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Assessing the Clinical and Endoscopic Efficacy of Extended Treatment Duration with Different Doses of Mesalazine for Mild-to-Moderate Ulcerative Colitis beyond 8 Weeks of Induction

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Keywords
Ulcerative colitis · Mesalazine · Disease extent · Maintenance · High dose · Faecal calprotectin · Mayo endoscopic subscore

Abstract
Introduction: High-strength mesalazine formulations play an important role in providing a convenient option to increase the dose in ulcerative colitis (UC) patients and therefore avoiding the switch to another therapeutic class. Higher doses of mesalazine may be required during periods of remission in order to prevent relapse. ***Aim:*** The aim of the study was to investigate clinical outcomes of three mesalazine maintenance doses adapted for post induction response. ***Methods:*** In this post hoc analysis, 675 UC patients entered an open-label extension study for a total of 38 weeks (including 8–12 week induction period with 3.2 g/day mesalazine). After the induction period, they were separated into three groups: remitters (in clinical and endoscopic remission), responders (decrease in Partial Mayo Clinic Score of ≥2 points and ≥30% from week 0), and nonresponders (failed to achieve endoscopic or clinical response at week 8) and received 1.6 g/day, 3.2 g/day, or 4.8 g/day of mesalazine (using a new 1,600 mg mesalazine tablet), respectively. ***Results:*** 133/202 (65.8%), 108/274 (39.4%), and 59/199 (29.6%) patients achieved clinical and endoscopic remission at week 38 with 1.6 g/day, 3.2 g/day, and 4.8 g/day, respectively. At week 38, 142/202 (70.3%), 93/274 (33.9%), and 61/199 (30.7%) patients achieved clinical remission (stool score of 0 and rectal bleeding score of 0) with 1.6 g/day, 3.2 g/day, and 4.8 g/day, respectively. ***Conclusions:*** Patients partially responding or not responding to an initial induction dose of 3.2 g/day mesalazine could benefit from an extended treatment period at the same dose, or an increase to 4.8 g/day in an attempt to achieve combined clinical and endoscopic remission.

Introduction

Ulcerative colitis (UC) is a lifelong and unpredictable disease, with a significant negative impact on patients' quality of life [1, 2]. Even with advances in treatment options, a gap remains between the elusive outcome patient's desire and reality.

From a physician's perspective, there has been a change in treatment goals for UC patients. The field has progressed from symptom control to emphasis on mucosal healing. Mucosal healing is fundamental because it predicts long-term remission, reduces the risk of dysplasia or cancer, lowers hospitalisation and surgery rates,

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and improves quality of life, thus modifying the natural course of UC by slowing down, or even preventing, disease progression [3].

The distinction between induction and maintenance therapy is convenient for labelling, guidelines, and clinical studies, but, in reality, patients often find themselves somewhere in between. As a result, in clinical practice, not all patients, in particular, those with more severe disease will achieve full control of symptoms following an 8-week induction course of mesalazine [4, 5]. In this situation, high-strength mesalazine formulations play an important role in providing a convenient option to increase the dose and avoid switching to another therapeutic class.

Unlike corticosteroids, with which approximately 50% of patients experience side effects [6], the mesalazine safety profile for both short- and long-term treatment duration is favourable [7, 8], and virtually, all patients tolerate the treatment. High-dose mesalazine (e.g., ≥4 g/day) has been administered in a number of studies for longer durations than used during the average induction period. In a 12-month open-label study, the intention-to-treat analysis revealed persistent remission in 75% of patients taking 4.8 g/day and in 64.2% of those taking 2.4 g/day. Patients with extensive disease benefitted most: 90.9% versus 46.7% in the 4.8 and 2.4 g/day groups, respectively ($p = 0.0064$) [9]. This observation was confirmed in a study by Takeshima et al. [10]; an open-label retrospective study which demonstrated that long-term continuous treatment with high-dose mesalazine (4.0 g/day) may be more effective than short-term treatment for maintenance of remission in UC patients. For some individuals, higher doses of mesalazine may be required during periods of remission in order to prevent relapse.

In the current analysis, the mesalazine maintenance dose received was determined by patients post-induction status. The maintenance dose was either 1.6 g/day for 26 weeks (in patients who reached clinical and endoscopic remission after 12 weeks induction treatment), 3.2 g/day (in those exhibiting a response after 12 weeks induction treatment) for 26 weeks, or 4.8 g/day (in nonresponders after 8 weeks induction treatment) for 30 weeks.

Materials and Methods

This is a post hoc analysis of a phase 3, randomised, active-controlled, double-dummy, multicentre, non-inferiority induction trial with an open-label extension (OLE) in patients with mild-to-moderate active UC at 179 centres in Europe and Canada [5]. The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice Guidelines and is registered at Clinicaltrials.gov (NCT01903252).

Design

Randomised Double-Blind Induction Phase

In the largest mesalazine induction trial reported to date, 737 mild-to-moderate UC patients (mean Mayo score 7.7 at screening assessed by central reading) completed an 8-week randomised induction period with 3.2 g of oral mesalazine, administered as two 1,600 mg tablets each morning ($n = 370$) or four 400 mg tablets twice daily ($n = 367$). To preserve blinding, all patients took the same number of identically appearing 1,600 mg or 400 mg placebo tablets. The results of the 8-week double-blind randomised induction (DBRI) period were previously published [5].

Maintenance Phase – Dose Adjusted according to Remission Status

Patients' maintenance mesalazine dose was assigned according to the post-induction remission status. Subjects who failed to show a response to 3.2 g mesalazine 1,600 mg at the week 8 visit were enrolled in an OLE-extended induction phase and increased their daily dose of mesalazine 1,600 mg from 3.2 g/day to 4.8 g/day (three 1,600 mg tablets in the morning) for eight additional weeks. Those subjects who failed to exhibit a response at week 16 were withdrawn from the study, while subjects (nonresponder group) exhibiting a clinical response or remission continued the OLE maintenance phase at the same dose of 4.8 g/day of mesalazine 1,600 mg for an additional 22 weeks. Total duration of exposure to 4.8 g/day was 30 weeks. Subjects were prohibited to take medications that were prohibited at study baseline during study participation, with the exception of antibiotics to treat illnesses unrelated to UC. These prohibited drugs included oral and rectal mesalazine, oral and systemic steroids, infliximab, immunosuppressants, anti-diarrhoeals, and antibiotic use related to UC. Subjects who required the initiation of prohibited medication were considered treatment failures and were withdrawn from the study. Therefore, for patients who responded to additional 8-week 4.8 g mesalazine treatment and that were allowed into the OLE study, no rescue therapy was provided.

Patients in clinical remission (stool frequency and rectal bleeding subscores of 0) at week 12 (end of the double-blind period) were assigned to open-label mesalazine 1.6 g/day OD (one 1,600 mg tablet per day) for 26 weeks (remitter group). Patients showing a clinical response (decrease from baseline in the Mayo score of ≥3 points and >30% of the baseline score, with an accompanying decrease in the rectal bleeding subscore of ≥1 point or an absolute rectal bleeding subscore of 0) at week 12 were assigned to open-label 3.2 g/day OD (two 1,600 mg tablets per day) for 26 weeks (responder group).

Study Population

Patient Characteristics

At baseline, the mean Mayo score was 7.7. The majority of subjects either had proctosigmoiditis (44.2%) or left-sided colitis (35.1%). An overview of patient characteristics is described in online supplementary Table 1 (for all online suppl. material, see https://doi.org/10.1159/000531372).

Inclusion/Exclusion Criteria

The main inclusion criteria for entry into OLE were (1) the attendance to the week 8 visit and completion of disease activity assessments prior to enrolment in the OLE at week 12 (responders or remitters) or week 8 (nonresponders); (2) at least 75% compliance with study medication in the DBRI phase. The exclusion criterion from OLE was a withdrawal from the DBRI phase prior to

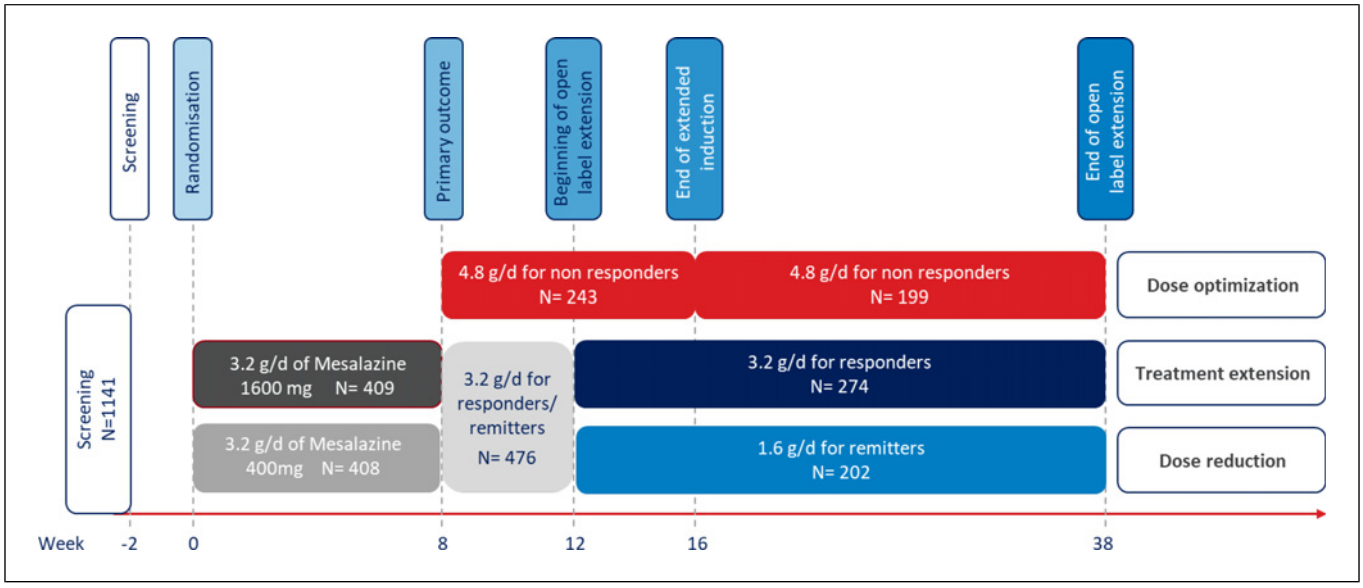

Fig. 1. Patient disposition. Mild-to-moderate UC patients were grouped according to their remission status after 8 weeks of treatment with 3.2 g/day of mesalazine.

the week 8 visit. In the OLE study, 199 patients were treated with 4.8 g/day, 274 patients were treated with 3.2 g/day, and 202 patients were treated with 1.6 g/day (see Fig. 1).

Efficacy and Safety Evaluation

The main objective of this OLE post hoc analysis was to assess the efficacy and safety of mesalazine 1,600 mg (with a daily dose of 1.6 g/day or 3.2 g/day) over a 26-week period in subjects achieving endoscopic and clinical remission or exhibiting a response during the initial phase of the DBRI study. Clinical and endoscopic remission, endoscopic remission, and clinical remission were assessed at the final visit (week 38). A secondary objective was to assess whether a dose escalation to 4.8 g/day of mesalazine 1,600 mg was effective in inducing clinical and endoscopic remission, endoscopic remission, and clinical remission in subjects who failed to respond to an initial induction dose of 3.2 g/day.

Faecal Calprotectin

Stool samples were collected at screening and weeks 8, 12, 16, and 38 for analysis of faecal calprotectin levels. A cut off of 150 µg/g was chosen as per the recommendations from the "CORE-IBD: A Multidisciplinary International Consensus Initiative to Develop a Core Outcome Set for Randomized Controlled Trials in Inflammatory Bowel Disease" [11].

Results

Clinical and Endoscopic Efficacy at Week 38 in the Entire Study Cohort

Independent of treatment assignment, of the 675 patients, 44.4% of all randomised patients were in clinical and endoscopic remission at week 38. At week 38, 53.8% of all patients were in endoscopic remission (Mayo endoscopic score (MES) ≤1) (shown in Fig. 2). Regardless of disease extent (including patients with distal disease), similar endoscopic remission rates were achieved (shown in Fig. 3).

Faecal Calprotectin Changes in the Entire Study Cohort

Faecal calprotectin levels at different timepoints of the study are shown in Figure 4. The median calprotectin levels, at week 38, were 29 µg/mg and 67 µg/mg when the Mayo endoscopic subscore was 0 or 1, respectively. The median calprotectin, at week 38, were 238 µg/g and 278 µg/g when the Mayo endoscopic subscore was 2 or 3, respectively. These results were similar to week 8 (shown in Fig. 5).

Endoscopic Remission at Week 38 by Responder Status at Week 8

At week 38, 133/202 (65.8%), 108/274 (39.4%), and 59/199 (29.6%) patients achieved clinical and endoscopic remission with 1.6 g/day, 3.2 g/day, and 4.8 g/day, respectively. At week 38, 142/202 (70.3%), 93/274 (33.9%), and 61/199 (30.7%) patients achieved clinical remission (stool score of 0 and rectal bleeding score of 0 with 1.6 g/day, 3.2 g/day, and 4.8 g/day, respectively (shown in Fig. 6a). At week 38, 143/202 (70.8%), 138/274 (50.4%), and 82/199 (41.2%) patients achieved endoscopic remission (MES ≤1) with 1.6 g/day, 3.2 g/day, and 4.8 g/day, respectively (shown in Fig. 6b). Seventy six (37.6%), 64 (23.4%), and 27 (13.6%) achieved a MES of 0 at week 38 with 1.6 g/day, 3.2 g/day, and 4.8 g/day, respectively.

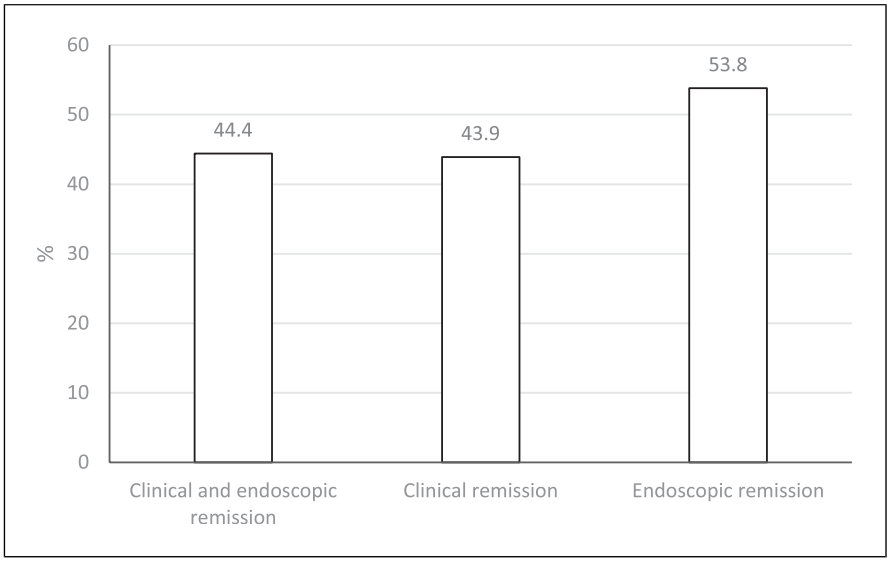

Fig. 2. Efficacy at week 38 in the total study population (n = 675).

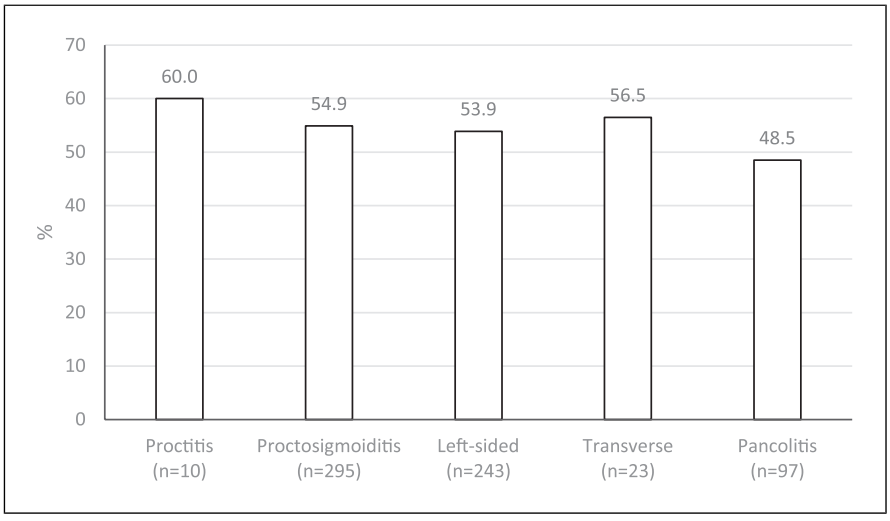

Fig. 3. Endoscopic remission (MES ≤1) by history of disease extent.

Faecal Calprotectin Changes by Responder Status at Week 8

In the remitter group, although the maintenance dose was reduced from 3.2 g/day to 1.6 g/day, 66.8% (n = 131) and 67.0% (n = 168) of the patients maintained a faecal calprotectin value below 150 μg/g at week 8 and week 38 of the study, respectively. In the responder group, the maintenance dose remained at 3.2 g/day during the whole duration of the study, 48.9% (n = 133) and 58.8% (n = 145) of the patients maintained a faecal calprotectin value below 150 μg/g at week 8 and week 38 of the study, respectively. In the nonresponder group, the maintenance dose was increased to 4.8 g/day during the maintenance period, 23.5% (n = 60) and 42.8% (n = 89) of the patients maintained a faecal calprotectin value below 150 μg/g at week 8 and week 38 of the study, respectively (shown in Fig. 7). The median calprotectin levels were below 100 μg/g when the Mayo endoscopic subscore was 0 or 1 and above 200 μg/g when the Mayo endoscopic subscore was 2 or 3.

Safety Data at Week 38

Treatment emergent adverse events were similar between the remitter, responder, and nonresponder treatment groups (29.2%, 26.6%, and 19.1%, respectively) (shown in online suppl. Table 2). Only one case of acute kidney injury (0.1% of 817 study subjects) occurred during the 38-week study period. The investigator considered the renal failure not related to study medication.

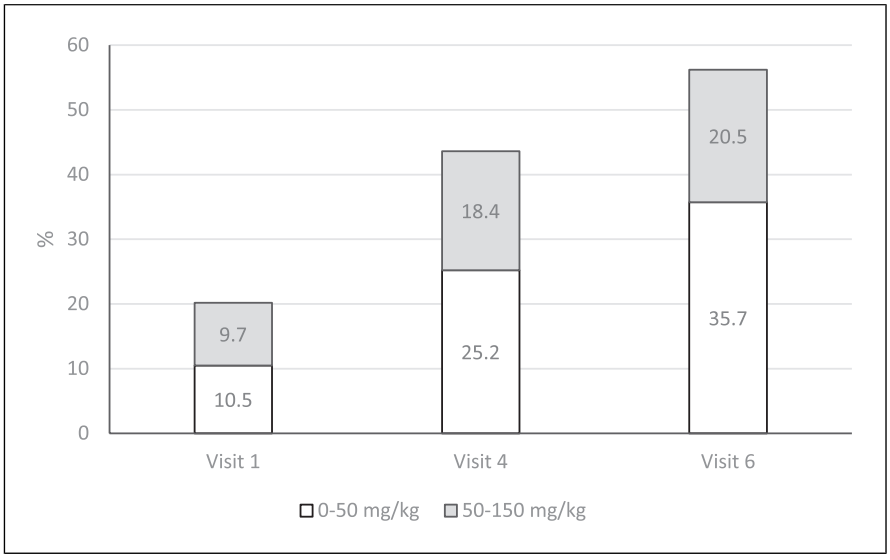

Fig. 4. Rate of patients with faecal calprotectin value below or equal to 150 mg/kg at visit 1 (screening), visit 4 (end of induction period, week 8), and visit 6 (end of maintenance period, week 38) in full population.

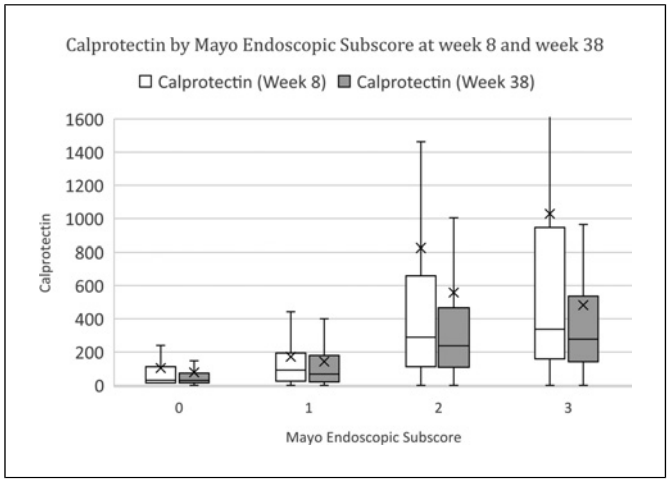

Fig. 5. Calprotectin by Mayo endoscopic subscore at visit 4 (end of induction period) and visit 6 (end of maintenance period). *The cross is for the mean values and the horizontal bar is for the median values.*

Discussion

The maintenance phase of the OLE was designed to approximate how patients are treated in clinical practice. Those patients in clinical and endoscopic remission after 8 weeks of 3.2 g/day mesalazine decreased their dose to 1.6 g/day, and those who were not adequately responding increased their dose to 4.8 g/day. After 38 weeks of treatment, 133 (65.8%), 108 (39.4%), and 59 patients (29.6%) achieved clinical and endoscopic remission with 1.6 g/day (remitters group), 3.2 g/day (responders group), and 4.8 g/day (nonresponders group), respectively. The results of the OLE demonstrate the importance of dose optimisation; firstly, the importance of being in clinical and endoscopic remission (i.e., a "remitter") before lowering the dose of mesalazine and hence entering the maintenance treatment phase. High rates (53.9%) of endoscopic remission were also achieved in patients with left-sided (distal) disease extent.

Secondly, the results demonstrate that increasing the dose to 4.8 g/day in those who have not responded adequately to an initial standard dose of 3.2 g/day mesalazine over 8 weeks (i.e., a "non-responder") can still induce remission in just under a third of patients. This group can be seen as "slow" responders, and further investigation is warranted in the treatment of this patient population. Moving straight from mesalazine to biologics or other novel agents is an effective option in this group that bypasses corticosteroid use. However, in most jurisdictions, second-line treatments are generally reserved for those who do not tolerate or have not responded to steroids [11]. A long-term cohort study (with over 20 years of follow-up) of UC patients treated with mesalazine demonstrated that the cumulative probability to remain free of second-line therapies after 20 years of follow-up was 65%, with the median time to treatment escalation being 2 years after diagnosis. This highlights the importance of close follow-up of patients in this early phase of the disease [12]. Therefore, prolongation of 4.8 g/day with mesalazine is a clinical option in certain circumstances as this reduces the likelihood that corticosteroids or biologics need to be utilised, which in comparison to mesalazine, have unfavourable toxicity profiles [13].

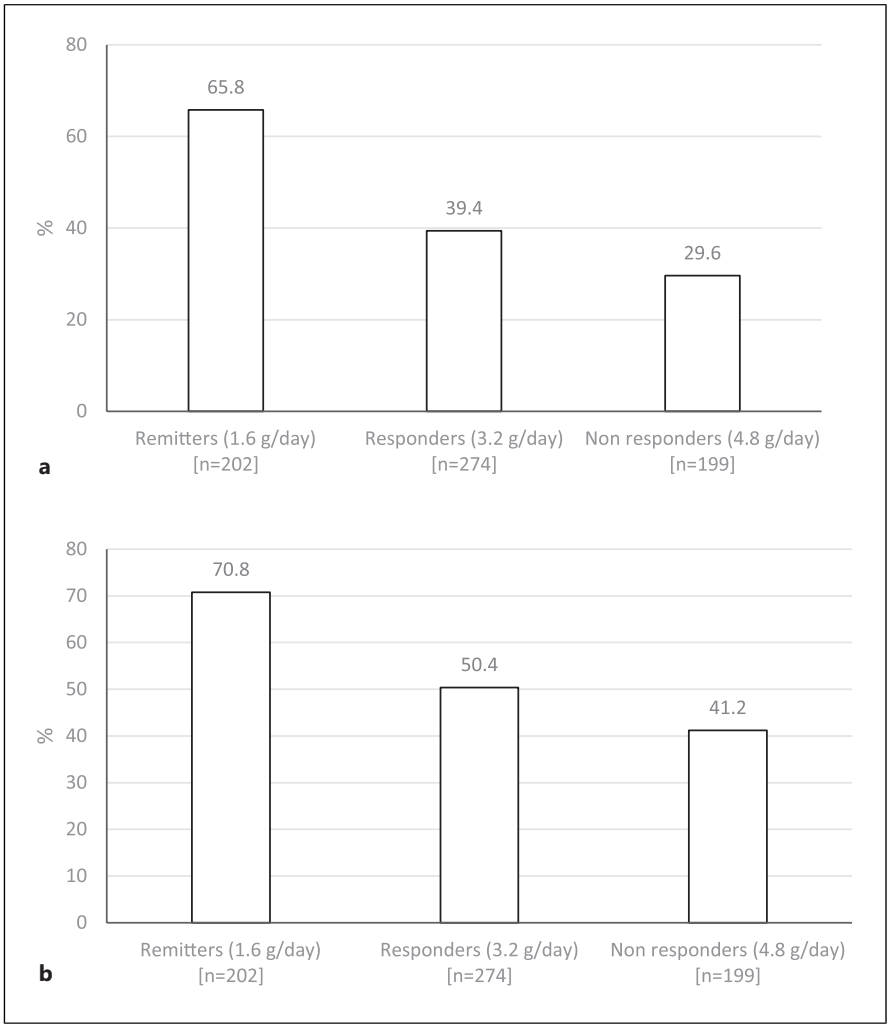

Fig. 6. a Clinical and endoscopic remission at week 38 by status after 8 weeks of induction with 3.2 g/day of mesalazine. **b** Endoscopic remission at week 38 by status after 8 weeks of induction with 3.2 g/day of mesalazine.

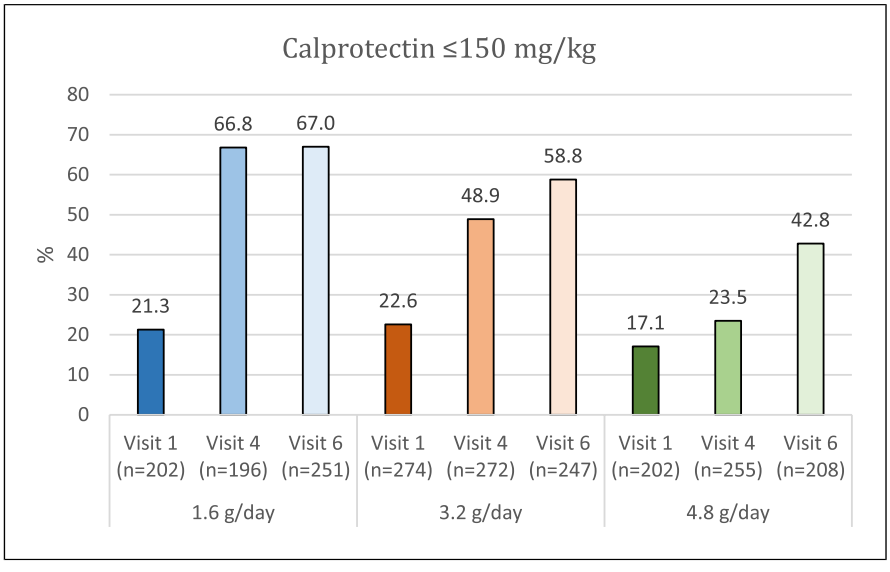

Fig. 7. Rate of patients with faecal calprotectin below or equal to 150 mg/kg at visit 1 (screening), visit 4 (end of induction period), and visit 6 (end of maintenance period), based on the maintenance dose administered.

With regards to the most effective mesalazine maintenance dose, a recent meta-analysis compared the efficacy and tolerability of candidate agents in patients with extensive or left-sided mild-to-moderate UC. High (>3 g/day), standard (2–3 g/day), and low dose (<2 g/day) mesalazine therapies were all superior to placebo [14]. Conventionally, the recommended dose of oral mesalazine to maintain remission is ≥ 2 g/day [15]. However, there is substantial evidence to suggest that 1.6 g/day is sufficient to maintain patients in remission with UC. In the OLE "remitter" group, 65.8% of patients maintained remission after 38 weeks of treatment with 1.6 g/day. Furthermore, D'Haens et al. [16] in a randomised, double-blind, 6 month active control trial demonstrated that a maintenance dose of 2.4 g/day once daily was non-inferior to twice daily 0.8 g/day (total dose 1.6 g/day) with a endoscopic remission rate at 6 months of 83.7 and 81.5%, respectively.

The efficacy of low-dose mesalazine for patients who have reached remission has also been demonstrated by Paoluzi et al. [17] in a randomised, single-blind, open-label study, reporting no statistical difference between Asacol 2.4 g/day compared to 1.2 g/day. Seventy percent of patients in the Asacol 2.4 g/day group relapsed compared to 74% in the 1.2 g/day group (RR 0.95; 95% CI: 0.78–1.16). Together, these studies demonstrate that low-dose mesalazine (e.g., <2 g/day) can maintain UC patients in clinical remission.

The negative consequences of non-adherence have been reiterated in numerous publications [18–20]. Non-adherence with mesalazine medication has been found to be associated with increased risk of clinical relapse among patients with quiescent UC [18]. Khan et al. [21] showed no differences in the long-term risk of UC flares between patients taking low versus high daily mesalazine dose, as long as patients have a medium to high level of adherence. This reiterates the importance of simplicity, which is delivered by high-strength tablets and once daily dosing regimens, as shown by the presented data of mesalazine 1,600 mg. Higher strength formulations offer the advantage of a lower tablet burden (in addition to once daily administration) as a means of achieving long-term adherence in clinical practice and thereby continued treatment success. These data suggest that adherence rather than dose is an important determinant in preventing disease flares [21]. In addition, a recent nationwide study also demonstrated that once daily dosing is also preferred [22]. A maintenance dose of 1.6 g/day with mesalazine 1,600 mg results in only one mesalazine tablet needed to be taken daily. This dose has also been shown to be well-tolerated and non-inferior to once daily MMX mesalazine for the maintenance of endoscopic remission in patients with UC [16].

Prolonged treatment at the same dose (e.g., 1.6 g/day, 3.2 g/day, or 4.8 g/day) results in improvement in endoscopic remission (MES ≤1) scores at week 38 (70.8%, 50.4%, and 41.2%, respectively). Given that greater than 60% of all UC patients have a disease course with mild clinical symptoms after a period of flare, it is likely that a large proportion of these patients can be managed with 5-ASA without the need for further escalation to advance therapies [23, 24]. This justifies that continued treatment with mesalazine should be attempted first before escalation to other treatment options (e.g., corticosteroids and biologics).

Biomarker data with faecal calprotectin support our observations. Improvement in faecal calprotectin, a reliable surrogate marker for disease activity in UC was also observed in all dosing groups, with 67.0%, 58.8%, and 42.8% of patients achieving a faecal calprotectin value of ≤150 mg/kg with 1.6 g/day, 3.2 g/day, and 4.8 g/day, respectively at week 38.

This open-label study has its limitations due to lack of control and blinding. However, despite this, the induction phase is one of the largest mesalazine studies to date, with central reading of endoscopy scoring.

Conclusion

This study demonstrates that in mild-to-moderate UC patients who achieve clinical and endoscopic remission after 8 weeks, low-dose mesalazine (1.6 g/day) is effective to maintain remission. While, patients partially responding or not responding to an initial induction dose of 3.2 g/day mesalazine could benefit from an extended treatment period at the same dose, or an increase to 4.8 g/day in an attempt to achieve total clinical and endoscopic remission. Long-term high-dose mesalazine (4.8 g/day) had similar safety profile to standard dose (3.2g/day) and low-dose mesalazine (1.6 g/day).

Statement of Ethics

The study, from which the data analysed in this post hoc analysis were derived, was conducted in compliance with current International Conference on Harmonization (ICH) Good Clinical Practices (GCP) guidelines relating to Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs) in each participating country/study site. The study protocol and any amendments were reviewed by an IEC/IRB prior to the initiation of any study procedures. This retrospective review of patient data did not require ethical approval in accordance with local/national

guidelines. Written informed consent from participants was not required in accordance with informed consent of study TP0503. The study is registered at clinicaltrials.gov (NCT01903252).

Conflict of Interest Statement

Geert D'Haens has received consulting fees from AbbVie, ActoGeniX NV, Amgen, AM-Pharma BV, Boehringer Ingelheim, ChemoCentryx, Centocor/Jansen Biologics, Cosmo Technologies, Elan/Biogen, enGene Inc, Ferring Pharmaceuticals, Gilead Sciences, Given Imaging, GSK, Merck Research Laboratories, Merck Serono, Millenium Pharmaceuticals, Novo Nordisk, NPS Pharmaceuticals, PDL Biopharma, Pfizer, Receptos, Salix Pharmaceuticals, Schering-Plough, Shire Pharmaceuticals, Sigmoid Pharma Ltd, Teva Pharmaceuticals, Tillotts Pharma AG, and UCB Pharma; research grants from AbbVie, GSK, Falk, Janssen, Merck, and Given Imaging; and lecture/speakers bureaux fees from AbbVie, Jansen, Merck, Takeda, UCB, and Shire. Ekaterina Safroneeva, Helen Thorne, and Raphaël Laoun are employees of Tillotts Pharma AG.

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Author Contributions

G.D., E.K., H.T., and R.L. participated equally in the design of the work; the acquisition, analysis, and interpretation of data, participated equally in drafting and reviewing the work, approved the final version to be published, and are accountable and would ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

Due to data sensitivity, the data that support the findings of this study are not openly available to the public. Further enquiries can be directed to the corresponding author.

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