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Original Article

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Mesalamine Enemas for Induction of Remission in Oral Mesalamine-refractory Pediatric Ulcerative Colitis: A Prospective Cohort Study

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ABSTRACT

Background: Paediatric ulcerative colitis [UC] is more extensive than adult disease, and more often refractory to mesalamine. However, no prospective trials have evaluated mesalamine enemas for inducing remission in children. Our goal was to evaluate the ability of mesalamine enemas to induce remission in mild to moderate paediatric UC refractory to oral mesalamine.

Methods: This was an open-label arm of a previously reported randomised controlled trial of once-daily mesalamine in active paediatric UC [MUPPIT trial]. Children aged 4–18 years, with a Paediatric Ulcerative Colitis Activity Index [PUCAI] score of 10–55, were enrolled after failing at least 3 weeks of full-dose oral mesalamine. Patients treated with steroids or enemas in the previous month and those with isolated proctitis were excluded. Children received Pentasa® enemas 25 mg/kg [up to 1g] daily for 3 weeks with the previous oral dose. The primary endpoint was clinical remission by Week 3.

Results: A total of 38 children were enrolled (mean age 14.6 ± 2.3 years; 17/38 [45%] with extensive colitis). Clinical remission was obtained in 16 [42%] and response was obtained in 27 [71%] at Week 3. Eight children deteriorated and required steroids. There were no differences in baseline parameters between those who entered or failed to enter remission, including disease extent [43% in left-sided and 41% in extensive colitis] and disease activity [44% in mild and 41% in moderate activity].

Conclusion: Clinical remission can be markedly increased in children who are refractory to oral mesalamaine by adding mesalamine enemas for 3 weeks, before commencing steroids.

Key Words: Drugs; ulcerative colitis; child

1. Introduction

According to the Paris classification, disease extent in paediatric ulcerative colitis [UC] is divided into isolated proctitis, left-sided colitis, extended colitis, and pancolitis.[1] Adult guidelines recommend prescribing mesalamine as first-line therapy in mild to moderate UC, based on disease severity and extent.[2] Oral mesalamine is advised for left-sided or extensive disease, topical mesalamine for mild distal disease, and combined treatment for more active or extensive disease.[2–4] Extrapolation from adult literature to paediatrics regarding topical therapy may not be adequate, since the majority of children have extensive disease whereas the majority of adults have left-sided disease.[5,6] On the other hand, the use of topical therapy in children may be particularly beneficial, since 60% of children starting 5-aminosalicylic acid [5ASA] therapy with new-onset UC require steroids within a year.[7] Despite the paucity of paediatric literature, ECCO-ESPGHAN guidelines for the management of paediatric UC recommend adding topical therapy to the oral route when needed, while acknowledging that children may be particularly resistant to using enemas. Only 17% and 32% of children received rectal therapy within 30 days and 1 year, respectively, in a recent report from a North American registry involving 213 children using 5ASA after diagnosis. This study did not include information separating suppositories from enemas, nor information regarding dose and duration of therapy.[7]

The goal of the current study was to determine the short-term effectiveness of adding mesalamine enemas to the treatment of children failing to achieve remission with high-dose oral mesalamine.

2. Methods

2.1. Design

This was a 3-week, prospective, open-label, extension enemas arm of a multicentre, investigator-initiated, single-blinded, randomised, controlled trial termed the MUPPIT [Multicenter Ulcerative Colitis Pediatric Pentasa Intervention Trial].[8] Briefly, MUPPIT was a 9-week trial comparing once- with twice-daily high-dose oral mesalamine in children 4–18 years of age, with a body weight ≥ 15 kg, a confirmed diagnosis of UC by accepted criteria,[1,9] and mild to moderate disease activity defined by the Paediatric UC Activity Index [PUCAI ≥ 10][10,11][ClinicalTrials.gov ID NCT01201122]. The MUPPIT included scheduled visits at Weeks 0, 3, and 6 and phone visits at Weeks 1, 2, and 9 [safety]. Participants were enrolled from 13 paediatric inflammatory bowel disease [IBD] centres, 12 in Israel and one in Finland. Patients could not have been enrolled if they were already using high-dose oral mesalamine. Thus, this study reports the results of an open-label feeding arm using enemas for patients failing 5ASA at screening (and not eligible for the main trial because of the use of high dose 5ASA), or those failing to respond to high-dose oral mesalamine during the trial.

2.2. Participants

Eligibility criteria to join the current enema study included children enrolled into the MUPPIT who had been defined as treatment failures [i.e. lack of improvement of at least 10 points from the baseline PUCAI score following at least 3 weeks of treatment] or those not achieving remission [i.e. PUCAI < 10 points] by Week 6. In addition, children with active disease, excluded at the screening visit based on current oral use of 5ASA > 50 mg/kg/day for at least 3 weeks, were also eligible for enrolment. All other inclusion criteria of the main trial held also for the open-label enema study: children, 4–18 years of age with a body weight ≥ 15kg, a confirmed diagnosis of UC by accepted criteria,[1] and mild to moderate disease activity [defined by a PUCAI score of 10–55 points].

Exclusion criteria were proctitis only, IBD unclassified, current systemic infection, presence of stool pathogens at screening [culture, parasites, and *Clostridium difficile*], significant concurrent illness [e.g. renal and hepatic failure or pancreatitis], and receiving any topical rectal therapy during the preceding 30 days. Immunomodulators were allowed if dose was stable for at least 90 days before screening and until the completion of the trial. Other medications (e.g. steroids, non-steroidal anti-inflammatory drugs [NSAIDs] and anti-diarrhoeal medications] were not allowed.

2.3. Interventions and procedures

Children received enemas of mesalamine [Pentasa® enemas 1g/60ml], at a dose of 25 mg/kg up to 1 g,[3] delivered once daily through a disposable bottle at bedtime after using the toilet. For patients weighing less 40 kg, the volume was rounded upto the nearest feasible volume [1/2 enema or 3/4 enema]. Children were asked to administer the enema in the left lateral position, remain in that posture for at least 10 min, and to refrain from using the toilet over the next hour. All patients continued their previous 5-ASA therapy with Pentasa® granules sachets at a set dose of 60–75 mg/kg/day rounded to multiples of 500 mg with a maximum of 3 g daily, as used in the MUPPIT study.[8] There were two in-house study visits at baseline and Week 3, when data were recorded including explicit demographic and baseline data, PUCAI score, physician global assessment of disease activity [PGA], medications, physical examination, blood test results, and compliance. Compliance was assessed using an explicit question ['Did you take the enemas daily? If not, how many did you skip?'], verified by returned enema count. Compliance was calculated as number of enemas given out of the required amount. In addition, a telephone visit was held at Week 1 to record PUCAI, reported compliance, and adverse events. Adverse events were explicitly registered in the case report forms at Weeks 1 and 3.

2.4. Outcomes

The primary endpoint was Week 3 clinical remission, defined as PUCAI < 10 points and a change of at least 10 points from baseline. Response was defined as improvement of ≥ 20 points or remission. The introduction of additional medication used for the treatment of UC, or dose change of the oral 5ASA at any time during the 3 weeks, was considered treatment failure.

2.5. Statistical analysis

Sample size was set *a priori* at 40 children, to allow a reasonable precision around the expected remission rate at Week 3 [e.g. the 95% confidence interval of 60% rate for this sample size is 46–74%]. Analyses were performed using the modified intention to treat [ITT] principle in which all patients receiving the study drug for at least 48 h were included. Missing follow-up values

were imputed using last observation carried forward [LOCF]. We used LOCF for patients who received additional therapy due to lack of response, and imputed their baseline PUCAI at Week 3. All such patients were considered treatment failures in the remission analysis (i.e. non-response imputation). Data are presented as frequency [%], mean +/- standard deviation or median [interquartile range, IQR] as appropriate. Data were compared using Student's t test for continuous variables or chi square for nominal variables. Logistic regression analysis with the Hosmer-Lameshow test for goodness of fit was used to identify factors predictive of 3-week remission. All tests were two-sided and considered significant at $p < 0.05$. Data were analysed on SPSS v22 statistical analysis software [IBM, USA]. The local research committee of each participating site approved the study. Informed consent was obtained from all participants and assent as appropriate.

3. Results

3.1. Patient disposition

A total of 39 patients entered the study and one withdrew consent within the first 48 h [Figure 1]. There were no differences in the baseline characteristics between the 14 children who entered the study after failing the main MUPPIT and the 25 who entered from the screening visit, including mean and median PUCAI score [Table 1]. Ten patients did not complete the Week 3 visit, one due to poor compliance with enemas, one lost to follow-up, and the other eight because of aggravation of the disease; their Week 3 data were imputed by LOCF. Only one child required < 1 g based on body weight, and received 3/4 of an enema nightly.

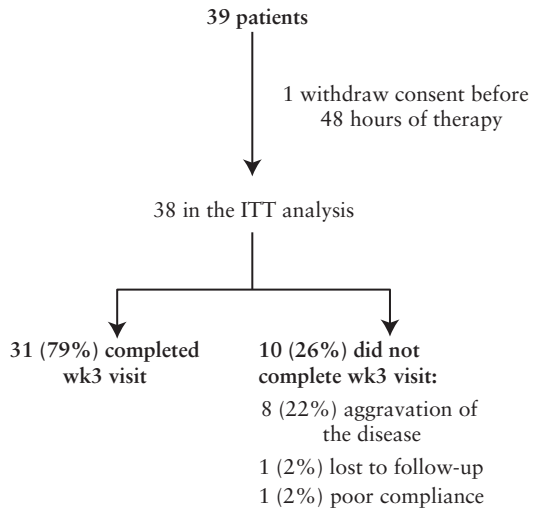

Figure 1. Participant flow diagram.

3.2. Remission and response

Of the 38 included children, 16 [42%] were in remission by Week 3 and 27 [71%] responded. Remission rate was identical when captured by PGA instead of the PUCAI [n = 16, 42%]. Half of those in remission [8/16] achieved remission by the Week-1 visit. Eight patients had worsening of the disease during this period and required steroids, of whom three required hospitalisation for intravenous steroids.

There were no differences in baseline parameters between patients who entered remission and patients who failed to enter remission, including disease extent [Figure 2a] and baseline disease activity [Figure 2b]. Other baseline variables were similarly non-predictive including gender, age, disease duration, and absolute PUCAI score [all $p > 0.2$; Table 1].

Remission rate of the MUPPIT failures was 7/13 [54%], and of those from the open-label group was 9/25 [36%].

3.3. Compliance and adverse events

One patient did not comply with enema use and withdrew from the study [Figure 1]. We assessed compliance among 23/29 [79%] patients who completed 3 weeks of therapy. Among these, 20/23 [87%] had at least 80% compliance. In six patients, compliance could not be assessed accurately by the physician or parent. Only one patient [labelled as a failure on intention to treat] refused to use enemas; 12 adverse events were recorded in 11 patients. Eight patients had events related to disease aggravation and four had one adverse event each [one nausea, one headache, one arthralgia, and one muscle pains]; none required stopping treatment. Three patients had serious adverse events, all due to exacerbation of the disease requiring hospitalisation.

4. Discussion

In this prospective open-label study, we found that topical enemas with mesalamine, after failing high-dose oral mesalamine, led to clinical remission in 42% of children and adolescents with

Table 1. Characteristics of patients at baseline.

Baseline	Total cohort [n = 38]	Remission by Week 3 [n = 16]	Not in remission by Week 3 [n = 22]	p-Value
Males/females	15/23	7/9	8/14	0.64
Age [years]	15 ± 2.3	14 ± 2.9	15 ± 2.0	0.73
Disease duration [years]	1.7 ± 1.8	1.5 ± 1.5	1.9 ± 2.1	0.49
Disease location				
Proctitis E1	1 [2.6%]	1 [6.3%]	–	
Left-sided E2	20 [53%]	8 [50%]	12 [54%]	
Extensive E3	3 [8%]	1 [6.3%]	2 [9%]	
Pancolitis E4	14 [37%]	6 [38%]	8 [36%]	
PUCAI baseline total cohort [mean]	41 ± 12	39 ± 14	41 ± 10	0.53
PUCAI from MUPPIT [mean]	40 ± 12	7 [44%]	6 [27%]	
PUCAI from screening [mean]	41 ± 10	9 [56%]	16 [73%]	

Thirteen patients entered trial as MUPPIT failures, 25 as non MUPPIT participants.
PUCAI, Paediatric Ulcerative Colitis Activity Index.

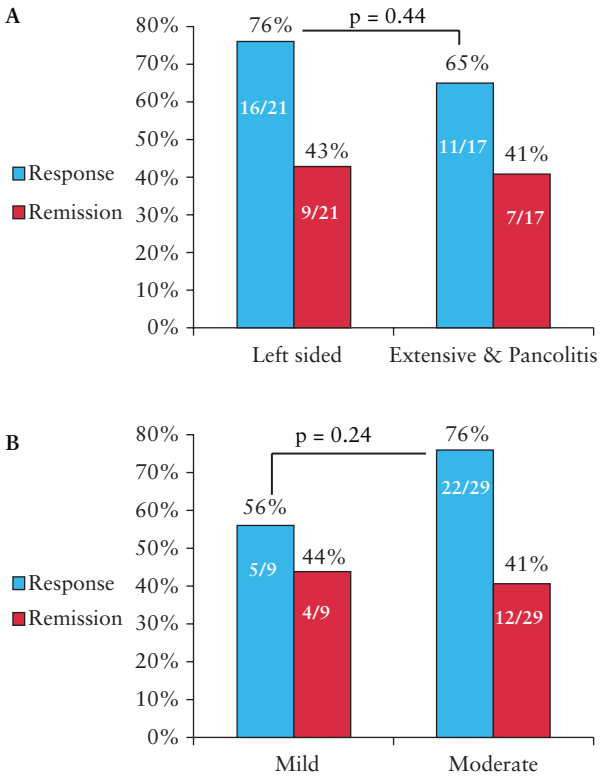

Figure 2. Response and remission by disease extent and disease severity at Week 3. a: percentage denotes outcome among patients with a specified extent. b: percentage denotes outcome among patients with a specified severity.

mild-moderate colitis and 44% with extensive or pancolitis. In the main MUPPIT randomized controlled trial [RCT] we have shown that oral mesalamine leads to remission in only 35% of children with mild to moderate UC, without significant difference between the drug being prescribed once or twice daily.[8] Our finding here adds that topical therapy may play an important role in inducing remission and as a steroid-sparing agent in those refractory to oral mesalamine. The dose of 25 mg/kg was based on experts' opinion in the ECCO-ESPGHAN guidelines for managing paediatric UC.[3] We used a maximum of 1 g, as it has been shown that there was no dose response above that threshold.[2,12]

Very limited data exist in children. Either mesalamine or hydrocortisone enemas resulted in a higher remission rate than placebo in 29 children with isolated left-sided colitis.[13] Mesalazine suppositories were effective in improving disease activity in children with proctitis.[14] Previous meta-analyses of adult studies confirmed the superiority of 5ASA rectal enemas over placebo, in both inducing and maintaining remission in UC.[15–17] These meta-analyses also demonstrated that 5ASA enemas are more effective than topical steroids and budesonide.[18] Beclomethasone dipropionate [BDP] enemas may be, however, at least as effective as 5ASA, but this remains to be further evaluated.[19,20]

ECCO guidelines recommend topical therapy for mild-moderate proctitis,[2] an uncommon phenotype in paediatric UC.[5] Nonetheless, enemas have proved to improve effectiveness of oral mesalamine also of adults with mild-moderate extensive colitis, leading to higher rate of both clinical and endoscopic remission. In the PINCE European trial, 127 adults with mild-moderate extensive UC were randomised to enemas of 1 g mesalamine or placebo, all patients receiving oral mesalamine 2 g twice daily.[6] Remission rate was 44% at Week 4 and 64% at Week 8 with the oral and topical mesalamine treatment, vs 34% and 43% with only oral treatment, respectively [$p = 0.03$]. Post hoc analysis of the PINCE trial showed a trend towards higher mucosal healing in the combination arm vs the oral only arm at 4 weeks [54% vs p39% of Mayo subscore 0 or 1; $P = 0.052$].[21] It is noteworthy that enemas may improve the rectosigmoid area only, thus showing improved clinical and sigmoidoscopic scores whereas a full colonoscopy might have shown residual proximal inflammation. Topical therapy achieves higher rectal mucosal 5ASA concentrations than oral therapy, and this is associated with improved clinical outcome.[22]

Our 42% remission rate is similar to that quoted in the PINCE trial at Week 4 and lower than at Week 8, but there are two major differences between the studies. First, we used a PUCAI –defined remission [< 10 points] which is more difficult to achieve as compared with a Mayo-defined remission [a Mayo-defined remission allows some blood in the stool and PUCAI does not]. A PUCAI < 15 correlates with a Mayo-defined remission [supporting data available from DT] and, according to this estimation, as many as 60% of children in our trial would have been defined as being in clinical remission. The second difference is that per eligibility criteria, none of the included adults in the PINCE trial were treated with oral mesalamine over 3 g daily before the study, whereas we focused on children failing adequate dosage of oral mesalamine. In doing so we followed the rationale of the ESPGHAN-ECCO guidelines on paediatric UC, which recommend topical therapy in UC particularly in those not responding to oral mesalamine.[3] This recommendation likely stems from the lean evidence available in extensive disease, the most common paediatric UC phenotype. Adult studies have shown that under-use of topical therapy is highest in extensive disease.[23,24] Our study fills that gap, by showing that 5ASA enemas are effective also in children refractory to high-dose oral 5ASA and that there was no difference in the effect, whether the disease was limited to the left colon or extensive. The other reason for recommending enemas only to children failing oral 5ASA is the fact that children may be more reluctant to accept this route of administration. However, only one patient stopped using enemas in our study due to non-compliance.

The main limitation of this study is the lack of comparison group. However, unlike in the previous adult PINCE trial, we included only children who failed adequate dosage of oral 5ASA, and thus the short-term 42% remission rate is unlikely to be related to placebo effect. The low rate of extensive disease found in our cohort is likely since active patients with extensive disease are more likely to be treated with steroids, and thus were less often enrolled into the study. The ECCO-ESPGHAN guidelines for managing paediatric UC state that response to oral 5ASA is less likely after 2 weeks, and we used a more conservative 3-week mark. Indeed, the main MUPPIT in paediatric UC showed that the majority of children responded within 2 weeks, and those not responding within 3 weeks were unlikely to respond thereafter.[3,8] The second limitation is the lack of endoscopic evaluation. However, according to the guidance of ECCO,[25] endoscopic evaluation may be waived in paediatric studies evaluating drugs that are not new category, and mesalamine most certainly falls into this criteria. The PUCAI has proved in different studies to have a high concordance with sigmoidoscopic appearance in children, with an accuracy of 80–90%; a PUCAI < 10 points is highly correlated with mucosal healing.[10,11,26] Finally, the PUCAI is approved by the European Medicines Agency [EMA] as a primary outcome measure when endoscopic evaluation is not used.

In this open-label prospective study, we show that adding 1 g 5ASA enema to children with mild-moderate UC is effective in inducing clinical remission in 42%, despite including children who failed high-dose oral 5ASA, and many had extensive or pancolitis. Adding topical 5ASA to the oral route should be advocated in children from the outset, and this should be particularly considered before escalating treatment to oral steroids in mild-moderate UC.

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Conflict of interest

DT received in the past 3 year consultation fee, research grant, royalties, or honorarium from Janssen, Pfizer, Hospital for Sick Children, Ferring, MegaPharm, AstraZeneca, Abbvie, Takeda, Rafa, Boehringer Ingelheim, Biogen, Atlantic Health. AL has received travel grants or speaker's honoraria, participated in advisory boards, or received research grants from Nestle, Jannsen, Abbvie, Takeda. OL received travel grant from Ferring. KLK received study support from the Finnish Paediatric Research Foundation and Helsinki University Hospital Research Fund, membership of Advisory Board Abbvie and MSD [Finland], consultant fees from Ferring and Tillotts Pharma. RS received Nestle research dupport, Jannsen research support, Megapharm research support, Golden Heart consulting, Enzymotec consulting, Wissotzki consulting, Materna speaking, Teva speaking, Mead Johnsson speaking, and Lapidot consulting fees.

Author Contributions

AL and DT initiated 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. 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**:1314–21.
2. Dignass A, Lindsay JO, Sturm A, *et al*. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. *J Crohns Colitis* 2012;**6**:991–1030.
3. Turner D, Levine A, Escher JC, *et al*.; European Crohn's and Colitis Organization; European Society for Paediatric Gastroenterology, Hepatology, and Nutrition. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. *J Pediatr Gastroenterol Nutr* 2012;**55**:340–61.
4. Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2010;**105**:501–23; quiz 524.
5. Levine A, de Bie CI, Turner D, *et al*.; EUROKIDS Porto IBD Working Group of ESPGHAN. Atypical disease phenotypes in pediatric ulcerative colitis: 5-year analyses of the EUROKIDS Registry. *Inflamm Bowel Dis* 2013;**19**:370–7.
6. Marteau P, Probert CS, Lindgren S, *et al*. Combined oral and enema treatment with Pentasa [mesalazine] is superior to oral therapy alone in patients with extensive mild/moderate active ulcerative colitis: a randomised, double blind, placebo controlled study. *Gut* 2005;**54**:960–5.
7. Zeisler B, Lerer T, Markowitz J, *et al*.; Pediatric Inflammatory Bowel Disease Collaborative Research Group. Outcome following aminosalicylate therapy in children newly diagnosed as having ulcerative colitis. *J Pediatr Gastroenterol Nutr* 2013;**56**:12–8.
8. Turner D, Yerushalmi B, Kori M, *et al*. Once versus twice daily mesalazine to induce remission in paediatric ulcerative colitis: A randomised controlled trial. *J Crohns Colitis* 2016, Oct 3. pii: jjw180. [Epub ahead of print.
9. Levine A, Koletzko S, Turner D, *et al*.; European Society of Pediatric Gastroenterology, Hepatology, and Nutrition. ESPGHAN revised Porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. *J Pediatr Gastroenterol Nutr* 2014;**58**:795–806.
10. 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.
11. Turner D, Hyams J, Markowitz J, *et al*.; Pediatric IBD Collaborative Research Group. Appraisal of the pediatric ulcerative colitis activity index [PUCAI]. *Inflamm Bowel Dis* 2009;**15**:1218–23.
12. Marshall JK, Thabane M, Steinhart AH, Newman JR, Anand A, Irvine EJ. Rectal 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2012;**11**:CD004118.
13. Odera G, Giuliani B, Santini B, *et al*. Topical treatment with 5-ASA and hydrocortisone. *Riv Ital Pediatr* 1986;**12**:674–8.
14. Heyman MB, Kierkus J, Spénard J, Shbaklo H, Giguere M. Efficacy and safety of mesalamine suppositories for treatment of ulcerative proctitis in children and adolescents. *Inflamm Bowel Dis* 2010;**16**:1931–9.
15. Cohen RD, Woseth DM, Thisted RA, Hanauer SB. A meta-analysis and overview of the literature on treatment options for left-sided ulcerative colitis and ulcerative proctitis. *Am J Gastroenterol* 2000;**95**:1263–76.
16. Marshall JK, Irvine EJ. Rectal corticosteroids versus alternative treatments in ulcerative colitis: a meta-analysis. *Gut* 1997;**40**:775–81.
17. Marshall JK, Thabane M, Steinhart AH, *et al*. Rectal 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2010; **1**:CD004115.
18. Hartmann F, Stein J; BudMesa-Study Group. Clinical trial: controlled, open, randomized multicentre study comparing the effects of treatment on quality of life, safety and efficacy of budesonide or mesalazine enemas in active left-sided ulcerative colitis. *Aliment Pharmacol Ther* 2010;**32**:368–76.
19. Crispino P, Pica R, Unim H, *et al*. Efficacy of mesalazine or beclomethasone dipropionate enema or their combination in patients with distal active ulcerative colitis. *Eur Rev Med Pharmacol Sci* 2015;**19**:2830–7.
20. Mulder CJ, Fockens P, Meijer JW, van der Heide H, Wiltink EH, Tytgat GN. Beclomethasone dipropionate [3 mg] versus 5-aminosalicylic acid [2 g] versus the combination of both [3 mg/2 g] as retention enemas in active ulcerative proctitis. *Eur J Gastroenterol Hepatol* 1996;**8**:549–53.
21. Probert CS, Dignass AU, Lindgren S, Oudkerk Pool M, Marteau P. Combined oral and rectal mesalazine for the treatment of mild-to-moderately active ulcerative colitis: rapid symptom resolution and improvements in quality of life. *J Crohns Colitis* 2014;**8**:200–7.
22. Pimpo MT, Galletti B, Palumbo G, *et al*. Mesalazine vanishing time from rectal mucosa following its topical administration. *J Crohns Colitis* 2010;**4**:102–5.
23. Seibold F, Fournier N, Beglinger C, Mottet C, Pittet V, Rogler G; Swiss IBD Cohort Study Group. Topical therapy is underused in patients with ulcerative colitis. *J Crohns Colitis* 2014;**8**:56–63.
24. Benazzato L, Ferronato A, Azzurro M, *et al*. Is topical therapy underused in patients with ulcerative colitis? Our experience. *Dig Liver Dis* 2014;**48**:e194–e5.
25. Ruemmele F, Hyams J, 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, 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.