalazine alone was sufficient to induce remission. Of note, there was no significant difference in the proportion of patients who received rectal treatment in the >6 versus ≤6 months dosing groups (42.9% vs 30.7%, respectively; p=0.12). For patients not achieving disease control despite optimised oral mesalazine therapy, introduction of rectal treatment should be encouraged.

Treatment acceptability for prolonged-release mesalazine, as reported by patients (and physicians), was high, mostly scored as good-to-excellent for overall rating (69-92%) and experience (73%), treatment outcome (61.9%), tolerability (80.2%), and administration (83.3%). The number of patients reporting possible treatment-related AEs was also low (15.2%), providing further confirmation that mesalazine is well-tolerated [4, 5]. The positive attitude of patients towards mesalazine was further reflected in the low rate of discontinuations due to non-compliance (12.7%) and high levels of self-reported adherence to therapy (8.5-10 out of 10). Adherence rates have been reported to be lower at around 40-60% in some studies [14, 15]. It may be that the self-reported nature of our results and the cohort make-up (e.g. median age was 46 years, whereas non-adherence has been associated with younger age [14]) produced overly optimistic adherence results. It has been reported that improvements in adherence can be made by a switch from tablets to granules in some patients [16]. Once daily dosing of oral mesalazine has also been shown to improve adherence [17]. This resonates with our data, where patients' preferred formulation was granules (66.1%) given once daily (77.7%).

There are limited data on the impact of mesalazine treatment on work productivity in patients with UC, with one clinical trial reporting significant improvements (measured by WPAI) across 1 year of treatment [18]. Our results confirm these findings in a real-world setting, with significant improvements found in terms of hours of work lost, impact on work productivity, and impact on other daily activities. These improvements appeared to reduce with time; however, this was likely due to inclusion of data from patients with flares who escalated to another therapy and left the study prematurely.

Our study observed a mixed population of newly diagnosed (71.5%) and relapsed (28.5%) patients, which might have influenced the results. Other limitations included that it was not adequately powered to fully assess differences between the dose duration groups and that adherence was assessed only by patients' self-reporting.

CONCLUSIONS

This study confirms that oral prolonged-release mesalazine is an effective and well-tolerated induction treatment for UC and is highly rated by patients. Most importantly, this study provides real-world evidence and support for an induction dose of ≥4 g/day that should be continued for at least 6 months.

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Authors' contribution: R.W., M.R., A.B., J.K., K.B.. conceived and designed the study. RW., M.R., A.B., J.K., K.B., J.J., A.v.d.M., E.K., L.W., R.O., G.B., V.K., T.T., A.v.D., M.v.N., IM., S.V., H.L. collected the data. R.W., A.B., J.K., L.W. critically revised the manuscript. All the authors approved the final version of the paper.

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