Comparison of Two Dosing Methods for Induction of Response and Remission with Oral Budesonide in Active Pediatric Crohn's Disease: A Randomized Placebo-Controlled Trial

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Background: Oral budesonide has been found to be comparable to systemic corticosteroids in mild to moderately active Crohn's disease (CD). Remission rates in pediatric studies to date have been suboptimal (47%–55%), even though patients with colonic involvement were excluded in some studies. In addition, the optimal pediatric dosing regimen has never been evaluated before.

Methods: This was a randomized, controlled, double-blind study in 70 children with mild or moderately active CD randomized to 1 of 2 groups: Group 1: Standard dose budesonide (9 mg/day) for 7 weeks followed by 6 mg budesonide daily for an additional 3 weeks. Group 2: Induction with 12 mg/day for the first month followed by the same regimen as Group 1. Outcome measures included a decrease in Pediatric Crohn's Disease Activity Index and remission rates. Patients with colonic disease were not excluded.

Results: At week 7 a clinical response was obtained in 51.4% in Group 1 versus 74.3% in Group 2. A significant decrease in C-reactive protein was seen only in Group 2. At the end of treatment, remission was obtained in 42.9% in Group 1 versus 65.7% in Group 2 ($P = 0.054$). There was no significant difference in adverse events or serum cortisol.

Conclusions: Use of an induction dose of budesonide followed by a budesonide taper resulted in a trend to higher rates of clinical remission and a decrease in inflammation, without an increase in steroid-associated side effects. Budesonide was also useful for patients with ileocolonic disease.

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Key Words: Crohn's disease, budesonide, pediatric, child, colitis, inflammatory bowel disease

Crohn's disease (CD) in children and adolescents is a complex inflammatory disorder of the gastrointestinal tract with a relapsing course that can be very difficult to manage. Like adults, children and adolescents are prone to the same diverse array of complications stemming from the disease and its therapy.[1,2] At present there is a paucity of data from randomized controlled trials regarding therapeutic strategies for pediatric CD. This is due to the small number of clinical trials performed in children to date, and the small number of children that have participated in these trials.

Although CD is often thought to be a disease primarily involving the ileum, the disease frequently affects the colon as well. Pediatric onset is characterized by more frequent colonic and upper intestinal involvement.[3,4] This difference in phenotype, as well as the lack of data from clinical trials in children, mean that therapeutic strategies in children might need to be different from strategies used in adult CD, and require pediatric evidence.

Although multiple treatment options exist, the mainstay of medical therapy for active disease over the last 2 decades has been corticosteroids.[1,2,5–8]

Budesonide, a nonhalogenated glucocorticosteroid (16α, 17-butylidendioxy-11β, 21-dihydroxy-1,4-pregnadien-3,20-dion) structurally related to hydroxyprednisolone, belongs to the corticoids with the highest receptor affinity. It has been shown to have a high ratio of topical to systemic activity, explained by a high first-pass metabolism in the liver and in the gut mucosa. For treatment of the distal parts of the

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intestine, such as the lower ileum, sustained release forms of budesonide have offered therapeutic potential, with remission rates ranging from 51%–69% for active CD.[9–14] First-pass metabolism and decreased systemic bioavailability lead to fewer side effects with budesonide in comparison to systemic corticosteroids,[10,14] and budesonide was shown to be superior to mesalamine with an equivalently benign side effect profile.[9] A daily dosage of 9 mg budesonide is currently regarded as optimum in adult patients.[12] Reduction of corticosteroid side effects in children with mild or moderate disease in which alternatives may exist is of particular importance, since the issues of cosmetic adverse events and growth retardation are particularly important in this age group.

Oral budesonide has been evaluated in mild to moderately active pediatric CD using the standard 9-mg dose. Remission rates have ranged from 47%–55%,[13–15] with fewer cosmetic and systemic side effects in comparison to prednisone/prednisolone. However, evaluation of pediatric dosing for oral budesonide has never been performed before. Furthermore, the high prevalence of diffuse ileocolonic disease or isolated colitis has led to the exclusion of large segments of pediatric CD both in practice and in clinical studies. Exclusion criteria based on site of disease varied between studies, thus making a generalization to real-life scenarios more difficult.

The high prevalence of colonic involvement in pediatric disease, and the lower remission rate in comparison to prednisone in some studies, has raised the issue of whether treatment can be optimized in order to treat a larger group of patients and achieve a higher response or remission rate. One such strategy may be a variation in the initial dose and use of a preparation with better colonic distribution.

Budenofalk (Dr. Falk Pharma, Freiberg, Germany) is a pH-modified release oral formulation of gastric-juice-resistant encapsulated pellets of budesonide which is appropriate for the treatment of patients with CD without upper gastrointestinal involvement or extraintestinal manifestations. It is primarily absorbed in the ileum; however, ≈25%–37% of a dose reaches the colon.[16] A previous study in adults using this preparation at a standard dose of 9 mg daily in patients with colonic involvement noted a similar efficacy to prednisone, if disease was confined to the ileum or ascending colon. Efficacy decreased with colonic involvement beyond the ascending colon, even though a significant proportion (47%) of patients with colonic involvement went into remission on the standard 9-mg dose.[10]

A Phase I study of 1 mg, 2 mg, and 3 mg capsules of Budenofalk was conducted in healthy adult volunteers.[17] The area under the time–effect curve indicated a dose-dependent effect. A study in which the dose was doubled from 9 mg/d to 18 mg/d achieved higher remission rates but more systemic side effects.[18]

We hypothesized that by increasing the initial dose from 9 to 12 mg/d we could increase the dose effect as well as increase the amount of budesonide reaching the colon, without increasing systemic exposure to a significant degree, due to the high rate of first-pass metabolism. Finally, we hoped to evaluate the optimal dosing of oral budesonide for pediatric and adolescent patients. In the present study the efficacy and safety of 2 dose regimens of Budenofalk capsules was to be investigated in children and adolescents age 10–19 years suffering from active CD.

MATERIALS AND METHODS

Protocol

The purpose of the present study was to evaluate the effect of 2 different dosing regimens of oral budesonide on disease activity and remission in mild to moderately active pediatric CD. This was a randomized, active-controlled, double-blind, parallel group, multicenter clinical study performed by the Israeli Society of Gastroenterology, Hepatology and Nutrition (ISPGHAN) budesonide study group in 10 pediatric gastroenterology units throughout Israel in 2003–2006. As a result, the study was not registered with the National Institutes of Health (NIH) trial registration site. Eligible patients with active CD, age 10–19, were randomized via a randomization scheme to 1 of the 2 following treatment groups.

Group 1: 9 mg budesonide daily for 7 weeks and then 6 mg budesonide daily for an additional 3 weeks (total treatment, 10 weeks).

Group 2: 12 mg budesonide daily for 4 weeks followed by 9 mg budesonide daily for 3 weeks and then 6 mg budesonide daily for additional 3 weeks (total treatment, 10 weeks).

All patients had an established diagnosis of CD determined by endoscopy and histology, a history of symptoms and disease, and/or definitive radiology.[19]

Patients of either sex meeting the following criteria were to be included in the study: signed informed consent, male or nonpregnant, nonbreast-feeding female between 10 and 19 years of age, negative stool culture and test for parasites at baseline for exclusion of infectious ileocolitis, a previous diagnosis of CD or newly diagnosed disease with symptoms for at least 1 month, and active CD defined by a Pediatric Crohn's Disease Activity Index (PCDAI) at baseline >12.5 and ≤ 40.[20] Patients presenting with any of the following were excluded from the study: macroscopic intestinal involvement above the ileum, short bowel syndrome, prior colostomy or ileostomy, abdominal abscess, intestinal fistula, or small bowel obstruction, symptomatic stenosis and/or ileal stricture, imminent surgery, evidence for infectious bowel disease at enrolment, lack of appropriate contraception in females of childbearing potential, a serious secondary illnesses of an acute or chronic nature, a history of tuberculosis, HIV, hepatitis B or C, impaired hepatic function

(alanine aminotransferase [ALT] >2 times upper normal limit), impaired renal function, or body weight <20 kg.

Exclusion criteria regarding medications were as follows: Any corticosteroid therapy within 6 weeks prior to inclusion, treatment with thiopurines for less than 12 weeks prior to inclusion or any change in dose of thiopurines in the last 8 weeks prior to inclusion or during the study, treatment with anti-tumor necrosis factor alpha (TNF-α) or experimental agents within 8 weeks prior to inclusion or need for treatment with any of these drugs during the study, treatment with combination therapy of 5-aminosalicylate (5-ASA) with 6-mercaptopurine (6-MP) or azathioprine, or treatment with cyclosporine or methotrexate 12 weeks prior to inclusion or during the study. Methotrexate use was excluded due to lack of safety data in pediatrics at the time, and the concern for development of hepatotoxicity as a confounding factor in budesonide metabolism. Cyclosporin may affect budesonide metabolism. Use of stable dose mesalazine (5-ASA) ≤4 g/d, or stable dose of thiopurines were permitted provided that the actual dose had not been changed within the last 8 weeks prior to inclusion in the study. Antibiotics had to be discontinued prior to enrollment.

The primary endpoint was the mean change from baseline of the PCDAI sum score after 7 weeks of treatment. The secondary objectives were to examine the remission rate at the end of therapy, defined as a PCDAI score ≤12.5 at the end of therapy, response defined as a decrease in PCDAI of at least 10 points or remission at week 7, tolerability (adverse events), and a decrease in C-reactive protein (CRP) between the 2 groups. Studies have shown that remission could be defined as a PCDAI of 10 or 12.5, or less.[21] The cutoff of 12.5 points was chosen since this was a short-term trial, and height velocity does not increase immediately when clinical remission is obtained (and is scored the same as entry if it does not) and may never increase if the patient is a pubescent female adolescent. In addition, hemoglobin and hematocrit may take time to normalize even if clinical and inflammatory remission are obtained.

Assignment and Masking

Allocation to treatment was to be performed by means of a computer-generated randomization scheme. To guarantee the double-blind design of the study in both treatment groups, all patients had to take the same number of capsules per day during the whole treatment period. Therefore, both medication and placebo capsules were supplied in prepackaged blisters to the patients. Both the capsules containing active treatment and the capsules containing placebo were indistinguishable, thus allowing double-blind conditions to be maintained. Patients were supplied with a symptom diary. The medication packets and remaining capsules were collected during patient visits to monitor compliance.

Follow-up

Patients' progress was assessed at the baseline enrollment visit, and visits at 2, 4, 7, and 10 weeks (all patients ceased budesonide after 10 weeks) from initiation of therapy. The PCDAI, height, weight, complete blood count, sedimentation rate, CRP, and biochemical parameters (albumin, ALT, AST, creatinine, BUN, electrolytes and glucose) were evaluated at each visit. In addition, at the end of the treatment visit the investigators recorded their global assessments of efficacy; patients and investigators recorded their global assessments of safety. Adverse events and other safety-related variables were recorded throughout the study. A rapid adrenocorticotropin hormone (ACTH; 0.25 mg/mL Synacthen, Novartis, Switzerland) with cortisol levels drawn at baseline, 30, 60 minutes was performed at the baseline visit and at week 7. Cortisol levels were considered normal if the baseline cortisol was ≥5.4 μg/dL and the 60-minute cortisol was ≥18 μg/dL, and the difference between pre- and post-ACTH test was ≥5.4 μg/dL. Patients who required an alteration in their treatment regimen because of disease activity during the study were withdrawn and considered failures.

Data Analysis

For statistical analysis, 3 datasets were defined: The safety dataset (all patients who had received study medication at least once), the full analysis set (FAS) (all patients of the safety data set who had CD at baseline), and the per-protocol (PP) dataset (all patients of the FAS, except those with a major protocol deviation or a premature study termination definitely not related to the study medication).

Descriptive statistical methods were used to analyze all variables. Whenever appropriate, standard summary statistics (number of valid cases, mean, standard deviation, minimum value, 1st quartile, median, 3rd quartile, maximum value) including 2-sided 95% confidence intervals (CIs) were calculated. Categorical values were presented in frequency tables.

Subgroup analyses by gender (male, female), PCDAI at baseline (high: ≥30, low: <30), duration of CD (<6 months, 6 to <24 months, ≥24 months), the presence of extraintestinal manifestations (yes, no) were performed for the primary efficacy variable.

Time to remission and time to improvement were analyzed with a time-to-event analysis. The mean and median time to event, standard error, and 95% CIs of the mean time-to-event, 95% CIs of the median time-to-event as well as the hazard ratio and its 95% CIs were derived from a Kaplan–Meier analysis.

Missing values were replaced by the corresponding values of the individual last observation (last observation-carried-forward [LOCF] method) including the baseline visit for the efficacy analyses and reported separately in the statistical tables. For the safety analyses, the baseline visit was

TABLE 1. Demographic and Baseline Characteristics (FAS)

		Group 1 (n = 35)	Group 2 (n = 35)
Sex			
Male	n (%)	22 (62.9%)	23 (65.7%)
Female	n (%)	13 (37.1%)	12 (34.3%)
Age [years]	Mean (SD)	13.6 (2.8)	14.4 (2.5)
Height [kg]	Mean (SD)	153.6 (13.9)	157.5 (14.5)
Weight [cm]	Mean (SD)	43.13 (12.68)	48.60 (16.15)
BMI [kg/m^2]	Mean (SD)	17.87 (3.03)	19.17 (4.49)
BSA [m^2]	Mean (SD)	1.35 (0.25)	1.45 (0.29)
Height percentile [th]	Mean (SD)	34.6 (27.9)	38.8 (29.8)
Duration of the disease [years]	Median (range)	7.90 (1.1-80.4)	12.92 (1.2-98.4)
Time since first confirmation of the disease (histo. or radio.) [months]	Median (range)	0.43 (0.0-78.9) [n = 35]	2.77 (0.0-74.1) [n = 34]
Persistence of present symptoms [months]	Median (range)	2.49 (0.3-28.6)	1.90 (0.2-83.6)
Course of the disease			
Continuous	n (%)	23 (65.7%)	19 (54.3%)
Recurrent	n (%)	12 (34.3%)	16 (45.7%)
Disease behavior			
Nonstricturing/nonpenetrating	n (%)	34 (97.1%)	34 (97.1%)
Stricturing	n (%)	1 (2.9%)	1 (2.9%)
Patients with extraintestinal manifestations	n (%)	8 (22.9%)	8 (22.9%)
Patients with intestinal fistulas	n (%)	0 (0.0%)	0 (0.0%)
Patients with perianal fistulas	n (%)	0 (0.0%)	0 (0.0%)
Sections affected by inflammation			
Ileum	n (%)	34 (97.1%)	33 (94.3%)
Cecum	n (%)	19 (54.3%)	16 (45.7%)
Ascending colon	n (%)	14 (40.0%)	11 (31.4%)
Transverse colon	n (%)	10 (28.6%)	6 (17.1%)
Descending colon	n (%)	9 (25.7%)	6 (17.1%)
Sigmoid	n (%)	9 (25.7%)	8 (22.9%)
Rectum	n (%)	7 (20.0%)	6 (17.1%)
Upper GI (incl. duodenum)	n (%)	1 (2.9%)	0 (0.0%)
PCDAI	Mean (SD)	28.86 (7.18)	26.29 (7.13)

not included. With a sample size of 70 subjects, the present study was designed to detect a true within-group difference in PCDAI scores between baseline and final visit of 10 ± 15 points using the t-test for paired samples.

RESULTS

A total of 72 patients were enrolled, of whom 70 actually received the study medication. Thus, 70 patients were available for efficacy and safety analysis (FAS), 35 in each group. Entry data for the 2 groups are presented in Table 1. The 2 groups did not differ with regard to disease activity or baseline entry criteria. Patients in Group 2 were slightly heavier and diagnosed slightly later than those in Group 1 (not significant). Four patients in Group 2 and 3 patients in Group 1 entered the trial on stable dose thiopurines, 2 patients in Group 1 and 1 in Group 2 received a PPI at any time during the study. Sixty-one patients remained in the per-protocol analysis; 9 patients were excluded from the FAS (5 Group 1 and 4 Group 2) because of protocol violations (primarily inclusion/exclusion criteria regarding change of dose of stable medications prior to or during the study, identification of disease above the ileum, or use of concomitant treatments such as metronidazole). One patient in Group 1 was excluded because of poor compliance in violation of the protocol. Two

TABLE 2. Primary and Secondary Efficacy Endpoints (FAS)

	9 mg/d $N = 35$	12 → 9 mg/d $N = 35$
Mean change of PCDAI from baseline to week 7	−10.79	−14.21
Clinical remission (PCDAI ≤ 12.5) end of treatment	42.9%	65.7%**
Clinical remission (PCDAI ≤ 12.5) wk 7	51.4%	68.6%
Clinical improvement (ΔPCDAI ≥ 10) Wk 10	51.4%	74.3%*

*$P = 0.05$; **$P = 0.054$.

patients (1 from each group) with questionable stricturing not detected or reported at onset were included in the FAS because they had received the full treatment. Both patients responded with complete remission.

Results of the primary endpoint variable, a decrease in PCDAI by group, are presented in Table 2. Both doses showed a statistically significant decrease in mean PCDAI from baseline ($P = 0.0001$). Although there was a trend favoring the 12-mg induction dose in both remission and response items, these differences were not statistically different for response (Group 1, −10.79 ± 14.18 points [95% CI −15.66, −5.92], versus −14.21 ± 10.65 [95% CI −17.87, −10.55] in Group 2). Differences in the rate of patients with remission or improvement between treatment groups were not statistically relevant at visit 5 (LOCF) except for the PP analysis set ($P = 0.02310$, χ^2 test, 2-sided). A decrease of 10 points or more occurred more significantly in Group 2 at week 10.

About one-third of the patients in Group 1 and about 60% of the patients in Group 2 showed remission at visit 3. Until visit 5 (LOCF), remission rates increased to about 50% in Group 1 and about 70% in Group 2. Thereafter, remission rates slightly decreased in Group 1 and remained about constant in Group 2. Remission rates were higher in Group 2 than in Group 1 at all visits. Differences in remission rates between treatment groups were statistically relevant at visit 3 and at visit 6 (LOCF) only in the PP analysis. At the end of treatment, remission rates (Table 2) in Group 2 were higher than in Group 1, with borderline significance (FAS $P = 0.054$, per-protocol $P = 0.029$).

The mean CRP (SD) at baseline was 46.98 ([46.97] mg/L for Group 1 and 37.13 [36.46] mg/L for Group 2; this was not statistically significant). The decrease in CRP concentration from baseline was statistically relevant only in Group 2 ($P = 0.0206$). From visit 2 to visit 5 CRP concentration (SD) decreased by −8.6 (20.4) mg/L in Group 1 and by −13.7 (27.7) mg/L in Group 2. According to the 95% CIs the decrease in CRP concentration was statistically relevant only in Group 2 (−25.194, −2.300). In Group 1 the level of significance was not quite reached (−17.202, 0.042). Mean albumin levels increased from baseline to visit 6 in both groups without significant differences between groups (3.49 to 3.67 g/dL in Group 1 and from 3.74 to 3.93 g/dL in Group 2). In Group 1, 31% had a low albumin at visit 6 in comparison to 25.8% in Group 2. Hemoglobin decreased in Group 1 from 12.02–11.55 g/dL, and increased slightly in Group 2 (11.83–11.98). At the last visit the percentage of patients with a normal rating (PCDAI score 0) for the 3 subjective scores in the PCDAI (pain, stools, and well being) were higher in Group 2 than in Group 1, as were the ESR, hematocrit, and albumin. These differences were not significant.

After 7 weeks of treatment the mean PCDAI sum score decreased in both treatment groups in patients with colonic involvement, whereas in patients without colonic involvement a clear decrease was observed only in Group 2 (−14.4 ± 8.7 points, 95% CI −10.3 to −18.5) for Group 2 versus (−5.2 ± 14.1, 95% CI +2.4 to −12.72) for Group 1. There was no difference in the decrease of the mean PCDAI sum score between treatment groups in patients with colonic involvement. A nonsignificant trend favoring Group 2 was found in patients with disease duration <6 months, above age 12, and a PCDAI <30.

Median time to remission was shorter in Group 2 compared to Group 1 (median and 95% CI: 17 days [15, 28] versus 28 days [18, 48], hazards ratio 1.54 [0.869, 2.729]). The data are presented in Figure 1. Weight gain over the 10-week period was slightly better in Group 2 (mean gain 1.31 kg Group 2 versus 0.79 kg in Group 1), although these were not significantly different.

There were no significant differences in adverse events, serious adverse events, drug-related adverse events, or serum cortisol levels (Table 3). Three patients in Group 1 and 1 patient in Group 2 developed acne that had not been noted to be present prior to therapy by visit 6 (LOCF). One patient in Group 2 and none in Group 1 noted increased facial hair. One patient in Group 1 and none in Group 2 noted new onset peripheral edema. A poor global tolerability was expressed

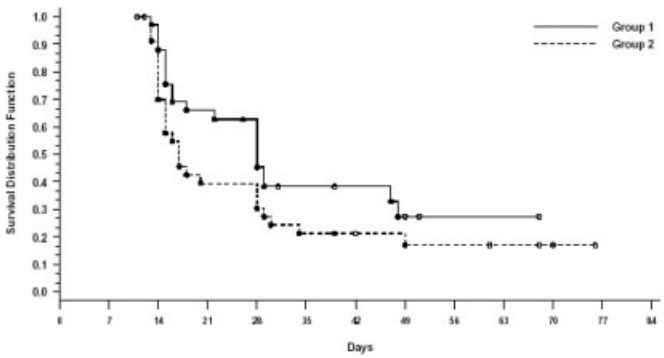

FIGURE 1. Median time to remission.

TABLE 3. Safety

		9 mg/d	12 → 9 mg/d
Patients with AEs[a]	[*n* (%)]	19/35 (54.3%)	23/35 (65.7%)
Patients with SAEs[a]	[*n* (%)]	0	0
Patients with any SAE	[*n* (%)]	10/35 (28.6%)	6/35 (17.1%)
Cortisol < 5.4 μg/dL	[*n* (%)]	15/24 (62.5%)	17/26 (65.4%)

[a]Documented as at least possibly drug-related. Treatment emergent adverse events (AEs), serious adverse events (SAEs).

by only 1 patient each in Group 1 and Group 2, and also in 1 patient for each group by the investigator-rated global tolerability rating.

DISCUSSION

Although systemic corticosteroids have been the mainstay of therapy for many years, they are less than optimal as a therapeutic agent. The major source of dissatisfaction has been due the side effects associated with their use. In pediatric disease, corticosteroid-related side effects such as cosmetic changes (acne, hirsutism, edema, and central obesity) or growth retardation may be a significant cause of dismay among parents, patients, and physicians. Furthermore, the use of systemic corticosteroids in mild to moderate disease may be even more difficult to justify if there are other effective agents with fewer side effects. Oral budesonide was designed to fill this niche, but its use in children has been slow to catch on. The 2 primary reasons for this may be the lower remission rate seen in comparison to oral corticosteroids, and the perception that it is not efficacious in patients with colonic involvement, which is common in children.

Our study design differed from all previous pediatric studies in that we included an arm with a higher induction dose, and did not exclude patients with distal colonic disease.[13–15] We found that both doses caused an improvement in response rates and remission rates, with a nonsignificant trend to higher response rates, and a faster time to remission in the 12-mg induction phase arm (Group 2). However, these differences were not statistically significant. More important, the end of treatment remission rate showed a strong trend toward clinical superiority for the 12-mg induction group (65.7% versus 42.9% ITT, $P = 0.054$, 74.2% versus 53.3% per-protocol, $P = 0.029$), and a significant reduction in CRP compared to baseline, suggesting a benefit for the higher induction dose as initial treatment. This effect was not compromised by an increase in serious adverse events, steroid-associated side effects or cosmetic events, or adrenal insufficiency, nor was it due to patients in Group 2 being smaller or lighter. The borderline *P*-value for remission compromises our ability to state categorically that use of an induction dose is superior at this point, and further studies in larger cohorts are needed to evaluate this measure.

Our initial hypothesis that a higher induction dose would be beneficial because of a higher response among patients with colonic disease was not validated by the results. In fact, the response rates among patients with colonic disease did not differ statistically by group. The major difference was accounted for by a higher remission rate in patients without colonic involvement. This result may suggest that current doses are suboptimal for ileal disease, and that response and remission rates might be improved by an initial increase in dose, without requiring longer exposure to medication or a longer taper.

An interesting outcome of the study was that budesonide (specifically pH-modified release oral budesonide) can be used effectively in patients with ileal disease even if colitis is present. Approximately one-quarter of patients also had disease of the distal colon. The remission rate seen in the 12-mg induction group is similar to the remission rate observed with oral corticosteroids,[9,10,13–15] even though the colon is affected. Oral budesonide has often been limited to therapy of the ileum and ascending colon[11,12,15,22] in clinical trials, which can introduce bias in trying to interpret the remission rates in real-life scenarios. A recent study performed in patients with ulcerative colitis given oral pH-modified budesonide detected significant levels in mucosal biopsies, and a better response rate after 9-mg once-daily dosing (71%) in the distal colon after 8 weeks than after 3 mg 3 times/day (38%),[21] further illustrating that pH-modified oral budesonide can be used in CD patients even if the colon is significantly involved.

There are only 2 small previous prospective studies that have evaluated oral budesonide in mild to moderately active CD; the combined number of patients from both these studies was similar to the number of patients in the present study. Escher et al[15] evaluated 9 mg/day of budesonide or 1 mg/kg/day prednisolone as initial therapy. The remission rate was 55% in the budesonide arm and 71% in the oral corticosteroid arm. Significantly, inclusion criteria included disease confined to the ileum or ascending colon. Levine et al[13] evaluated oral budesonide 9 mg/day versus prednisone 2 mg/kg/day as initial therapy. In that study, patients with distal colonic involvement were not excluded. The remission rate was 47% in the budesonide arm and 50% in the prednisone treated group. The results from the 12-mg/d induction dose in our present study appear to be as good as the results from the oral corticosteroid arms in both these studies, without the increase in cosmetic side effects.

Previous studies have shown that remission using PCDAI could be defined by cutoffs ranging from 10–12.5. A North American task group recommended defining remission as a PCDAI of 10 or less.[24] Recalculating the remission rates

based on that recommendation would reduce the remission rates to 48.6% in Group 2 versus 31.4% in Group 1 ($P = 0.14$). Similarly, response was defined by the same task group as a drop of 12.5 points or more; using this criterion the response rate was 62.9% for Group 2 versus 45.7% in Group 1. These guidelines were based on data that included long-term remission as an endpoint, and may be problematic in evaluating remission in short-term trials such as ours. The PCDAI was shown to be problematic for detecting early remission in a short-term European budesonide study in children, even though they met criteria for remission using CDAI and physicians global assessment.[15,24]

In conclusion, we have shown that use of a slightly higher induction dose of budesonide followed by a budesonide taper can give excellent results in both clinical remission and a decrease in markers of inflammation. This occurred without an increase in steroid-associated or serious adverse events. Although our results suggest that this treatment approach could be used in mild to moderate pediatric CD, larger cohorts are needed to confirm our findings.

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