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Original Article

Once- Versus Twice-daily Mesalazine to Induce Remission in Paediatric Ulcerative Colitis: A Randomised Controlled Trial

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Abstract

Background: Trials in adults suggested that, in ulcerative colitis [UC], once-daily [OD] dosing of 5-ASA [5-amino salicylic acid] may be as or more effective than twice-daily [BD] dosing. In this induction of remission, investigator-blinded, randomised controlled-trial, we aimed to compare effectiveness and safety of once- versus twice-daily mesalazine in paediatric UC.

Methods: Children, aged 4–18 years with a PUCAI [Paediatric Ulcerative Colitis Activity Index] of 10–55 points at inclusion, were randomised in blocks of six with blinded allocation to OD or BD mesalazine, using a weight-based dosing table. The primary outcome was mean PUCAI score at Week 6.

Results: A total of 83/86 randomised children were eligible and analysed: 43 in the OD group and 40 in the BD group (mean age 14 ± 2.7 years, 43 [52%] males, 51 [62%] extensive colitis). The groups did not differ with regard to disease activity or any other parameter at baseline. There was no difference in median PUCAI score between the OD group and BD group at Week 6: 15 (interquartile range [IQR] 5–40) versus 10 [0–40]; *p* = 0.48). Response was seen in 25 [60%] OD versus 25 [63%] BD dosing [*p* = 0.78]. Proportion of children in remission [PUCAI < 10] at Week 6 was 13 [30%] OD versus 16 [40%] BD; *p* = 0.35. Most adverse events were related to disease aggravation; the rates of serious adverse events were similar [*p* > 0.2].

Conclusions: In this first randomised controlled trial in children, no differences were found between OD and BD dosing for any clinical outcome. Remission was achieved in 35% of children treated with mesalazine for active UC.

Key Words: Drugs; ulcerative colitis; child

1. Introduction

Several randomised controlled trials performed in children and adults have affirmed the efficacy of 5-aminosalicylic acid [5-ASA] and sulphasalazine in the treatment of mild to moderate flares of ulcerative colitis [UC], as well as in maintaining remission.[1–6] Initially, common practice was to prescribe 5-ASA in three divided doses. Since transit time of the colon is much slower than the small bowel, and since the active ingredient acts locally on the colon, less frequent dosing of the regular formulation may provide sufficient colonic coverage. Indeed, two studies among adults with UC suggested that once-daily dosing of mesalazine may be as or more effective than twice-daily dosing and superior to placebo.[7–10] Similarly, the non-inferiority hypothesis was met for once daily dosing of mesalazine in a 1-year maintenance controlled trial.[11] Slow release once-daily mesalazine with Multi Matrix System [MMX] technology was also shown to be effective in induction and maintenance of remission in adult UC.[12,13]

To date, most controlled trials regarding 5-ASA have been conducted among adult patients, and efficacy in children has been extrapolated from these data. However, the prevalence of extensive colitis proximal to the splenic flexure is doubled in paediatric-onset UC[14,15] compared with adults,[16] and extensive disease is consistently associated with more severe phenotype.[17–21] It has been found that less than 50% of children with inflammatory bowel diseases [IBD] are adherent to treatment.[22] Therefore, the advantage of once-daily dosing of 5-ASA over twice-daily may be greater in children.

The primary aim of this trial was to evaluate effectiveness of once-daily dosing of mesalazine compared with twice-daily in children with active UC. We hypothesised the once-daily dosing is superior to twice daily, mainly given the increased adherence. As secondary aims we also evaluated adherence to treatment and adverse events. This manuscript is reported according to the CONSORT statement.

2. Materials and Methods

2.1. Design

This was a multicentre, investigator-initiated, randomised controlled, investigator-blinded, induction of remission trial of once-versus twice-daily dosing of mesalazine for active UC in paediatric patients with 1:1 allocation ratio.

2.2. Participants

Children, 4–18 years of age with a body weight ≥ 15 kg, a confirmed diagnosis of UC by accepted criteria,[23] and in mild to moderate disease activity according to the Paediatric UC Activity Index [PUCAI; score 10–55 points] were eligible for enrolment regardless of disease duration. Exclusion criteria were proctitis only, IBD unclassified, current systemic infection, presence of stool pathogens at screening [culture, parasites, and *Clostridium difficile*], and significant concurrent illness [eg, renal and hepatic failure or pancreatitis]. Rectal therapy was allowed if stable during the 14 days preceding screening and without any change until the completion of the trial. Immunomodulators and biologics were allowed if dose was stable for at least 90 days preceding screening and until the completion of the trial. Other medications (eg, steroids, nonsteroidal anti-inflammatories] NSAIDs and anti-diarrhoeal) were not allowed. We enrolled children naïve to 5-ASA or those who were treated with a low dose < 50 mg/kg/day. A sensitivity analysis was planned *a priori* excluding those treated with low 5-ASA dosing, but since there were less than five such children this was not performed.

Participants were enrolled from 13 secondary and tertiary hospitals and medical centres, 12 in Israel and one in Finland.

2.3. Interventions

Children were randomised into two arms: once [OD]- and twice [BD]-daily mesalazine granules in 1- g sachets using a weight-based dosing table [Table 1]. Doses was based on the standard paediatric 5-ASA dosing [75 mg/kg/day[24]] rounded to a multiples of 500 mg, with a maximum of 3 g daily, as used previously in the adult trials of once-daily mesalazine.

Seven visits were scheduled until Week 9 when safety was assessed; four in-house visits [screening at Weeks -2 to -1, Week 0, Week 3, and Week 6 which was the primary outcome visit], and three telephone visits [Week 1, Week 2, and Week 9 to assess safety and PUCAI score].

2.4. Outcomes

The primary outcome was the PUCAI score between the two arms at Week 6. The PUCAI is a valid and reliable disease activity score, recently approved by the European Medicines Agency to be used as the primary outcome when endoscopic evaluations are not performed, as in this trial, following the guidelines of the paediatric committee of ECCO [P-ECCO].[25] Cutoff values that correspond to remission [< 10 points], mild [10–34 points], moderate [35–60 points], and severe [> 60 points] disease activity as well as response [change of at least 20 points] have been established and validated.[15,26]

Complete remission was defined as remission [PUCAI < 10 points] and a change of at least 10 points from baseline. Response was defined as improvement of at least 20 points but still active disease [PUCAI ≥ 10]. Treatment failure was defined as a lack of improvement of at least 10 points from baseline to Week 3, or requirement of corticosteroids at any time. Patients with treatment failure have been treated at the discretion of the responsible physician, and their latest observations were carried forward for the intention to treat [ITT] analysis.

Secondary outcomes included remission rate [PUCAI < 10 points] and treatment success [ie, ΔPUCAI of 20 points or remission] at Weeks 3 and 6, adverse events [including urinalysis exploring for proteinuria, haematuria, leukocytes, and glycosuria], faecal calprotectin [FC], C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], haemoglobin and albumin at Week 6, quality of life at Week 6 measured by the validated IMPACT questionnaire, and compliance with treatment between the groups judged by self-reporting and the Medication Adherence Rating Scale [MARS].[11]

2.5. Randomisation and concealment of allocation

Patients were randomised in blocks of six stratified by weight groups [15–< 30 kg, 30–40 kg, > 40 kg], at a 1:1 ratio. Randomisation code

Table 1. Dosing schedule.

Weight range	Group	Morning mesalazine dosing	Evening mesalazine dosing
15–< 20 kg	Once daily	1000 mg	
	Twice daily	500 mg	500 mg
20–< 30 kg	Once daily	1500 mg	-
	Twice daily	1000 mg	500 mg
30–< 40 kg	Once daily	2000 mg	-
	Twice daily	1000 mg	1000 mg
≥ 40 kg	Once daily	3000 mg	-
	Twice daily	1500 mg	1500 mg

was prepared and held by the pharmacy of the coordinating site. Each patient allocation appeared in a sealed, opaque, numbered, and pre-packed box containing the study medications, opened after obtaining consent and age-appropriate assent. The box contained all required medications and instructions whether to take the prescribed total daily dose in two divided doses or once daily. A physician not involved in the study provided further instructions.

2.6. Blinding

This was an investigator-blinded and analysis-blinded study. Blinding of the patients was not desired as adherence to therapy was considered an important factor in determining the optimal number of daily doses. The physicians who completed the PUCAI were blinded to the treatment allocation. In addition, the allocation code was revealed only after the completion of the analysis, to ensure blinding of the person who analysed the data. Families and the caring physician were instructed not to discuss treatment with the study personnel. At completion of the study, the investigators were asked to guess the treatment allocation, in order to verify success of the investigator-blinded process.

2.7. Sample size calculations

A sample size of 40 children in each group [totalling 87 patients assuming 10% dropout] was calculated to have 80% power to detect a difference in the mean PUCAI score of 10 points in the primary analysis, assuming standard deviation of 15 points, with an alpha of 0.05.

2.8. Statistics

Wilcoxon rank sum testing was used to compare the median PUCAI scores of the OD arm over the BD arm, and the other continuous data without normal distribution. Normally distributed variables were compared using Student's t test. Categorical variables were compared using chi-square or Fisher's exact tests, as appropriate. Missing data were imputed using the last observation carried forward [LOCF] method; analyses were performed using the modified ITT approach in which all patients taking at least one study medication were included in the analysis. No interim analyses were performed.

Statistical analyses were performed using SPSS [IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY] with $p < 0.05$ taken as the significance threshold.

All authors had access to the study data and reviewed and approved the final manuscript.

2.9. Ethics

The local research committee of each participating site approved the study. Informed consent was obtained from all participants and assent as appropriate. This investigator-initiated trial was partially funded by an educational grant from Ferring who also provided the study medication and monitoring service; however, Ferring were not involved in any part of the trial design, management, analyses, or manuscript preparation. No professional writing assistance has been provided.

3. Results

3.1. Patient disposition

A total of 86 children with UC were randomised in 13 centres affiliated with the authors of this manuscript; three were excluded from the ITT analysis, with a final total of 43 in the OD group and 40 in the BD group [Figure 1]. One child had severe disease according to the PUCAI and was mistakenly randomised due to an impression of general well-being; this child was not excluded. There were no statistical differences in any baseline parameters between the groups, including blood tests and disease activity [Table 2]. A total of 24 [29%] children dropped out due to disease aggravation, two [2%] were lost to follow-up, and one [1%] had an adverse event [5-ASA intolerance in the OD group] [Figure 1]. There was no difference in completion rates on the primary allocation between the OD (28 [65%]) and BD (28 [70%]) groups; $p > 0.2$.

3.2. Primary and secondary outcomes

The study failed to show superiority of the OD group over the BD group in the PUCAI score at Week 6 (mean 23 ± 20 versus 19 ± 20; median 15 [IQR 5–40] versus 10 [0–40]; absolute risk difference 4 ± 4.4 [95%
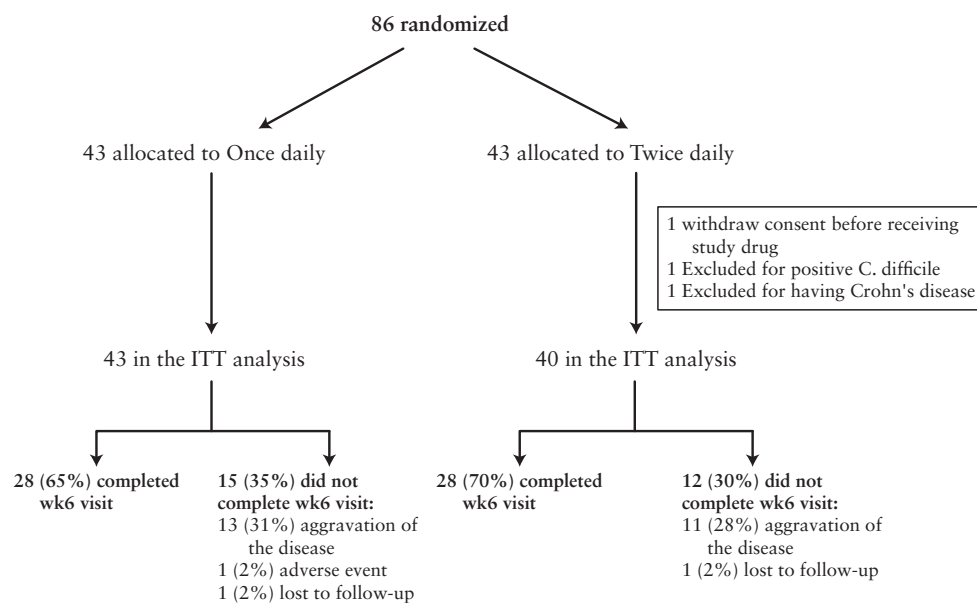

Figure 1. Participant flow diagram (Consolidated Standards of Reporting Trials [CONSORT diagram).

Table 2. Baseline characteristics.

	Total [n = 83]	Once daily [n = 43]	Twice daily [n = 40]
Males	43 [52%]	25 [58%]	18 [45%]
Age [years]	14 ± 2.7	14 ± 2.9	13.9 ± 2.6
Range	7–18	7–18	8–18
Disease duration [years]	0.2 [0.1–0.95]	0.2 [0.1–1]	0.2 [0.1–0.6]
New onset	36 [43%]	17 [40%]	19 [47%]
Disease extent			
Left sided	32 [39%]	13 [30%]	19 [48%]
Extensive	8 [10%]	5 [12%]	3 [8%]
Pancolitis	43 [52%]	25 [58%]	18 [45%]
Family history of IBD	16 [19%]	11 [26%]	5 [13%]
EIM	2 [2%]	2 [5%]	0 [0%]
Concomitant medications			
Thiopurines	4 [5%]	4 [9%]	0 [0%]
Low dose 5-ASA	2 [2%]	1 [2%]	1 [2%]
Probiotics	1 [1%]	1 [2%]	0 [0%]
Rectal therapy	1 [1%]	1 [2%]	0 [0%]
Biologics/steroids	0 [0%]	0 [0%]	0 [0%]
5-ASA dose after randomisation [g/day]	2.8 ± 0.5	2.8 ± 0.4	2.7 ± 0.5
Baseline PUCAI	40 [30–50]	42.5 [30–50]	40 [32.5–47.5]
Mild	22 [27%]	12 [28%]	10 [25%]
Moderate	60 [72%]	31 [72%]	29 [73%]
Severe	1 [1%]	0 [0%]	1 [3%]
Baseline 100 mm VAS	41 ± 19	42 ± 17	41 ± 21
Baseline CRP [mg/l]	5 [1.6–12.2]	5 [1.8–14.4]	5 [1.5–10.5]
ESR	26 ± 19	25 ± 18	26 ± 19
Baseline albumin [g/dL]	4 ± 0.7	4 ± 0.5	4.1 ± 0.9
Baseline haemoglobin [g/dl]	12 ± 2.2	12.1 ± 2.1	11.8 ± 2.2

Medians [interquartile range] and means [± standard deviation] are presented as appropriate for the data distribution; none of the variables were statistically different between the groups.

IBD, inflammatory bowel disease; 5-ASA, 5-aminosalicylic acid; EIM, extraintestinal manifestations; PUCAI, paediatric UC activity index; VAS, visual analogue scale; ESR, erythrocyte sedimentation rate.

confidence interval -4.6 to 12.6]; $p = 0.48$ [Figure 2]. No difference in the PUCAI score was found either in the secondary visits at Weeks 2, 3, and 9 (mean 24 ± 17 versus 21 ± 16, 19 ± 17 versus 17 ± 17, and 22 ± 21 versus 20 ± 20; median 20 [IQR 10–40] versus 15 [5–25], 15 [5–35] versus 15 [0–20], and 15 [0–35] versus 5 [0–20], respectively; all $p > 0.2$).

Under the secondary outcomes, the proportion of children in remission [PUCAI < 10] at Weeks 6 and 9 was similar between the OD and BD groups (13 [30%] versus 16 [40%]; $p = 0.35$, and 15 [35%] versus 17 [43%]; $p = 0.48$, respectively0 [Figure 5 and Figure 3]. The proportion of children in complete remission at Week 6 was also similar (13 [31%] versus 13 [33%]; $p = 0.88$). The proportion of children who responded [ΔPUCAI ≥ 20] was similar at both Weeks 6 and 9 (25 [60%] versus 25 [63%]; $p = 0.78$, and 25 [60%] versus 22 [55%]; $p = 0.68$, respectively) [Figure 5]. The proportion of treatment success at Week 6 [PUCAI < 10 and a change of at least 10 points, or an improvement of at least 20 points] was 61% in the OD group versus 55% in the BD group [$p = 0.61$].

The mean IMPACT QOL [quality of life] questionnaire at Week 6 was similar between the OD [70 ± 12 points] and BD [75 ± 13] arms; $p = 0.14$ [Figure 4B]. Mean reported compliance with treatment was 94% in the OD versus 89% in the BD arms; $p = 0.17$ [Figure 4C]. Similarly, MARS was similar between the groups [$p = 0.29$]. Median Week 6 CRP was similar between the OD and the BD groups (2.01 mg/l [IQR 0.83–7] versus 5 mg/l [1.23–6.1], respectively; $p = 0.45$) [Figure 4A]. There were no differences in the median values of albumin, haemoglobin, or ESR at Week 6 [all $p > 0.1$].
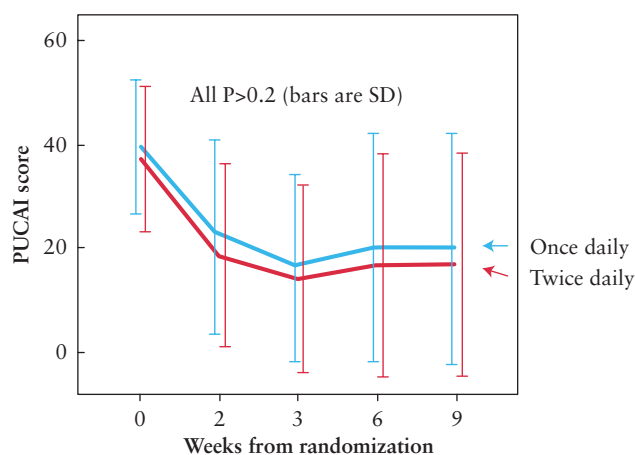

Figure 2. Paediatric Ulcerative Colitis Activity Index [PUCAI] scores in all study visits (last observation carried forward [LOCF] imputation).

Since this was an investigator-initiated study with limited funding, stool collection for faecal calprotectin [FC] was voluntary. Nonetheless there were 17 samples collected at the study completion (median 1590 g/g [IQR 653–2520]). The median nine FC values among the BD group tended to be lower than the eight values in the OD group but this did not reach statistical significance (653 g/g [IQR 398–2230] versus 2350 g/g [1426–3220]; $p = 0.074$).

In both groups combined, 29 of the 83 enrolled children [35%] were in clinical remission at Week 6. Most responders did so by Week 2 and
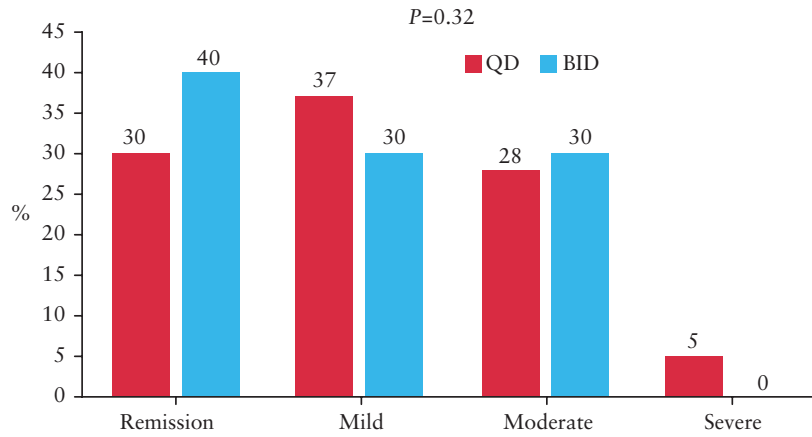
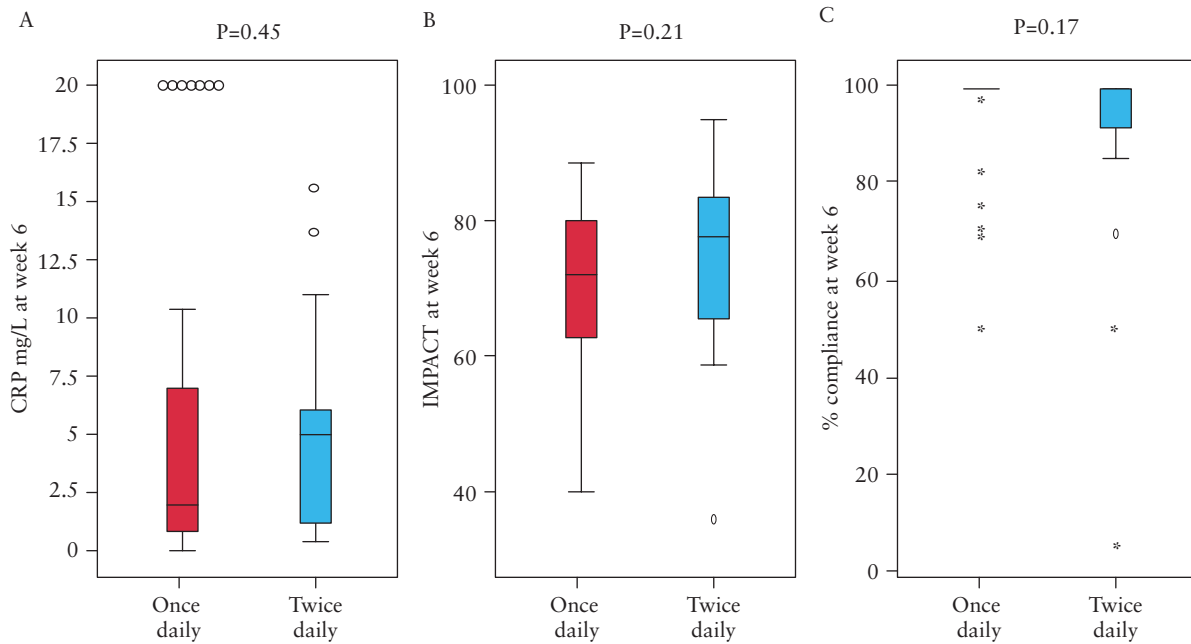**Figure 3.** Disease activity at Week 6 categorised by the Paediatric Ulcerative Colitis Activity Index [PUCAI].

Figure 4. Main outcomes at the primary Week 6 visit. CRP values were truncated at 20 mg/l for graphic presentation.
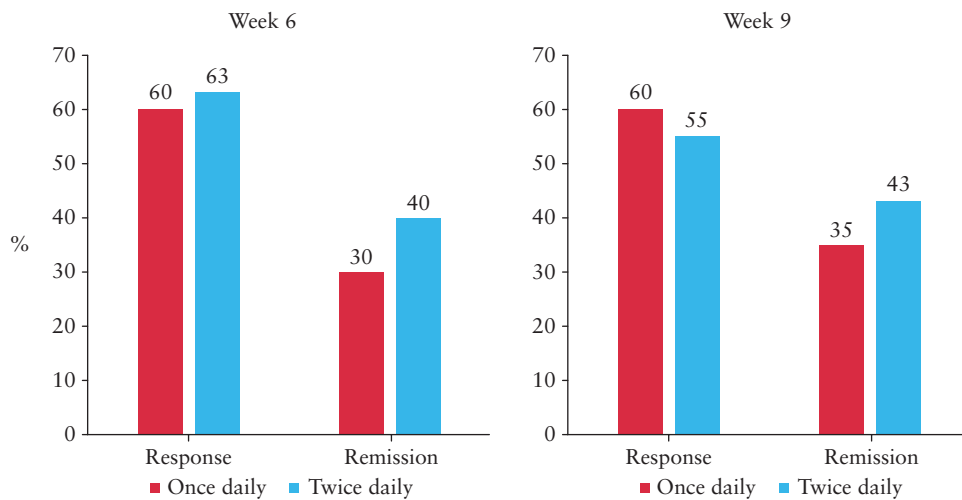

Figure 5. Response (a Paediatric Ulcerative Colitis Activity Index [PUCAI] change of at least 20 points or PUCAI < 10) and remission [PUCAI < 10 points] at Week 6.

no further response was seen after Week 3. There was no association between remission rate and disease extent or duration [data not shown].

The sample sise of this trial was based on the hypothesis that OD would be superior to BD dosing. Although we failed to show superiority, a *post-hoc* analysis demonstrated that the observed difference meets the criteria for proving non-inferiority. The difference in the group's mean PUCAI score at Week 6 was 3.3 points with a 95% confidence interval [CI] of ± 4.4, indicating that the 95% CI of the mean difference is -1.1 to 7.7, crossing 0 from one hand but < 10 points on the other hand. A difference of 10 points on the PUCAI is considered the minimal change score to be considered real beyond statistical error [ie, minimal detectable difference] and our difference is below that threshold.[15] Nonetheless, this exploratory *post-hoc* analysis does not alter the conclusion of a failed superiority trial.

3.3. Safety

A total of 26 children had 35 adverse events; 17 [40%] in the OD group and nine [23%] in the BD group [$p = 0.095$], of which seven were severe (severe adverse events [[SAEs] four in the OD group and three in the BD group] [Table 3]. Withdrawals due to aggravation of disease or drug-related adverse events were similar, 14/43 [33%] in the OD and 11/40 [28%] in the BD, number needed to harm [NNH] = 20. None of the SAEs were thought to be related to the study drug [five aggravations of the colitis and need for intravenous steroids, one viral infection, and one peri-appendicular abscess].

Six children had AEs possibly related to the study drug: three in the OD group [one flu-like intolerance which required cessation of the drug, one abdominal pain, and one elevated transaminase] and three in the BD group [one headache, one chest pain, and one nausea with limb pain].

There were no differences between the OD and BD groups in Week-6 blood tests including creatinine, amylase, liver enzymes, bilirubin, γ-glutamyl transpeptidase [GGT], white blood cells, absolute neutrophil count and platelets, in any of the study visits. Urinalysis at both Weeks 3 and 6 did not reveal any alarming signals as compared with baseline urinalysis [data not shown].

4. Discussion

In this first randomised controlled trial in children comparing once versus twice daily mesalazine in mild to moderate UC, we could

not demonstrate superiority of the former for any of the outcomes including response, remission, safety, or adherence.

A high proportion of patients required additional therapy or a change in therapy before Week 6, suggesting overall low effectiveness for mesalazine in mild to moderate paediatric UC. The intention-to-treat 35% remission rate at Week 6 is consistent with published data from other studies. Clinical remission in adults has been reported in only 28–46% of active patients.[9] Comparisons between adult and paediatric results, however, are not straightforward. A PUCAI-defined remission is more difficult to achieve as compared with a Mayo-defined remission, used in the aforementioned adult trials. A Mayo-defined remission may still allow some blood in the stool. We believe that complete remission should be measured, since it has been associated with favourable long-term outcome.[27] Paediatric data to benchmark our results are scarce. A small trial with only 15 patients in the 5-ASA arm had a similar PUCAI-defined remission rate of 35% at 8 weeks.[5] Another paediatric trial found a PUCAI-defined remission rate of 40% in the standard-dose and 48% in the high-dose mesalazine groups, slightly higher than in our study.[6] However, that trial included a higher proportion of children with mild disease [25% of children in our trial versus ~ 50% in the aforementioned study]. A North American paediatric registry found that only 31% of children with UC treated with 5-ASA at disease onset were in steroid-free remission and no treatment escalation at 1 year.[28]

According to the ESPGHAN-ECCO [European Society for Paediatric Gastroenterology Hepatology and Nutrition and European Crohn's and Colitis Organisation] guidelines, 5-ASA is the first-line treatment in mild-moderate paediatric UC.[24] However, paediatric gastroenterologists should be cognisant of the fact that this strategy will likely fail in most patients, requiring rapid treatment escalation, as recently recommended.[27] In our study, time to response was 2–3 weeks, such that lack of response by 3 weeks should trigger a change in treatment.

Theoretically, once daily dosing may be associated with better adherence to therapy, especially in children. Surprisingly, adherence and quality of life did not differ between the groups. This could be explained by the fact that our study enrolled active patients who are more likely to adhere to therapy. It is possible that adherence would be superior in the once-daily dosing group in a long term maintenance trial.

Our trial is the first to explore the utility of once-daily 5-ASA dosing in children, but it is not without limitations. We did not perform endoscopic evaluation of the bowel mucosa. However, according to the guidance of ECCO,[25] endoscopic evaluation may be waived in paediatric trials of drugs which are not new category, and 5-ASA most certainly falls into this class. Moreover, the PUCAI has proven in different studies to have a high concordance with sigmoidoscopic appearance in children, with an accuracy of 80–90%.[15,26,29] The OD arm had numerically more patients on immunomodulators and higher pancolitis rate [none reaching statistical significance]. We thus cannot exclude the possibility that the OD arm were still more severe, exerting a type II bias. Nonetheless, the two groups had similar disease activity as reflected by the PUCAI, PGA, and blood tests. Most of the patients in this study were not on concurrent topical therapy, which could have introduced a bias towards milder disease even though the PUCAI reflected mild-to-moderate disease at inclusion. This is due to the study protocol which had an open-label extension arm in which patients unresponsive to oral therapy were treated with mesalazine enemas; the data are to be published as a separate study. This is unlikely to have influenced the outcomes, as over 70% of patients in both arms had moderate disease, and OD was still not superior to BD dosing.

Table 3. Adverse events.

	Total [$n = 83$]	Once daily [$n = 43$]	Twice daily [$n = 40$]
Disease exacerbation	16	13	3
Headache	4	2	2
Abdominal pain	4	3	1
Fever	3	1	2
Nausea	2	0	2
Elevated liver enzymes, transient	2	2	0
5-ASA intolerance[a]	1	1	0
Macrohaematuria[b]	1	1	0
Chest pain	1	0	1
Peri-appendicular abscess	1	0	1
Death	0	0	0

Table presents the numbers of individual events and not number of children; some may have had more than one event.

5-ASA, 5-aminosalicylic acid.

[a]Fever, diarrhoea, abdominal pain, arthralgia.

[b]Known to exist before the trial.

Although our *a priori* hypothesis was that OD dosing would be superior to BD, mainly due to increased adherence and due to higher peak dose to the colon, a *post hoc* calculation showed that the difference between the groups falls also in the non-inferiority margin. This, along with similar numerical data across different outcomes and the consistent results of non-inferiority reported in several large adult trials, allows us to speculate that there are no differences between once daily or twice daily dosing in efficacy, safety, adherence, or quality of life; however, a fully powered large non-inferiority trial is needed to prove this assumption.

Whereas once-daily dosing may be a valid option in children, our results are sufficient to enable a patient on twice-daily dosing who missed the morning dose to take the total daily dose later on. Our study adds another layer of evidence for developing guidelines for the treatment of UC in children and adolescents.

Funding

Conflict of Interest

OL received travel grant from Ferring. KLK received study support from the Finnish Paediatric Research Foundation and Helsinki University Hospital Research Fund, member of Advisory Board Abbvie and MSD [Finland], consultant fees from Ferring and Tillotts Pharma. RS received Nestle-Research Support, Jannsen-Research Support, Golden heart-Consulting, Enzymotec-Consulting, Wissotzki–Consulting, Materna-Speaking, Teva-Speaking, Mead Johnsson-Speaking, Megapharm-Research Support, Lapidot-Consulting. DT received consultation fee, research grant, royalties, or honorarium from Janssen, Pfiser, Hospital for Sick Children, Ferring, MegaPharm, AstraZeneca, Abbvie, Takeda, BMS, Rafa, Boehringer Ingelheim, Biogen, Atlantic Health. HS, MK, AL have received consultation fees, research grants, or honoraria from Jannsen, Abbvie, Falk pharma, Nestle, Ferring, Megapharm, Pharmabest, and Takeda

Author Contributions

AL and DT conceived and planned the study, recruited patients, interpreted the data and drafted the manuscript. BY, MK, EB, YM, RS, KLK, ES, HS, OL, SC, SP, and AO recruited patients and provided critical revision of the manuscript. All authors approved the final version of the manuscript.

References

1. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomised study. *N Engl J Med* 1987;**317**:1625–9.

2. Rachmilewitz D. Coated mesalazine [5-aminosalicylic acid] versus sulphasalazine in the treatment of active ulcerative colitis: A randomised trial. *BMJ* 1989;**298**:82–6.

3. Sutherland L, Macdonald J. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2006:CD000544.

4. Sutherland L, Macdonald J. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2006:CD000543.

5. Romano C, Famiani A, Comito D, et al. Oral beclomethasone dipropionate in pediatric active ulcerative colitis: A comparison trial with mesalazine. *J Pediatr Gastroenterol Nutr* 2010;**50**:385–9.

6. Winter HS, Krzeski P, Heyman MB, et al. High- and low-dose oral delayed-release mesalamine in children with mild-to-moderately active ulcerative colitis. *J Pediatr Gastroenterol Nutr* 2014;**59**:767–72.

7. Gordon GL, Zakko S, Murthy U, et al. Once-daily mesalamine formulation for maintenance of remission in ulcerative colitis: A randomised, placebo-controlled clinical trial. *J Clin Gastroenterol* 2016;**50**:318–25.

8. Flourie B, Hagege H, Tucat G, et al. Randomised clinical trial: Once- versus twice-daily prolonged-release mesalazine for active ulcerative colitis. *Aliment Pharmacol Ther* 2013;**37**:767–75.

9. Feagan BG, MacDonald JK. Once daily oral mesalamine compared to conventional dosing for induction and maintenance of remission in ulcerative colitis: A systematic review and meta-analysis. *Inflamm Bowel Dis* 2012;**18**:1785–94.

10. Dignass AU, Bokemeyer B, Adamek H, et al. Mesalamine once daily is more effective than twice daily in patients with quiescent ulcerative colitis. *Clin Gastroenterol Hepatol* 2009;**7**:762–9.

11. Sandborn WJ, Korzenik J, Lashner B, et al. Once-daily dosing of delayed-release oral mesalazine [400-mg tablet] is as effective as twice-daily dosing for maintenance of remission of ulcerative colitis. *Gastroenterology* 2010;**138**:1286–96, 96 e1–3.

12. 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.

13. Sandborn WJ, Kamm MA, Lichtenstein GR, et al. MMX multi matrix system mesalazine for the induction of remission in patients with mild-to-moderate ulcerative colitis: A combined analysis of two randomised, double-blind, placebo-controlled trials. *Aliment Pharmacol Ther* 2007;**26**:205–15.

14. Griffiths AM. Specificities of inflammatory bowel disease in childhood. *Best Pract Res Clin Gastroenterol* 2004;**18**:509–23.

15. Turner D, Otley AR, Mack D, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: A prospective multicenter study. *Gastroenterology* 2007;**133**:423–32.

16. Moum B, Ekbom A, Vatn MH, Elgjo K. Change in the extent of colonoscopic and histological involvement in ulcerative colitis over time. *Am J Gastroenterol* 1999;**94**:1564–9.

17. Gulati R, Rawal KK, Kumar N, et al. Course of severe ulcerative colitis in Northern India. *Trop Gastroenterol* 1995;**16**:19–23.

18. Oshitani N, Kitano A, Fukushima R, et al. Predictive factors for the response of ulcerative colitis patients during the acute-phase treatment. *Digestion* 1990;**46**:107–13.

19. Chakravarty BJ. Predictors and the rate of medical treatment failure in ulcerative colitis. *Am J Gastroenterol* 1993;**88**:852–5.

20. Truelove SC, Jewell DP. Intensive intravenous regimen for severe attacks of ulcerative colitis. *Lancet* 1974;**1**:1067–70.

21. Meyers S, Lerer PK, Feuer EJ, Johnson JW, Janowitz HD. Predicting the outcome of corticoid therapy for acute ulcerative colitis. Results of a prospective, randomised, double-blind clinical trial. *J Clin Gastroenterol* 1987;**9**:50–4.

22. Mackner LM, Crandall WV. Oral medication adherence in pediatric inflammatory bowel disease. *Inflamm Bowel Dis* 2005;**11**:1006–12.

23. Levine A, Griffiths A, Markowitz J, et al. Pediatric modification of the Montreal Classification for inflammatory bowel disease: The Paris Classification. *Inflamm Bowel Dis* 2011;**17**:8.

24. Turner D, Levine A, Escher JC, et al. Management of pediatric ulcerative colitis: Joint ECCO and ESPGHAN evidence-based consensus guidelines. *J Pediatr Gastroenterol Nutr* 2012;**55**:340–61.

25. Ruemmele FM, Hyams JS, Otley A, et al. Outcome measures for clinical trials in paediatric IBD: An evidence-based, expert-driven practical statement paper of the Paediatric Ecco Committee. *Gut* 2015;**64**:438–46.

26. Turner D, Hyams J, Markowitz J, et al. Appraisal of the pediatric ulcerative colitis activity index [PUCAI]. *Inflamm Bowel Dis* 2009;**15**:1218–23.

27. Schechter A, Griffiths C, Gana JC, et al. Early endoscopic, laboratory and clinical predictors of poor disease course in paediatric ulcerative colitis. *Gut* 2015;**64**:580–8.

28. Zeisler B, Lerer T, Markowitz J, et al. Outcome following aminosalicylate therapy in children newly diagnosed as having ulcerative colitis. *J Pediatr Gastroenterol Nutr* 2013;**56**:12–8.

29. Turner D, Griffiths AM, Veerman G, et al. Endoscopic and clinical variables that predict sustained remission in children with ulcerative colitis treated with infliximab. *Clin Gastroenterol Hepatol* 2013;**11**:1460–5.