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High- and Low-Dose Oral Delayed-Release Mesalamine in Children With Mild-to-Moderately Active Ulcerative Colitis

*Harland S. Winter, †Piotr Krzeski, ‡Melvin B. Heyman, §Eduardo Ibarguen-Secchia, ||Barbara Iwanczak, ¶Maciej Kaczmarski, #Jaroslaw Kierkus, **Sanja Kolaček, ††Bankole Osuntokun, ‡‡J. Antonio Quiros, §§Manoj Shah, ||||Bruce Yacyshyn, and ¶¶Preston M. Dunnmon

ABSTRACT

Objective: The aim of the study was to assess the safety and efficacy of high- and low-dose oral, delayed-release mesalamine in a randomized, double-blind, active control study of children with mild-to-moderately active ulcerative colitis.

Methods: Patients ages 5 to 17 years, with a Pediatric Ulcerative Colitis Activity Index (PUCAI) score of $\geq$10 to $\leq$55 and a truncated Mayo Score of $\geq$1 for both rectal bleeding and stool frequency, were enrolled. They received body weight–dependent doses of oral, delayed-release mesalamine for 6 weeks in a low- (27–71 mg $\cdot$ g^{-1} $\cdot$ day^{-1}) or high-dose group (53–118 mg $\cdot$ g^{-1} $\cdot$ day^{-1}). The primary endpoint was treatment success, defined as the proportion of patients who achieved remission (PUCAI score $<$10) or partial response (PUCAI score $\geq$10 with a decrease from baseline by $\geq$20 points). Secondary endpoints included truncated Mayo Score and global assessment of change of disease activity.

Results: The modified intent-to-treat population included 81 of 83 patients enrolled. Treatment success by PUCAI was achieved by 23 of 41 (56%) and 22 of 40 (55%) patients in the mesalamine low- and high-dose groups, respectively ($P = 0.924$). Truncated Mayo Score (low-dose 30 [73%] and high-dose 28 [70%] patients) and other efficacy results did not differ between the groups. The type and severity of adverse events were consistent with those reported in previous studies of adults with ulcerative colitis and did not differ between groups.

Conclusions: Both low- and high-dose oral, delayed-release mesalamine doses were equally effective as short-term treatment of mild-to-moderately active ulcerative colitis in children, without a specific benefit or risk to using either dose.

Key Words: children, inflammatory bowel disease, mild-to-moderate ulcerative colitis, oral mesalamine, Pediatric Ulcerative Colitis Activity Index

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Ulcerative colitis is a type of inflammatory bowel disease characterized by chronic mucosal inflammation of the colon. With the exception of patients who have a cecal patch, the

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From the *MassGeneral Hospital for Children, Boston, MA, †Medpace, Warsaw, Poland, the ‡Department of Pediatrics, University of California, San Francisco, the §Methodist Children's Hospital, San Antonio, TX, the ||Department of Pediatrics, Gastroenterology and Nutrition, Medical University of Wroclaw, Wroclaw, the ¶Department of Pediatrics, Gastroenterology and Allergology, Medical University of Bialystok, Bialystok, the #Department of Gastroenterology, Hepatology, and Immunology, Children's Memorial Health Institute, Warsaw, Poland, the **University Children's Hospital Zagreb, Zagreb, Croatia, the ††Cook Children's Medical Center, Fort Worth, TX, ‡‡Pediatric Gastroenterology, MUSC Pediatric Center for Inflammatory Bowel Disorders, Charleston, SC, the §§Loma Linda University Children's Hospital, Loma Linda, CA, the ||||Division of Digestive Diseases, University of Cincinnati, Cincinnati, OH, and the ¶¶US Food and Drug Administration, Silver Spring, MD.

Address correspondence and reprint requests to Harland S. Winter, MD, MassGeneral Hospital for Children, 175 Cambridge St, CRPZ 5-560, Boston, MA 02114 (e-mail: hwinter@mgh.harvard.edu).

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inflammatory response usually begins in the rectum and extends proximally with a diffuse, continuous pattern. Approximately 15% to 20% of patients with ulcerative colitis are children. In the United States, the incidence of pediatric ulcerative colitis varies between 1 and 4/100,000 individuals per year (1). Estimates of the average age-at-onset in children vary, although 80% to 90% of patients are age ≥9 years when symptoms develop (2,3). The incidence and disease pattern seen in the United States are similar to those observed in other developed countries (4). Evidence from the medical literature suggests that the clinical course and manifestations of ulcerative colitis are similar in children and adults (5,6); however, younger children tend to have increased colitis and more diffuse involvement with pancolitis compared with older children and adults (7). The most common symptoms of ulcerative colitis—diarrhea, abdominal pain, rectal bleeding, fever, and weight loss—are found in comparable proportions of both children and adults, and are more dependent on the disease activity than on age.

Oral mesalamine (Asacol; Warner Chilcott, Rockaway, NJ) is often used as maintenance treatment of ulcerative colitis in adults and children. Although some evidence points to a dose-response relation in adult patients with active ulcerative colitis treated with oral mesalamine (8), data are sparse to support the claim of a relation between dose and clinical efficacy in the pediatric population. Moreover, the safety of oral mesalamine, which is well established in the adult population, lacks confirmation in children. Among practicing pediatric gastroenterologists, the daily dose of oral mesalamine administered to children with active ulcerative colitis ranges from 30 to >100 $mg \cdot g^{-1} \cdot day^{-1}$. The purpose of this study was to investigate the safety and efficacy of low- and high-dose oral, delayed-release mesalamine for the treatment of children with active, mild-to-moderate ulcerative colitis.

METHODS

Study Design

This was a randomized, multicenter, double-blind, active control, parallel group study. It was conducted in accordance with the ethical principles of Good Clinical Practice and approved at all sites by the appropriate institutional review boards or independent ethics committees, as applicable. The study was conducted in 26 clinical practice centers across the United States, Canada, Romania, Croatia, and Poland.

Patients

Written informed consent was obtained from each patient's parent or legal guardian according to the US Code of Federal Regulations (US CFR; Title 21, Part 50, §55, 56), International Conference on Harmonisation harmonized tripartite guideline for good clinical practice, and ethical principles that have their origin in the Declaration of Helsinki. In addition, age-appropriate patient information sheets were provided, and patients who were >7 years of age were asked to sign a form indicating their assent to participate in the study. Both male and female patients ages 5 to 17 years with a history of biopsy- and endoscopy-confirmed ulcerative colitis were enrolled. Inclusion criteria included mild-to-moderately active ulcerative colitis (relapsed or newly diagnosed) as defined by Pediatric Ulcerative Colitis Activity Index (PUCAI) scores of ≥10 to ≤55 (9); baseline scores of ≥1 for the symptomatic components of the Mayo Score, rectal bleeding, and stool frequency (Table 1); and body weight ≥17 to ≤90 kg. Patients had to be able to swallow the study drug tablets. In addition, female patients were either premenarchal or had a negative urine pregnancy test. If sexually active, patients had to practice a reliable form of contraception. Exclusion criteria, including medical history and previous therapies, are listed in supplementary Table S1 (*http://links.lww.com/MPG/A366*). Patients were prohibited from taking exclusionary drugs and any drugs that may interfere with the evaluation of the study medication during the study. Patients were required to stop their oral mesalamine at randomization.

TABLE 1. Truncated Mayo Score for rectal bleeding and stool frequency

Rectal bleeding scale	
0	No blood seen
1	Streaks of blood with stool less than half of the time
2	Obvious blood with stool most of the time
3	Blood alone passed
Stool frequency scale	
0	Normal stool frequency per day
1	1–2 stools greater than normal per day
2	3–4 stools greater than normal per day
3	≥5 stools greater than normal per day

Protocol

Patients were seen at screening, baseline (within 1 week of screening), week 3, and week 6/withdrawal visits. In addition, a follow-up telephone call was made 1 week after baseline. Screening and baseline visits were allowed to take place on the same day (supplementary Fig. S1, *http://links.lww.com/MPG/A364*). At screening, patient eligibility was determined by PUCAI score, physical examination findings, clinical laboratory tests (hematology, serum biochemistry, and urinalysis), and pregnancy test results. At baseline, samples were taken for clinical laboratory tests if the baseline visit occurred >7 days after screening, and for pregnancy testing. Patients underwent clinical assessments of disease activity at baseline and at week 6/withdrawal visit. These included all domains of the PUCAI and the truncated Mayo Score components (stool frequency and rectal bleeding). A PUCAI diary card was completed on each of the 2 days preceding the visit. Bristol stool charts were used to assist with the relevant PUCAI domain assessment. Questions were addressed to the patient initially, wherever appropriate, based on age and responsiveness, followed by the parent for an additional perspective or confirmation. In addition, at week 6/withdrawal visit the patient was asked, "How do you rate the change in disease activity since starting?" A 7-point scale was used for the global assessment of change of disease activity: significantly improved, moderately improved, mildly improved, no change, mildly worse, moderately worse, and significantly worse.

Fecal calprotectin and lactoferrin samples were collected at baseline and visits at weeks 3 and 6/withdrawal. Endoscopy was not mandated by the study protocol. Rescue medication was not permitted during the study, and any patient requiring additional treatment for ulcerative colitis was removed from the trial. Compliance was assessed at visits at weeks 3 and 6/withdrawal by counting the unused pills.

Study Drug Assignment

Patients were randomly assigned in a 1:1 ratio to either a high or low dose of oral, delayed-release mesalamine in a double-blind fashion. Randomization was stratified by body weight (17 to <33, 33 to <54, and 54–90 kg) and by disease severity (mild: defined as a baseline PUCAI score of 10–30; or moderate: a baseline PUCAI

TABLE 2. Mesalamine dose groups

Body weight range, kg	Mesalamine dose groups, g/day	Dosing range, $mg \cdot g^{-1} \cdot day^{-1}$
17 to <33	Low dose: 1.2	36–71
	High dose: 2.0	61–118
33 to <54	Low dose: 2.0	37–61
	High dose: 3.6	67–109
54–90	Low dose: 2.4	27–44
	High dose: 4.8	53–89

score of 31–55). Subjects received body weight–dependent doses of oral, delayed-release mesalamine for 6 weeks in a low- (27–71 $mg \cdot g^{-1} \cdot day^{-1}$) or high-dose group (53–118 $mg \cdot g^{-1} \cdot day^{-1}$). The high doses in each body weight category were approximately 1.67-, 1.8-, and 2-times the low doses, respectively, keeping within the $mg \cdot g^{-1} \cdot day^{-1}$ limits described above, as well as the 400-mg tablet constraint (Table 2). Patients were given identical-looking placebo tablets to match the number of tablets in each body weight group and instructed to take their drug in 2 divided doses approximately 12 hours apart.

Primary Objective and Outcome

The primary efficacy objective was to assess the proportion of patients in each dose group that achieved treatment success after 6 weeks of treatment with mesalamine using the validated PUCAI. Treatment success was defined as either a complete response (a PUCAI score of <10) or a partial response (defined by a reduction in the PUCAI score of ≥ 20 points from baseline to week 6/withdrawal, but with a week 6/withdrawal absolute PUCAI score of ≥ 10).

Secondary Objectives and Outcomes

Secondary efficacy objectives included assessment of the proportion of patients who achieved PUCAI-defined complete and partial responses, and truncated Mayo Score treatment success (defined as either a complete response with stool frequency and rectal bleeding scores $= 0$; or a partial response with an improvement from baseline of either stool frequency or rectal bleeding, with no worsening of the other parameter). In addition, efficacy was measured as the proportion of patients for whom the investigator declared improvement at week 6/withdrawal using the global assessment of change of disease activity question.

Biomarker endpoints included mean change from baseline and the proportion of patients who had a reduction in the fecal lactoferrin and calprotectin from baseline to weeks 3 and 6/withdrawal.

Safety was assessed by monitoring adverse events (AEs), compliance, and tolerability (eg, patient withdrawals, AEs); and changes in vital signs, clinical laboratory test results, and standardized and replicated body weight and height.

Study Populations

The modified intent-to-treat (MITT) population was used for all efficacy analyses and included all of the patients who were randomized and took ≥ 1 dose of study medication. Patients in the MITT population were analyzed based on the mesalamine dose level to which they were randomized (high vs low), regardless of the treatment that they actually received during the study. If a patient was withdrawn for safety or efficacy reasons, he or she was counted as a treatment failure for the MITT analysis. Voluntary withdrawals without outcome data were not included in the MITT analysis. The evaluation of safety was based on the safety population, that is, those who were randomized and received ≥ 1 dose of study medication. For safety assessments patients were reported according to the dose they actually received.

Statistical Analyses

The primary categorical efficacy endpoint was analyzed using the Cochran-Mantel-Haenszel test to compare mesalamine dose levels (high vs low), adjusting for body weight group and disease severity. The test was 2-sided at the $\alpha = 0.05$ level.

Continuous endpoints, that is, change from baseline to weeks 3 and 6/withdrawal in fecal lactoferrin and calprotectin levels, were analyzed using analysis of variance with mesalamine dose level (high vs low), body weight group, and disease severity as main effects. Interaction effects and the baseline value as a covariate were assessed for significance and included in the model as appropriate. No formal statistical analyses were carried out on any secondary endpoints except for the mean change in fecal biomarkers. Data for these endpoints were summarized appropriately for the evaluable population using descriptive statistics and frequency counts. Safety data were summarized for the study population.

RESULTS

Patient Demographics

Of 100 patients assessed for eligibility, 83 were randomized from December 2008 to March 2011; 16 patients were excluded for not meeting inclusion criteria and 1 patient declined to participate. One patient in the mesalamine high-dose group withdrew consent before dosing. Of the remaining 82 patients, 41 were randomized to each dose group comprising the MITT and safety populations. Patient demographics were similar for both dose groups (supplementary Table S2, *http://links.lww.com/MPG/A367*). One patient in the high-dose group withdrew voluntarily from the study without collecting clinical efficacy outcome data (supplementary Fig. S2, *http://links.lww.com/MPG/A365*).

Overall, 40% of the patients in the high-dose group had pancolitis at baseline versus 24% in the low-dose group. Nevertheless, the median PUCAI scores were similar in the low- and high-dose groups at 30 and 35 points, respectively. Approximately two-thirds of patients in each group had an endoscopy performed within 6 weeks of entering the study. Approximately 60% of all patients were newly diagnosed as having ulcerative colitis, and the median time from ulcerative colitis diagnosis was 1.1 and 2.2 months in the low- and high-dose group, respectively. Approximately half of the patients in each group presented with mild disease. Overall, 95% and 98% of patients in the low- and high-dose groups, respectively, were $\geq 85\%$ compliant with their study medication during the entire study period. Less than half of all of the patients in both groups reported exposure to oral mesalamine (or sulfasalazine) before the study entry, 18 and 16 patients in low- and high-dose groups, respectively.

Efficacy

Patients in the low-dose mesalamine group received 27 to 71 $mg \cdot g^{-1} \cdot day^{-1}$ compared with 53 to 118 $mg \cdot g^{-1} \cdot day^{-1}$ in the high-dose group. A total of 23 of 41 (56.1%) and 22 of 40 (55.0%) patients achieved PUCAI-defined treatment success in the low- and high-dose groups, respectively (95% CI for difference −22.7 to

TABLE 3. Efficacy outcomes

	Mesalamine dose groups, n (%)	
	Low dose (n = 41)	High dose (n = 40)
PUCAI treatment success*	23 (56.1)	22 (55.0)
PUCAI complete response	19 (46.3)	17 (42.5)
PUCAI partial response	4 (9.8)	5 (12.5)
Truncated Mayo Score treatment success	30 (73.2)	28 (70.0)
Truncated Mayo Score complete response	14 (34.1)	17 (42.5)
Truncated Mayo Score partial response	16 (39.0)	11 (27.5)

* Treatment success was defined as either a complete response (PUCAI score <10) or a partial response (defined by a reduction in the PUCAI score of ≥20 points from baseline to week 6/withdrawal, but with a week 6/withdrawal absolute PUCAI score of ≥10). PUCAI = Pediatric Ulcerative Colitis Activity Index.

20.5, $P = 0.924$). The vast majority of patients achieved treatment success as assessed by the truncated Mayo Score (Table 3). Approximately 78% of all of the patients had improvement (significantly, moderately, or mildly improved) in disease activity at week 6/withdrawal weeks, with approximately half demonstrating clinically significant improvement as assessed by the global assessment of change of disease activity (Table 4).

The reduction in fecal biomarkers, especially lactoferrin, tended to be greater and occurred in a higher proportion of patients in the high-dose group, but this did not reach statistical significance (Table 5).

Safety

Treatment-emergent AEs (TEAEs) in the safety population were reported in 23 patients (56.1%) in the low-dose group and in 21 patients (51.2%) in the high-dose group (Table 6). TEAEs occurring in ≥5% of patients were exacerbation of ulcerative colitis, nasopharyngitis, headache, dizziness, and sinusitis in the low-dose group, and nasopharyngitis, fatigue, and pyrexia in the high-dose group. The number and percentage of patients who withdrew from the study because of AEs were 5 patients (12.2%) reporting 6 AEs in the low-dose group, and 2 patients (4.9%) reporting 3 AEs in the high-dose group (supplementary Table S3, *http://links.lww.com/MPG/A368*). In addition to the 3 cases of ulcerative colitis flare in the low-dose group, 3 other AEs were reported to result in early discontinuation in the low-dose group: adenovirus infection, sclerosing cholangitis, or pancreatitis. In the high-dose group, 1 patient withdrew because of increased serum amylase and lipase levels and 1 patient withdrew because of upper abdominal pain.

The majority of AEs were classified as mild or moderate. Of the TEAEs reported, 2 (4.0%) were severe in the low-dose group and 7 (17.1%) were severe in the high-dose group. No deaths occurred during the study.

AEs suggestive of salicylate toxicity, as well as events involving the kidneys, liver, heart, pancreas, stomach, and gallbladder, were carefully considered. No case of tinnitus was reported during the study. Pancreatitis, considered possibly related to the study drug, and sclerosing cholangitis, considered doubtfully related to the study drug, were reported in 1 patient each in the low-dose group; each of these events led to the patient's discontinuation from the study. Increased serum amylase and lipase levels were reported in 1 patient in the low-dose group who also had elevated lipase levels at screening; this patient was terminated from the study. Increased lipase was also reported in 1 patient in the high-dose group who had elevated lipase levels at screening. Increased alanine transaminase levels were reported in 1 patient in the high-dose group who also had elevated lipase levels at screening. Bilirubinuria, without elevated serum bilirubin levels, was reported in 1 patient in the high-dose group. No clinically relevant trends in changes in laboratory test values, including serum creatinine, were observed during the study that could point toward drug-related renal toxicity.

TABLE 4. Global assessment of change of disease activity

	Mesalamine dose groups, n (%)	
	Low dose (n = 41)	High dose (n = 40)
Significantly improved	19 (46.3)	22 (55.0)
Moderately improved	8 (19.5)	4 (10.0)
Mildly improved	4 (9.8)	6 (15.0)
No change	2 (4.9)	4 (10.0)
Mildly worse	4 (9.8)	1 (2.5)
Moderately worse	2 (4.9)	1 (2.5)
Significantly worse	2 (4.9)	2 (5.0)

DISCUSSION

The study confirmed that oral, delayed-release mesalamine is an efficacious medication in children with mild-to-moderately active ulcerative colitis, and that it resulted in a clinically significant improvement in half of the patients treated for 6 weeks. The study, however, did not demonstrate a difference in efficacy or tolerability of therapy with either high- or low-dose mesalamine. The study was prospectively powered for efficacy assuming that the low-dose response rate resembled a placebo. A 2-sided $\alpha = 0.05$ Fisher exact test had an estimated power of 0.74 to detect a clinically meaningful difference between P (response on low dose) = 0.20 and P (response on high dose) = 0.50, with 40 patients per dose level. In retrospect, the expected low-dose response may have been too great in patients with mild-to-moderate disease activity, and a larger sample size may be necessary to demonstrate a difference between low- and high-dose mesalamine in this population.

Owing to the limitations imposed by having only a 400-mg tablet of mesalamine available, overlap between the 2 groups was unavoidable. The recommended dose in the joint European Crohn's and Colitis Organization and European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guideline was 60 to 80 mg $\cdot g^{-1} \cdot day^{-1}$ (1). The response of the low-dose group may have been favorably affected because some patients were receiving therapeutic doses. Conversely, response to treatment in the high-dose group may have been adversely affected because some patients were receiving doses below what is recommended. Having

TABLE 5. Analysis of change from baseline in fecal biomarker levels by visit

Biomarker	Mesalamine dose groups		P^*
	Low dose (n = 41)	High dose (n = 41)	
Fecal lactoferrin, μg/g			
Week 3	n = 33	n = 33	0.0667
Baseline mean (±SE)	505 (± 132)	583 (± 179)	
Mean change (±SE)	22 (± 146)	−224 (± 139)	
Patients with reduction, n (%)	20 (60.6)	20 (60.6)	
Week 6	n = 30	n = 30	0.1537
Baseline mean (±SE)	353 (± 85)	582 (± 192)	
Mean change (±SE)	105 (± 142)	−176 (± 84)	
Patients with reduction, n (%)	17 (56.7)	21 (70.0)	
Fecal calprotectin, μg/g			
Week 3	n = 33	n = 32	0.8388
Baseline mean (±SE)	1215 (± 338)	1710 (± 409)	
Mean change (±SE)	−234 (± 218)	−275 (± 435)	
Patients with reduction, n (%)	20 (60.6)	22 (68.8)	
Week 6	n = 30	n = 29	0.8142
Baseline mean (±SE)	902 (± 199)	1699 (± 451)	
Mean change (±SE)	−189 (± 216)	−762 (± 483)	
Patients with reduction, n (%)	16 (53.3)	22 (75.9)	

* P values for mean change difference between the 2 dose groups based on Koch nonparametric analysis of covariance test with fixed effects for treatment, bodyweight group, and disease severity. SE = standard error of the mean.

formulations specifically for children, which allow for more accurate body weight dosing in the recommended therapeutic range, may demonstrate better efficacy for delayed-release mesalamine.

The present study is limited owing to the lack of a placebo control group and the overlap in dosing between the 2 groups. Placebo-controlled trials in children with active disease have more than a minimal risk and would not provide any benefit to patients. For these reasons, approval of a placebo-controlled trial by an institutional review board is highly unlikely.

Some may argue that the full Mayo Score should have been used in this study; however, the truncated Mayo Score accurately determined disease activity in 3 of the 4 clinimetric properties (9). The truncated Mayo Score was used as a secondary outcome measure because it provided a useful benchmark for comparison with clinical efficacy data collected in previous placebo-controlled studies in adult patients (10,11). In these studies, the placebo response rate using the same outcome measure was approximately 30% (unpublished data). In the present study, the overall truncated Mayo Score treatment success rate (partial and complete response) was observed in 73% and 70% of patients in the mesalamine low- and high-dose groups, respectively. This compares with overall response rates (complete and partial response using the same endpoint) of 55%, 57%, and 79% in adult patients treated with mesalamine 1.6 g/day, 2.4 g/day, and 4.8 g/day, respectively. Using these parameters, children appear to have a better response to mesalamine compared with adults. This may be because some adult patients could have more established inflammation with more fibrosis, which may not be as responsive to anti-inflammatory medication.

TABLE 6. Overall treatment-emergent AE profile of mesalamine (safety population; N = 82)

Category	Mesalamine dose groups	
	Low dose (n = 41)	High dose (n = 41)
AEs		
No. people with AE, n (%)	23 (56.1)	21 (51.2)
No. AEs	50	41
Serious AEs		
No. people with AE, n (%)	5 (12.2)	2 (4.9)
No. AEs	8	3
Withdrawn because of AEs		
No. people with AE, n (%)	5 (12.2)	2 (4.9)
No. AEs	6	3
AE severity, n (%)	n = 50	n = 41
Mild	34 (68.0)	25 (61.0)
Moderate	14 (28.0)	9 (22.0)
Severe	2 (4.0)	7 (17.1)
AE causality, n (%)	n = 50	n = 41
Doubtful	38 (76.0)	29 (70.7)
Possible	11 (22.0)	10 (24.4)
Probable	1 (2.0)	2 (4.9)

AE = adverse event.

The present study suggests that the effective difference between the low and high doses of oral, delayed-release mesalamine in a pediatric population is small, if any. Although large dose-response studies resembling those in adults are unlikely to be carried out in the pediatric population, a dose-response outcome may become more apparent in certain subgroups of pediatric patients, similar to what was found in adult patient studies (8,12,13).

In this study, fecal lactoferrin and calprotectin were investigated as biomarkers of inflammation. The biomarker data suggest a numerical trend toward higher efficacy at the high dose versus the low dose. The decrease in mean fecal calprotectin appears to support its utility as a noninterventional outcome measure in children with ulcerative colitis. Xiang et al (14) in their study used fecal markers to evaluate the response to treatment with promising results. Among 27 patients with ulcerative colitis and 11 with Crohn disease, 97% of patients had higher calprotectin levels, which normalized with treatment (14). Similarly Wagner et al (15) evaluated the utility of fecal calprotectin and reported significant decreases in levels with treatment. The data regarding the use of

fecal lactoferrin and calprotectin as biomarkers should be interpreted with caution because the demonstrated trends could be driven by baseline differences and not reflect a response to medication. Additional studies should be powered to investigate the predictability of fecal lactoferrin and calprotectin in determining response to therapy.

The study identified no dose-related patterns of AEs. Pancreatitis is a known complication of mesalamine in adults and is a plausible drug-related adverse effect in children. Because this study allowed for mesalamine treatment for >7 days before study entry, the patients who had elevated pancreatic enzymes before enrollment could have had mesalamine-related pancreatitis before study entry. As with the other safety measures in this study cohort, the number of patients with pancreatitis or elevation of pancreatic enzymes was not higher in the high-dose group. This finding is consistent with the postulated idiosyncratic nature of mesalamine-induced pancreatitis (16). The safety of high-dose mesalamine, up to 117 $mg \cdot g^{-1} \cdot day^{-1}$, in this limited pediatric patient population supports the safety of escalating doses in patients who may benefit by higher doses to achieve response.

In conclusion, oral, delayed-release mesalamine is an effective treatment in children with mild-to-moderately active ulcerative colitis treated for 6 weeks. Low and high doses of delayed-release mesalamine were similarly effective, and both doses were generally well tolerated, with only 8.5% of patients discontinuing treatment owing to an AE.

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