ALIMENTARY TRACT

A Multicenter Trial of 6-Mercaptopurine and Prednisone in Children With Newly Diagnosed Crohn's Disease

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See editorial on page 1158.

Background & Aims: **Clinical experience suggests that 6-mercaptopurine (6-MP) is effective therapy for children with active steroid-dependent Crohn's disease (CD). We report the results of a prospective, placebo-controlled, multicenter trial evaluating the combination of 6-MP and prednisone as therapy for children with newly diagnosed moderate-to-severe CD.** ***Methods:*** **Fifty-five children (age, 13 ± 2 years) were randomized to treatment with 6-MP (1.5 mg · kg^{-1} · day^{-1}) or placebo within 8 weeks of initial diagnosis. Both groups also received prednisone (40 mg/day). Prednisone dosage adjustments were based on a defined schedule determined by the change in a subject's disease activity score, and steroid administration was discontinued as remission was achieved. Study treatment with 6-MP or placebo continued for 18 months.** ***Results:*** **Groups were comparable for age, sex, and site and activity of disease. In the 6-MP group, the duration of steroid use was shorter ($P < 0.001$) and the cumulative steroid dose lower at 6, 12, and 18 months ($P < 0.01$). Although remission was induced in 89% of both groups, only 9% of the remitters in the 6-MP group relapsed compared with 47% of controls ($P = 0.007$). Growth was comparable in both groups. No clinically significant adverse events occurred, although mild leukopenia and increases in aminotransferase activity were noted in the 6-MP group.** ***Conclusions:*** **Addition of 6-MP to a regimen of corticosteroids significantly lessens the need for prednisone and improves maintenance of remission. 6-MP should be part of the initial treatment regimen for children with newly diagnosed moderate-to-severe CD.**

The inadequacies of current therapy for pediatric Crohn's disease (CD) have stimulated the search for treatments to maintain remission while limiting corticosteroid exposure.[1] 6-Mercaptopurine (6-MP) and azathioprine are increasingly used as therapeutic alternatives.[2,3] Controlled trials in adults with chronic, intractable, or corticosteroid-dependent CD show that these agents effectively induce and maintain remission.[4–10] There have been no controlled trials of either agent in pediatric CD, but clinical experience[3,11–14] supports the observations in adults. In addition, no study has explored the role of 6-MP or azathioprine in the treatment of adults or children with newly diagnosed CD.

The primary objective of this multicenter trial was to determine whether 6-MP decreased the need for corticosteroids in children and adolescents with newly diagnosed moderate-to-severe CD. Secondary objectives included determining whether the addition of 6-MP to a therapeutic regimen of corticosteroids improves disease remission rates, decreases the frequency of relapses, or promotes improved linear growth.

Materials and Methods

Study Design

This prospective, double-blind, placebo-controlled 18-month clinical trial involved 18 U.S. pediatric centers (Appendix 1). The protocol was approved by the institutional review board of each collaborating investigator. Written informed consent was obtained from parents. Children older than 12 years signed a statement of assent. All subjects were <18 years of age, had CD diagnosed within 8 weeks of randomization, and had disease activity scores in the moderate-to-severe range. Children with body weights <24 kg were excluded. CD was diagnosed after a standardized evaluation that included upper gastrointestinal series with small bowel follow-through and colonoscopy with biopsy.

Abbreviations used in this paper: HB, Harvey–Bradshaw score; ΔHB, difference between current and previous partial HB; 6-MP, 6-mercaptopurine; PCDAI, Pediatric Crohn's Disease Activity Index; pHB, partial Harvey–Bradshaw score.

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Subjects were enrolled before receiving any treatment or after ≤2 weeks of unsuccessful treatment with a 5-aminosalicylate medication (immediate enrollment). Subjects could also be enrolled if they had received ≤6 weeks of prednisone (delayed enrollment), as long as the prednisone had been prescribed and decisions regarding dosage adjustment made exactly according to the study's dosing protocol. In the case of delayed enrollment, a child was considered to have begun protocol treatment when corticosteroid treatment began.

Disease Activity

Disease activity was primarily assessed using the Harvey–Bradshaw (HB) score (Table 1),[15] although a Pediatric Crohn's Disease Activity Index (PCDAI) was also determined at the time of initial randomization.[16] For subject inclusion and decisions during telephone follow-up regarding changes in steroid dosing (see below), only the first 3 parts of the HB score, labeled the partial HB (pHB) score, were considered. Preliminary investigation before the inception of the study showed that most children's total HB scores were derived primarily from the first 3 parts of the score (unpublished observations). Previous work had shown a high degree of correlation between the physician's global assessment of disease activity and HB score; 75% of children with moderate CD and virtually all children with severe CD activity have total HB scores of ≥4.[16] Based on these observations, for this study moderate-to-severe disease activity was defined as pHB of ≥5 points. For all other purposes, the total HB score was used. Inactive disease was defined as a total HB score of <3, remission as 2 successive monthly total HB scores of <3, and relapse as 2 successive scores of ≥4 obtained no closer than 1 week apart.

Table 1. Modified Harvey–Bradshaw Score

	Possible subscore	
General well-being		Score____
Very well	0	
Slightly below par	1	
Poor	2	
Very poor	3	
Terrible	4	
Abdominal pain		Score____
None	0	
Mild	1	
Moderate	2	
Severe	3	
Number of liquid stools		Score____
0	0	
1–2	1	
3–4	2	
5–6	3	
7–8	4	
>8	5	
Abdominal mass		Score____
None	0	
Dubious	1	
Definite	2	
Definite and tender	3	
Complications		Score____
Arthralgia, uveitis, *E. nodosum,* aphthous ulcers, pyoderma gangrenosum, draining fistula, abscess, temperature > 38°, cutaneous vasculitis	Score 1 for each item	
Total HB score (sum of parts 1–5 inclusive)		Score____
Partial HB score (sum of parts 1–3 inclusive)		Score____

Treatment Protocol

Subjects were randomized using permuted blocks to 1 of 2 treatments. Subjects in the experimental (6-MP) group received both prednisone and 6-MP. Controls received prednisone plus placebo tablets identical to 6-MP. Prednisone (5-mg scored tablets; Roxanne Laboratories, Columbus, OH, or Danbury Pharmacal Inc., Florham, NJ) was purchased by the coordinating center and dispensed to all subjects. The 6-MP (50-mg tablets) and matching placebo were donated by Glaxo-Wellcome (Research Triangle Park, NC) and dispensed precut in half to facilitate accurate daily dosing. Subjects in the 6-MP group received 6-MP, 1.5 mg/kg body wt daily, rounded to 25-, 50-, or 75-mg doses (½, 1, or 1½ tablets per day). The control group received placebo tablets prescribed as ½, 1, or 1½ tablets per day according to the same parameters used for 6-MP. The 6-MP/placebo dose remained constant throughout the 18-month study. 6-MP metabolite levels were not assessed because the assays were not commercially available when the study began. However, 6-MP/placebo dosage was halved if leukopenia (defined as absolute neutrophil count $<1500/mm^3$) was determined during routine laboratory follow-up, and discontinued and the subject withdrawn from the study if leukopenia persisted on a repeat white blood cell (WBC) count 2 weeks later. Parents were permitted to crush all study tablets and administer the medications mixed with food if necessary. Subjects could receive only the study medications dispensed by the coordinating center. Appropriate nutritional supplementation was encouraged, but nasogastric or gastrostomy feedings and parenteral nutrition were disallowed. No other treatments for CD were permitted.

Subjects in both groups received corticosteroids according to an identical dosing regimen (Tables 2 and 3). Corticosteroids were initiated as either 32 mg/day of intravenous methylprednisolone (for pHB ≥ 9) or 40 mg/day of oral prednisone (for pHB 5–8). Changes in corticosteroid dose were allowed only at predetermined times (Table 2), and the dosage was increased, decreased, or left unchanged based on the difference (designated ΔHB) between the pHB and its immediate predecessor. Decreasing disease activity was defined as a negative ΔHB, increasing activity as a positive ΔHB (Table 3). Reductions in corticosteroid dose were made if the ΔHB was negative, or if the pHB was ≤2. A positive ΔHB required an increase in the dose of corticosteroid to the next higher level. For every corticosteroid level, the minimum duration of use was predetermined by protocol. If disease activity permitted,

Table 2. Corticosteroid Adjustment Timetable

Level	Corticosteroid dose	Minimum duration of use[a]
1	Methylprednisolone 16 mg IV every 12 h	1–2 wk
2	Prednisone 40 mg PO every morning	1 mo
3	Prednisone 30 mg PO every morning	2 wk
4	Prednisone 20 mg PO every morning	2 wk
5	Prednisone 20 mg alternating with 15 mg PO every morning	8 days
6	Prednisone 20 mg alternating with 10 mg PO every morning	8 days
7	Prednisone 20 mg alternating with 5 mg PO every morning	8 days
8	Prednisone 20 mg PO every other day	8 days
9	Prednisone 15 mg PO every other day	8 days
10	Prednisone 10 mg PO every other day	8 days
11	Prednisone 5 mg PO every other day	8 days
12	Discontinue prednisone	

IV, intravenous; PO, orally.
[a]Actual duration of use of each corticosteroid level depends on the pHB score and the change from the previously determined pHB score (see text and Table 3).

prednisone could be weaned to every-other-day dosing and eventually discontinued (Table 2). Once remission was achieved and prednisone discontinued, a flare of disease activity could dictate another course of prednisone. Dosage adjustments during this second course were determined in the same manner as the initial corticosteroid course.

Office follow-up for physical examination, height and weight measurements, and calculation of pHB and total HB score occurred monthly, and more frequently if disease activity was required. Medication compliance was determined by pill count. Complete blood count with differential, erythrocyte sedimentation rate, and serum amylase and biochemistry levels were measured at predetermined intervals. Between visits, there were telephone contacts as often as every 8 days to determine the pHB and ΔHB. In all office visits and during telephone contacts, corticosteroid dosage adjustments were standardized from center to center (Tables 2 and 3). Subjects could be withdrawn from the study at any time because of treatment failure, adverse reaction to treatment medications, or noncompliance. Treatment failure was defined as HB score ≥ 9 despite 2 weeks of intravenous corticosteroid treatment. Treatment failure was also defined as any patient who required therapy for symptoms or complications of CD, which was not allowed by study protocol.

Statistical Analysis

Cumulative prednisone dose was calculated based on the daily steroid dose prescribed. For these calculations, 32 mg/day of intravenous methylprednisolone was considered equivalent to 40 mg/day of prednisone. Based on the intent-to-treat principle, all subjects who began therapy and withdrew before completion of the study had their last daily prednisone dose carried forward to the end of the study. Differences in cumulative prednisone dose between groups were compared using the Mann–Whitney test.

The incidence density ratio method[17] was used to determine observed-to-expected ratios for "time until" calculations (such as time until steroids were discontinued or until remission) to take into account the differing lengths of follow-up among subjects. In this method, the null hypothesis is that the number of days for any measure in each group will be proportional to the total number of days of observation for each group (Appendix 2). "Time until" event distributions were calculated using the product-limit method and compared using the log-rank test. Additional comparisons were performed using the unpaired t test, Fisher exact test, or Mann–Whitney test as appropriate. All analyses were computed using SAS software (Cary, NC). Unless otherwise noted, data are expressed as means $\pm$ SD or medians with 95% confidence intervals. Differences between groups were considered significant for $P < 0.05$.

Results

Study Population

Sixty-five children were randomized at 18 collaborating sites (range, 1–12 subjects per site), but 10 were excluded from analysis, including 7 whose parents changed their minds about participating in the study before initiating treatment and 2 (1 from each treatment group) whose poor compliance with follow-up appointments resulted in significantly incomplete and noninterpretable data records. One additional randomized subject took <85% of the prescribed dose of medication within the first 2 months of study, was withdrawn per protocol by the local investigator, and was therefore not included in the analysis. The remaining 55 subjects were comparable for age, sex, sites of disease, disease activity, and "immediate" vs. "delayed" enrollment (Table 4). Subjects in both groups had comparable disease activity, with all

Table 3. Corticosteroid Adjustment Schedules

Current pHB score	ΔHB[a]	Mandatory dose adjustment[b]
9–12	−4 to +12	Level 1
5–8	−1 or less	Decrease 1 level
	0	No change
	+1 or more	Increase to level 4 or next highest level (whichever is highest)
3–4	−1 or less	Decrease 1 level
	0	No change
	+1 or more	Increase 1 level
0–2	−12 to +2	Decrease 1 level

[a]Change in pHB score calculated by determining the difference between the current and immediately preceding pHB scores.
[b]Levels correspond to those defined in the corticosteroid adjustment timetable (Table 2).

Table 4. Study Population at Randomization

	6-MP group	Controls
No. of subjects	27	28
Age (*yr*)	13.0 ± 2.3	13.4 ± 2.5
Sex (*M/F*)	15/12	18/10
Race (*% white*)	93	93
Sites of CD involvement [n (%)]		
Small bowel only	4 (14.8%)	1 (3.6%)
Small bowel + colon	19 (70.4%)	22 (78.6%)
Colon only	4 (14.8%)	5 (17.9%)
Disease activity scores		
Total HB score	7.7 ± 1.8	7.4 ± 1.9
pHB score	6.6 ± 1.3	6.5 ± 1.3
PCDAI	46.7 ± 13.9	44.7 ± 16.4
Enrollment category		
Immediate (%)	78	89
Delayed (%)	22	11
Initial daily prednisone dose ($mg \cdot kg^{-1} \cdot day^{-1}$)	1.12 ± 0.31	1.05 ± 0.28
Proportion of group with initial prednisone dose > 1 $mg \cdot kg^{-1} \cdot day^{-1}$	59%	54%

NOTE. All differences between groups do not reach statistical significance.

disease activity measures (HB score, pHB, and PCDAI) falling in the moderate-to-severe range. The initial mean prednisone dose per kilogram body weight per day and the proportion of each group whose initial prednisone dose was >1 mg/kg body wt per day were also similar.

The 18-month trial was completed by 21 of 27 (78%) patients in the 6-MP group but only 11 of 28 (39%) controls ($P < 0.01$). The primary reason for early withdrawal was treatment failure (3 6-MP subjects, 15 controls). Additionally, 1 6-MP subject was withdrawn for leukopenia and 2 for noncompliance, while 1 control was withdrawn for fever and 1 for noncompliance. These 23 subjects are included in the analysis.

Corticosteroid Use

Subjects in the 6-MP group required fewer days of corticosteroid treatment than controls, as evidenced by an observed-to-expected ratio of days on prednisone of 0.73, compared with 1.34 in the control group ($P < 0.001$). Although both groups required comparable periods for initially weaning from prednisone (6-MP median, 121 days; 95% confidence interval [CI], 117–143; control median, 131 days; 95% CI, 120–178; P = NS), subjects in the 6-MP group were able to remain off of prednisone treatment significantly longer than controls (Figure 1). After being weaned off of prednisone, only 1 of the 6-MP subjects required another course of steroids within 540 days. By contrast, 31% of controls required a second course of steroids within 90 days, and 57% resumed prednisone within 1 year ($P < 0.0001$). As a result, the difference in cumulative prednisone dose gradually diverged in the 2 study groups after 3 months and became significantly different by 6 months. These differences were maintained through completion of the study, irrespective of whether the cumulative prednisone dose was calculated by the "last value carried forward" method (Figure 2) or by the actual amount of prednisone taken (Figure 3).

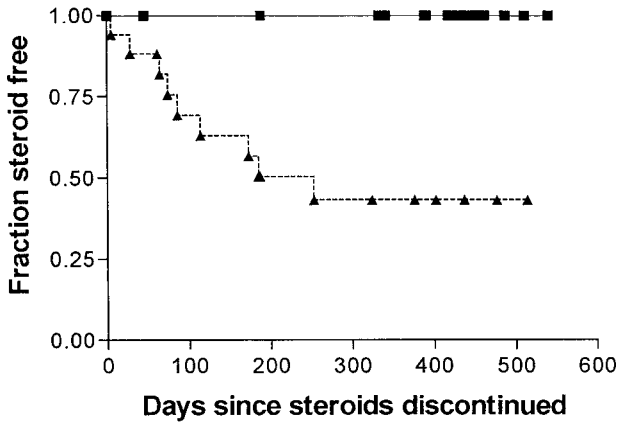

Figure 1. Time (days) off of corticosteroid treatment after initial discontinuation, depicted as a Kaplan–Meier survival curve. ■, 6-MP; ▲, controls. $P < 0.0001$.

Remission Analysis

After 1 month of treatment, 93% of the 6-MP group and 79% of controls had inactive total HB scores. By 3 months, all 6-MP subjects and all but 1 control had achieved at least 1 inactive HB score. By 12 months, both groups had a cumulative remission rate of 89%. However, remission was maintained significantly better in the 6-MP group (Figure 4). Among those in remission, only 1 (4%) 6-MP subject had a relapse within 180 days of achieving remission, compared with 7 (28%)

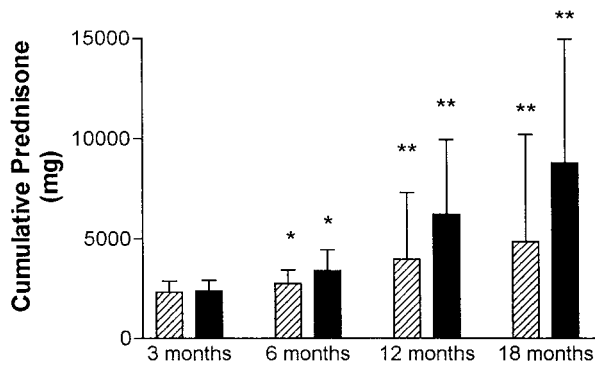

Figure 2. Cumulative prednisone dose (mean ± SD). All subjects who withdrew from the study had their last prednisone doses carried forward to the conclusion of the 18-month study period. ▨, 6-MP (n = 27); ■, controls (n = 28). *$P < 0.02$; **$P < 0.004$.

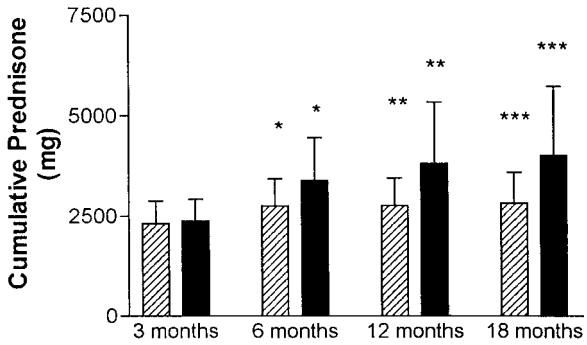

Figure 3. Cumulative prednisone dose (mean ± SD) actually taken by subjects in both groups from day of entry into the study until completion of the 18-month treatment period or until withdrawal. ▨, 6-MP (n = 27); ■, controls (n = 28). $*P < 0.03$; $**P < 0.007$; $***P < 0.008$.

controls. By 548 days after remission, only 9% of the 6-MP group had relapses, compared with 47% of controls ($P = 0.007$). Similarly, the observed-to-expected ratios for days in remission (6-MP = 1.07; control = 0.91) favored the 6-MP group ($P < 0.001$).

Growth

Linear growth did not differ between groups over the 18-month clinical trial (Table 5). Growth between groups was also comparable during each 6-month period after randomization.

Adverse Effects

Six of 27 (22%) 6-MP subjects had 1 or more WBC counts of $<4000/mm^3$, compared with 0 of 28 controls ($P = 0.01$). This included 1 6-MP subject who had a WBC count of $3800/mm^3$ before receiving 6-MP. The lowest WBC count was $3100/mm^3$, and the lowest absolute neutrophil count was $1221/mm^3$. This WBC count resulted in the subject being withdrawn from the study but was not associated with any untoward clinical event. No unusual or severe infections occurred in the leukopenic subjects or in any of the other subjects in either treatment group. However, 1 subject receiving 6-MP had multiple intra-abdominal abscesses secondary to enteric fistulas.

Five subjects (4 in 6-MP and 1 in control group) had 1 or more elevations of aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels. The control subject had increased values at baseline (AST, 231 U/L; ALT, 195 U/L). These persisted without clinical evidence of liver disease throughout the entire study. The 4 6-MP subjects had normal baseline AST and ALT levels but mild increases (maximum AST, 152 U/L; ALT, 137 U/L) at months 1 and 2. Three of the 4 had normal values at month 3 with no change in 6-MP dosing and did not subsequently demonstrate abnormalities. The fourth subject withdrew from the study at month 3 never having entered remission. None of these subjects had increases in serum bilirubin level or clinical evidence of liver disease.

No subject developed symptoms of pancreatitis or drug hypersensitivity. In addition, serum amylase levels remained normal in all subjects.

Surgery

One of 27 6-MP subjects required intestinal surgery within 18 months of diagnosis, compared with 3 of 28 controls ($P = 0.63$). All 4 were withdrawn from the study because of treatment failure between months 3 and 12. Resection or colectomy was performed 1–9 months after withdrawal.

Discussion

This is the first prospective, placebo-controlled trial to evaluate the effects of 6-MP in a pediatric population with CD. It is also the first to assess the efficacy of 6-MP as part of an initial treatment regimen for patients of any age with newly diagnosed CD. The results clearly support the use of 6-MP in the initial treatment of children and adolescents with moderate-to-severe CD. Compared with subjects treated with prednisone alone, those receiving 6-MP in addition to prednisone maintained remission longer and were exposed to significantly lower cumulative corticosteroid doses over the 18-month clinical trial. This was accomplished without significant adverse reaction.

We used many different statistical methods to evaluate the data derived during the course of the study. We based the analysis on the incidence density ratio method[17] to compare total time of corticosteroid therapy,

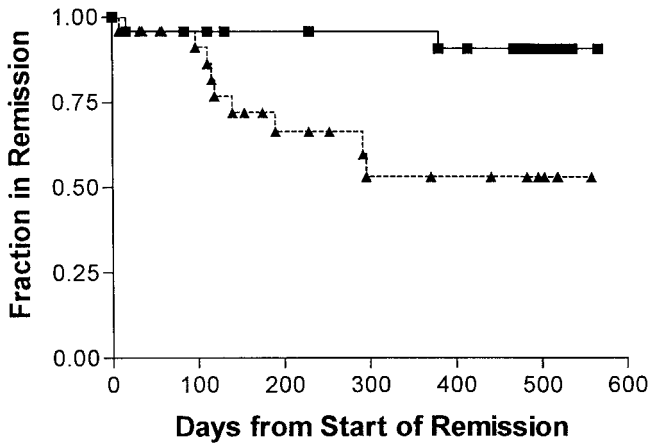

Figure 4. Kaplan–Meier survival curve of relapse-free duration of remission. ■, 6-MP; ▲, controls. $P < 0.007$.

Table 5. Linear Growth

Study time periods	Linear growth (*cm*)						
	6-MP			Controls			
	Mean ± SD	Median	n	Mean ± SD	Median	n	*P*
0–18 mo	6.8 ± 4.1	8.0	23	5.3 ± 4.0	5.0	24	0.3
0–6 mo	3.4 ± 2.9	3.5	26	1.9 ± 2.4	1.0	25	0.06
6–12 mo	0.7 ± 1.5	0	23	1.3 ± 2.1	0	24	0.4
12–18 mo	2.8 ± 2.6	3.0	23	2.3 ± 2.0	2.5	24	0.5

when a subject can have "on" and "off" periods. To use this method, one of the assumptions is that the likelihood of a subject using corticosteroids remains constant over the entire follow-up period. It is not unreasonable to consider that the likelihood of corticosteroid use actually decreases over time and, if follow-up in the 2 treatment arms is not the same, the treatment arm with the shorter follow-up (in this case the control group) may be biased toward higher corticosteroid usage. To account for this potential bias, we reanalyzed the data by artificially inflating the control follow-up to be equal to the 6-MP group follow-up without increasing the number of observed steroid days for the control group. Although this modification biases the hypothesis against 6-MP, the reanalysis also yielded a P value of <0.001, strongly suggesting that this bias, if it actually existed in our study, did not affect the results. The Kaplan–Meier survival curves further support these findings.

A recent meta-analysis[18] assessed the effectiveness of 6-MP or azathioprine for the treatment of adults with intractable or corticosteroid-dependent CD. It showed a favorable odds ratio for 6-MP or azathioprine therapy for induction of remission in active CD. Favorable odds ratios also supported their use as steroid-sparing agents, to close fistulas, and for maintaining remission. Duration of therapy was an important determinant of efficacy, with odds ratios favoring treatment becoming significant at 17 weeks after initiation of 6-MP or azathioprine. This delayed time until clinical response is similar in children, with the open-label trials identifying a mean response time of 3–4 months.[3,11–14] The steroid protocol adopted in the present study (minimum duration 16.3 weeks) was designed to compensate for 6-MP's slow onset of action.

Although there have been no previous controlled trials evaluating 6-MP or azathioprine in children and adolescents with CD, these drugs are frequently used. In a 1990 survey of pediatric gastroenterologists, 88 of 105 physicians reported prescribing them.[3] Small retrospective case series[11–14] and a larger multicenter survey[3] report positive clinical effects in children with steroid-dependent or intractable CD that closely mirror those in adult trials. Overall, 60%–75% of children treated with 6-MP/azathioprine experience significant lessening of disease activity, despite reduction or elimination of corticosteroids. Our study extends these observations to children with newly diagnosed CD.

There are no data in children with moderate-to-severe CD to suggest when, in what dosage, and for what period corticosteroids should optimally be used, but these agents have become the gold standard against which other treatments are judged.[19,20] Corticosteroids acutely induce remission,[21–23] but continued use does not prevent relapse. No previous study has determined what proportion of children with CD become steroid dependent. However, the corticosteroid regimen used in this study was designed to mimic the clinical approach used by many pediatric gastroenterologists. The control group shows that only 39% of children with newly diagnosed CD achieve long-term remission when treated with prednisone. Steroid dependence develops in 50%, and 11% are steroid resistant. These response rates are similar to but somewhat worse than those reported for an adult Danish population[24] and suggest that children may be somewhat more resistant to corticosteroid therapy than adults. The large number of control subjects who withdrew early from the study because of "treatment failure" included many who were steroid dependent, and all who were steroid resistant. The high dropout rate was probably influenced by pediatric gastroenterologists' reluctance to keep children on corticosteroid therapy for extended periods. Addition of 6-MP to the corticosteroid regimen reduces the rate of steroid dependence to 0 and significantly improves the long-term remission rate to 89%.

Although 6-MP subjects required less prednisone than controls, both groups grew comparably. Prednisone taken daily for 7–10 days decreases serum procollagen levels, a marker for linear bone growth.[25] As a consequence, corticosteroids have the potential to interfere with growth, even in the face of adequate dietary intake.[26] Growth failure in CD has frequently been ascribed to the use of corticosteroids, but studies also

suggest that the disease process itself, possibly because of circulating cytokines, may be responsible.[27,28] The comparable growth in our 2 treatment groups supports the latter hypothesis. However, our growth analysis should be interpreted with caution. The large number of early withdrawals in the control group resulted in uncontrolled treatments, in many cases including 6-MP or surgery, for a significant part of the 18-month trial. These treatments may have influenced the heights recorded 12 and 18 months after randomization.

Despite 6-MP's efficacy, concern about its use remains because of the potential for significant toxicity. However, extensive experience in both adult and pediatric inflammatory bowel disease patients has been characterized by a minimum of untoward reactions. Present et al.[29] reported on 18 years' follow-up of 396 patients with inflammatory bowel disease. Toxicity associated with 6-MP use included pancreatitis (3.3%), bone marrow suppression (2%), allergy (2%), and hepatitis (0.3%). Although occasional case reports in the pediatric literature have described serious complications such as overwhelming infection,[30] 2 large pediatric series report serious adverse reactions to be rare.[3,31] In clinical practice at the University of Chicago, 18% of children required discontinuation of 6-MP or azathioprine because of adverse reactions including pancreatitis (4%), fever (4%), gastrointestinal intolerance (3%), recurrent infections (3%), rash (2%), and leukopenia or thrombocytopenia (2%).[31] Pancreatitis, bone marrow suppression, and infections were each noted in $\leq$5% of the 165 cases compiled by a multicenter survey.[3] However, no adverse reactions were serious or life threatening. In our study, only 1 subject required discontinuation of 6-MP (for leukopenia without infection), and the 4 subjects with mild but self-limited increases in serum aminotransferase levels remained clinically well without changes in their 6-MP dose. However, we do not have liver biopsy results to assess possible subclinical hepatotoxicity in these subjects. In addition, there were no cases of pancreatitis, severe gastrointestinal intolerance, or allergy.

The other potential toxicity of persistent concern is malignancy. Small but definable increases in certain types of neoplasia, especially non-Hodgkin's lymphoma, have been described in patients treated with azathioprine for rheumatoid arthritis or after organ transplantation.[32,33] Despite extensive use of azathioprine and 6-MP in CD, however, a similarly increased risk has not been identified.[34] In the series of Present et al.,[29] 1 diffuse histiocytic lymphoma of the brain (0.3%) was possibly related to 6-MP. In a larger series from the St. Mark's Hospital, London, no excess of lymphoma or other neoplasia was noted in patients treated with 6-MP or azathioprine compared with those who did not receive these immunomodulators.[35] No malignancies have developed in any of our subjects, nor have any been described in children receiving either 6-MP or azathioprine for CD in clinical practice.

It appears, therefore, that 6-MP is safe, effective therapy for children with newly diagnosed moderate-to-severe CD activity. The addition of 6-MP to a therapeutic course of prednisone reduces the need for steroids and improves maintenance of remission over the first 18 months of treatment. Based on these data, 6-MP use should be considered as part of the initial treatment prescribed for children with newly diagnosed moderate-to-severe CD activity.

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Appendix 2: Incidence Density Ratio Method

The null hypothesis for the incidence density ratio method of analysis[17] is that the number of days each group is receiving corticosteroid therapy (or in remission) will be proportional to the number of days of observation for each group. This method was used to take into account the differing lengths of follow-up among subjects. First, the total number of subject days in the placebo arm (T0) and the total number of subject days in the 6-MP arm (T1) were computed. Next, the proportions of the total number of subject days (T0 + T1) represented by each experimental group were computed as $P0 = T0/(T0 + T1)$ and $P1 = 1 - P0$, respectively. Subsequently, the observed number of days on steroids for each group (S0 and S1) was computed. The expected number of days on steroids for each arm was then computed as $E0 = (S0 + S1) \cdot P0$ and $E1 = (S0 + S1) \cdot P1$. The χ^2 statistic, $[(S0 - E0)^2/E0] + [(S1 - E1)^2/E1]$ was computed and compared with the χ^2 distribution with 1 degree of freedom.