

Early Administration of Azathioprine vs Conventional Management of Crohn's Disease: A Randomized Controlled Trial

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This article has an accompanying continuing medical education activity on page e14. Learning Objective: Upon completion of these exercises, successful learners will be able to discuss the advantages and limits of early prescription of azathioprine (and other classical immunosuppressants) compared with conventional management in patients diagnosed with Crohn's disease.

Podcast interview: www.gastro.org/gastropodcast. Also available on iTunes. See **Covering the Cover synopsis on page 699; see editorial on page 714.**

BACKGROUND & AIMS: Immunomodulator therapy is effective for patients with Crohn's disease (CD) but has not been shown to affect disease progression, presumably because it is given too late after diagnosis. We compared the efficacy of early treatment (within 6 months after diagnosis) with azathioprine versus conventional management of patients at high risk for disabling disease. **METHODS:** We performed an open-label trial of adults with a diagnosis of CD for less than 6 months who were at risk for disabling disease. From July 2005 to November 2010, patients at 24 French centers were randomly assigned to treatment with azathioprine (2.5 mg · kg⁻¹ · day⁻¹, n = 65) or conventional management (azathioprine only in cases of corticosteroid dependency, chronic active disease with frequent flares, poor response to corticosteroids, or development of severe perianal disease) (n = 67). The primary end point was the proportion of trimesters spent in corticosteroid-free and anti-tumor necrosis factor (TNF)-free remission during the first 3 years after inclusion. **RESULTS:** During the 3-year follow-up period, 16 patients in the azathioprine group were switched to mercaptopurine or methotrexate therapy because of intolerance or poor efficacy. Forty-one patients in the conventional management group required immunosuppressant therapy (61%; median time to first prescription, 11 months). In the azathioprine group, a median 67% of trimesters were spent in remission (interquartile range, 11%–85%) compared with 56% in the conventional management group (interquartile range, 29%–73%) (P = .69). Among secondary outcomes, a higher cumulative proportion of patients in the azathioprine group were free of perianal surgery than in the conventional management group (96%

± 3% and 82% ± 6% at month 36, respectively; P = .036). The cumulative proportion of patients free of intestinal surgery and anti-TNF therapy did not differ between groups. **CONCLUSIONS: Based on results from a clinical trial, administration of azathioprine within 6 months of diagnosis of CD was no more effective than conventional management in increasing time of clinical remission. Clinical trials.gov, Number NCT00546546.**

Keywords: Inflammatory Bowel Disease; IBD; Comparison of Treatment Strategies; Drug.

Crohn's disease (CD) is a chronic, progressive, disabling, and destructive inflammatory disorder.^{1,2} The conventional "step-care" incremental approach using corticosteroids and immunomodulators (thiopurines or methotrexate) sequentially has no clear effect on disease progression and the rate of surgery.^{3,4} The lack of efficacy of immunomodulators could be related to a delayed prescription at a time when irreversible damage has already occurred.⁵⁻⁷ An alternative concept of "accelerated step care" using early intervention with immunomodulators was proposed by pediatricians more than 10 years ago; in a small randomized placebo-controlled trial conducted in 53 children with disease duration ≤8 weeks, combination therapy with corticosteroids (induction) and mercaptopurine for maintenance significantly lessened the need for prednisone and improved maintenance of remission.⁸ This strategy needs to be evaluated in adult cases of CD, which are often less severe than pediatric cases of CD. There is a subgroup of adult patients who experience a

Abbreviations used in this paper: CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; IBDQ, Inflammatory Bowel Disease Questionnaire; IQR, interquartile range; TNF, tumor necrosis factor.

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mild to moderate disease course, never requiring the use of immunomodulators or biologic therapies,⁹ and increasing concern about the toxicity of thiopurines¹⁰ would likely preclude their early use in unselected patient populations. However, clinical features associated with high risk of progression to disabling disease have been identified¹¹ that can be used to select patients at diagnosis who might benefit the most from early intervention with immunomodulators.

The aim of this randomized, open-label, controlled trial was thus to evaluate the benefits on the 3-year course of CD of an early prescription of azathioprine compared with conventional step-care therapy in patients with a high risk of disabling disease.

Patients and Methods

Study Design and Patients

This 3-year, randomized, parallel, open-label trial (Résultat de l'Adjonction Précoce d'ImmunoDépresseurs; RAPID) compared early prescription of azathioprine (within the first 6 months after diagnosis) with conventional step-care strategy in patients at high risk for disabling CD.

Eligible patients were at least 18 years of age and had been diagnosed with CD according to validated criteria within 6 months before screening. Patients were considered at high risk for disabling disease based on the presence of at least 2 of the following criteria: age younger than 40 years, active perianal lesions, and corticosteroid use within 3 months of diagnosis.¹¹

Patients who had previously received treatment with immunomodulators or anti-tumor necrosis factor (TNF) or with an immediate need for surgery or anti-TNF therapy, severe comorbidity, documented infection, renal or liver failure, contraindication to thiopurines according to labeling recommendations, malignancy, history of drug abuse, or predictable poor compliance were excluded. Pregnant women were also ineligible.

The study was performed at 24 centers in France. Investigators were members of the Groupe d'Etude Thérapeutique des Affections Inflammatoires du tube Digestif (GETAID). The institutional review board at each center approved the protocol, and all patients provided written informed consent. This trial was registered with ClinicalTrials.gov, number NCT00546546.

Randomization

At baseline, patients were randomly assigned (1:1) to one of 2 therapeutic strategy groups: immediate introduction of azathioprine or conventional management. Randomization was performed centrally with computer-derived permutation tables of size 4 and stratified by center. Patients were assigned identification codes, which were sent to the investigator after receipt and validation of the inclusion form by the statistical center (this center was independent from the funding source). Patients and investigators were not masked to the therapeutic strategy.

Procedures

Patients randomized to the early azathioprine group were prescribed azathioprine $2.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$. This dosage was adapted subsequently according to tolerance and efficacy using a predefined scheme of modification per steps of 25 mg/day. Thiopurine methyltransferase phenotyping/genotyping was not systematically performed. Mercaptopurine could be used in

case of early intolerance to azathioprine as ascertained by the investigator. In case of pancreatitis or failure of thiopurines, treatment with subcutaneous methotrexate 25 mg weekly was initiated. In case of flare (defined by a Crohn's Disease Activity Index [CDAI] score >150), prednisone 40 mg to 1 mg/kg daily for 3 weeks tapered within 2 months or budesonide 9 mg for 1 month tapered within 2 months was prescribed. Anti-TNF (infliximab or adalimumab) was introduced in patients who failed to respond to or refused treatment with corticosteroids and in those who did not achieve remission with immunomodulator therapy. The recommendation in this group was to maintain immunosuppression for as long as possible. Patients randomized to the conventional management group were treated with azathioprine only when the following events occurred: corticosteroid dependency defined according to Lemann et al,¹² chronic active disease with frequent flares, poor response to treatment with corticosteroids, or development of severe perianal disease (complex fistula, recurring abscesses, sphincter damage). The initial dose and adaptation to azathioprine, switch to mercaptopurine or methotrexate, and treatment of flares followed the same modalities as in the early azathioprine group.

Medical history and current medications were recorded at study inclusion. Disease activity was measured by the CDAI. Patients were seen 6 and 12 weeks after inclusion and then every 3 months through month 36. Physical examination (including perianal examination) and laboratory tests (C-reactive protein, blood counts, liver tests) were performed at screening and at each visit. The number of days out of work was recorded at each visit. The Inflammatory Bowel Disease Questionnaire (IBDQ) was completed at inclusion and at months 12, 24, and 36. The IBDQ measures disease-specific quality of life, and higher scores indicate better quality of life. Monitoring for adverse events was performed through month 36. In case of symptoms occurring before the next planned visit, the patient was seen promptly, CDAI score was calculated, and treatment was adapted.

End Points

The primary efficacy outcome was the proportion of trimesters in remission during patient follow-up. Remission was defined as the absence of flare throughout the trimester, with no corticosteroid or anti-TNF use, no active perianal disease, no hospitalization related to CD (including hospitalization related to a side effect), and no surgical procedures. Flare was defined by a CDAI score >150. Active perianal disease was defined as perianal pain or discharge with induration, skin tags, ulceration, fissure, or fistula at physical examination.

Prespecified secondary outcomes were proportions of trimesters during patient follow-up with flare, CD-related hospitalization, active perianal disease, perianal surgery, intestinal surgery, any corticosteroid use, or any anti-TNF use; duration of significant corticosteroid exposure (number of days with daily dose >10 mg of prednisone or >3 mg of budesonide) per trimester; total exposures (in milligrams) of prednisone and budesonide per trimester; time to first perianal surgery, first intestinal resection, and first anti-TNF use; median of CDAI scores and C-reactive protein concentrations at the successive visits throughout patient follow-up; values of IBDQ at months 12, 24, and 36; total number of days of hospitalization; and total number of days out of work per trimester.

Statistical Analysis

Demographic and baseline characteristics were summarized using descriptive statistics. Categorical variables were

described using frequencies and percentages. Their distributions were compared between treatment groups with the χ^2 test or the Fisher exact test when necessary. Continuous variables were summarized using the frequency, median, and interquartile range (IQR). Their distributions were compared between treatment groups with the Mann-Whitney test. Proportions of trimesters in remission and those with each event not associated with remission (flare and so on), number of days with significant corticosteroid exposure, and total exposures to prednisone and budesonide per trimester were compared between treatment groups with the Mann-Whitney test. In addition, for the primary end point, the median of the difference between the 2 treatment groups was estimated with the Hodges-Lehmann method, associated with the rank sum test.¹³ Cumulative probabilities of remaining free of events (perianal surgery, intestinal resection, anti-TNF use) were calculated using the Kaplan-Meier method and compared with the log-rank test. Medians of CDAI scores and C-reactive protein values and IBDQ values at 12, 24, and 36 months; total number of days of hospitalization; and total number of days out of work per trimester were compared between treatment groups with the Mann-Whitney test.

All analyses were performed at the reference date: August 1, 2012. Because 8 patients were still participating in the study at that date, 2 simulations were performed for the primary end point. In the first simulation, it was assumed that only remissions were observed in all forthcoming visits of patients treated with early azathioprine only and nonremissions were observed in all visits of patients treated with conventional management. In the second simulation, the reverse was applied

(no remissions in patients treated with early azathioprine and remissions in patients treated with conventional management).

We initially hypothesized, based on the percentages of years in remission during the first years of CD in a Danish cohort¹⁴ and in the St-Antoine cohort (MICISTA),¹⁵ that early treatment with azathioprine may increase the proportion of trimesters in remission from 50% to 75% (a 50% relative increase) during the first 3 years after diagnosis. Because our primary end point was never used before, no information on the standard deviation of the proportion of trimesters for 3-year follow-up was available and we used the binomial distribution as an approximation. Thus, assuming that 25% of patients would be excluded or lost to follow-up, 120 patients were needed to detect a difference between the 2 groups using a 2-sided test with a type I error of 5% and a power of 80%. An interim analysis was planned after 2 years of recruitment (82 included patients) to re-estimate the sample size from the proportion of trimesters in remission during follow-up in the conventional management group. A rate of 40% with a 35% standard deviation was observed in this group. Assuming that early treatment with azathioprine may increase this proportion from 40% to 60% (a 50% relative increase) and taking into account early loss of patients and use of nonparametric tests led to an increase in the total number of patients to 140 (2-sided test, with a type I error of 5% and a power of 80%).

We used SPSS Software for Windows, release 15.1 (SPSS Inc, Chicago, IL) for our analyses. The significance threshold was 0.05 for all analyses.

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

Table 1. Baseline Characteristics of Patients

| | Early azathioprine group (n = 65) | Conventional management group (n = 67) | P value |
|--|-----------------------------------|--|---------|
| Sex (male) | 31 (48) | 34 (51) | .73 |
| Age (y) | 25.6 (21.3–29.0) | 24.7 (21.2–28.7) | .84 |
| Time from diagnosis to inclusion (mo) | 2.1 (0.9–3.6) | 2.3 (1.4–3.9) | .19 |
| Disease location | | | |
| L1 (ileum) | 16 (25) | 20 (30) | .45 |
| L2 (colon) | 10 (15) | 14 (21) | |
| L3 (ileum + colon) | 39 (60) | 33 (49) | |
| L4 (upper digestive tract) | 12 (18) | 6 (9) | |
| Predictors of disabling CD | | | |
| Age <40 y | 65 (100) | 64 (96) | .13 |
| Corticosteroid use | 63 (97) | 64 (96) | .51 |
| Perianal lesions | 13 (20) | 16 (24) | .59 |
| 3 predictors | 11 (17) | 10 (15) | .75 |
| Smoking | | | |
| Current | 28 (43) | 23 (34) | .58 |
| Former | 12 (18) | 15 (22) | |
| Never | 25 (38) | 29 (43) | |
| Perianal examination | | | |
| No lesion | 54 (83) | 51 (76) | .32 |
| Skin tags | 2 (3) | 1 (1) | |
| Fissure or ulcer | 7 (11) | 9 (13) | |
| Simple fistula | 4 (6) | 5 (7) | |
| Complex fistula | 0 | 1 (1) | |
| CDAI score | 85 (39–121) | 79 (47–129) | .96 |
| IBDQ ^a | 173 (158–189) | 170 (142–183) | .19 |
| Hemoglobin concentration (g/dL) | 13.4 (12.0–14.3) | 13.8 (12.7–14.6) | .12 |
| C-reactive protein concentration (mg/L) ^b | 8 (4–18) | 6 (2–15) | .15 |

NOTE. Data are expressed as number (%) or median (IQR).

^aCompleted by 54 patients in the early azathioprine group and 52 in the conventional management group.

^bCompleted by 60 patients in the early azathioprine group and 62 in the conventional management group.

Results

Patient Characteristics and Disposition

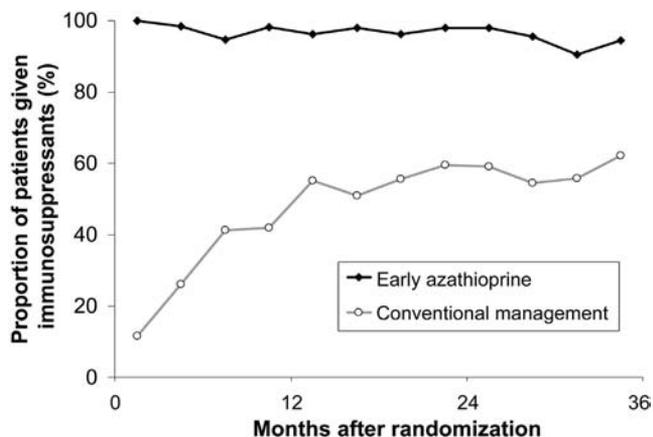
Recruitment began on July 12, 2005, and ended on November 30, 2010, because the sample size was reached. Of the 147 randomly assigned patients, 72 were assigned to the early azathioprine group and 75 to the conventional management group (Supplementary Figure 1). Five patients were excluded immediately after randomization for screening failure or withdrawal of consent. Eight other patients declined further participation within the first 3 months; 5 withdrew consent, and 3 in the early azathioprine group did not tolerate the drug and refused to continue the trial. Furthermore, 2 patients, one in each group, did not receive the intended treatment. Thus, data from 132 patients were analyzed: 65 in the early azathioprine group and 67 in the conventional management group. Baseline disease characteristics were similar in the 2 groups (Table 1). Fifty-two patients in the early azathioprine group and 53 patients in the conventional management group achieved clinical remission (CDAI score <150) before randomization.

Forty-three patients dropped out of the study prematurely (Supplementary Figure 1). Eight patients were still participating in the study at the reference date of ongoing follow-up (August 1, 2012). The duration of follow-up was 2 years or more in 107 patients (53 in the early azathioprine group and 54 in the conventional management group). In the early azathioprine group, 44 of 65 patients remained on azathioprine therapy until the end of follow-up, 8 were switched to mercaptopurine because of intolerance to azathioprine, and 10 (including 2 of the latter) were switched to methotrexate because of intolerance to (6 patients with pancreatitis) or poor response to thiopurines (4 patients); 20 patients (31%) required anti-TNF therapy, and 16 were still on anti-TNF therapy at last follow-up. In the conventional management group, 41 of 67 patients

(61%) required immunosuppression during follow-up. For the whole group, the median time to first prescription of an immunosuppressant was 11 months (range, 7–36 months). Azathioprine was used as first-line therapy in 38 cases, with a switch to mercaptopurine and methotrexate in 7 and 8 patients, respectively. Anti-TNF therapy was initiated before treatment with an immunomodulator in 3 patients and after failure to respond to treatment with an immunomodulator in 15 patients. Twelve patients in the conventional management group were still on anti-TNF therapy at last follow-up. The proportion of patients who were treated with immunomodulator therapy, anti-TNF therapy, or both throughout the study in the 2 groups is shown in Figure 1.

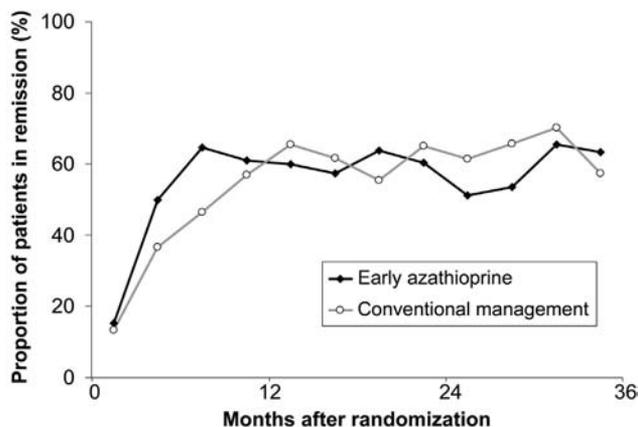
Primary Efficacy End Point

The rate of trimesters in remission per patient (median [IQR]) was 67% (11%–85%) in the early azathioprine group and 56% (29%–73%) in the conventional management group ($P = .69$). The Hodges–Lehmann point estimate of the median of the difference between the rates of trimesters in remission in the early azathioprine group and in the conventional management group was 3%. Figure 2 shows the percentage of patients in remission during the consecutive trimesters of the study in the 2 groups. The proportion of patients in remission was higher in the early azathioprine group than in the conventional management group during the third trimester of the study, and then the proportions became similar. In the 2 extreme simulations applied to forthcoming trimesters of the 8 patients still participating in the study, the rates of trimesters in remission per patient were 67% (13%–85%) versus 50% (27%–67%) for the first simulation ($P = .42$) and 55% (9%–83%) versus 56% (29%–73%) for the second simulation ($P = .98$) in the early azathioprine group and the conventional management group, respectively.



| No. patients | | | | | | | | | | | | |
|--------------|----|----|----|----|----|----|----|----|----|----|----|----|
| Early aza. | 65 | 64 | 59 | 56 | 54 | 53 | 53 | 52 | 50 | 48 | 43 | 41 |
| Conv. m. | 67 | 65 | 63 | 62 | 58 | 55 | 54 | 52 | 49 | 44 | 43 | 40 |

Figure 1. Proportion of patients who were treated with immunosuppressant therapy (including immunomodulators and anti-TNF) per trimester over time. All trimesters of follow-up are included.



| No. patients | | | | | | | | | | | | |
|--------------|----|----|----|----|----|----|----|----|----|----|----|----|
| Early aza. | 61 | 58 | 54 | 50 | 45 | 47 | 48 | 48 | 43 | 41 | 35 | 41 |
| Conv. m. | 65 | 60 | 59 | 55 | 55 | 47 | 45 | 46 | 39 | 38 | 37 | 40 |

Figure 2. Proportion of patients in corticosteroid-free, anti-TNF-free remission per trimester over time. The concomitant proportions were significantly different only at trimester 3 ($P < .05$). Trimesters ended by a missing visit are excluded.

Table 2. Events and Proportion of Trimesters With Any Event

| | Early azathioprine group (n = 65) | | | Conventional management group (n = 67) | | | P value ^a |
|---------------------------------|---|------------------------------------|-----------------------------------|---|------------------------------------|-----------------------------------|----------------------|
| | No. of patients with at least one event (%) | Total no. of trimesters with event | Percent per patient, median (IQR) | No. of patients with at least one event (%) | Total no. of trimesters with event | Percent per patient, median (IQR) | |
| Flare | 37 (57) | 96 | 9 (0-39) | 51 (76) ^b | 105 | 17 (8-29) | .18 |
| Hospitalization | 22 (34) | 33 | 0 (0-11) | 26 (39) | 40 | 0 (0-10) | .74 |
| Active perianal lesions | 9 (14) | 23 | 0 (0-0) | 18 (27) | 42 | 0 (0-9) | .049 |
| Perianal surgery | 2 (3) | 7 | 0 (0-0) | 9 (13) ^b | 11 | 0 (0-0) | .04 |
| Intestinal surgery ^c | 5 (8) | 8 | 0 (0-0) | 4 (6) | 5 | 0 (0-0) | .68 |
| Corticosteroids | 58 (89) | 140 | 25 (9-43) | 61 (91) | 184 | 33 (14-50) | .13 |
| Anti-TNF | 20 (31) | 125 | 0 (0-47) | 17 (25) | 87 | 0 (0-10) | .30 |

^aComparison of the proportion of trimesters with each event between the 2 groups.

^bSignificantly different from the early azathioprine group ($P < .05$).

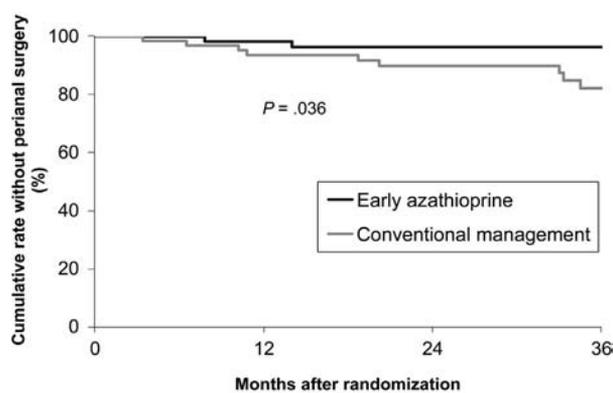
^cIncluding intestinal resection, temporary stoma, and reestablishment of intestinal continuity.

Secondary Efficacy End Points

Table 2 shows the total number of events and the proportion of trimesters with any event in the 2 groups. Overall, patients in the early azathioprine group had a similar proportion of trimesters with flare, hospitalization, intestinal surgery, and use of anti-TNF therapy compared with patients in the conventional management group but had less active perianal lesions. There was a trend, albeit not significant, for a decreased proportion of trimesters with any corticosteroid use. The median duration of a significant dose corticosteroid exposure per trimester was 9 days (1-15) in patients in the early azathioprine group and 11 days (6-20) in patients in the conventional management group ($P = .052$). Total exposure to prednisone and budesonide per trimester was 128 mg (0-251) and 0 mg (0-7), respectively, in the early azathioprine group versus 177 mg (23-324, $P = .17$) and 0 mg (0-41, $P = .15$), respectively, in the conventional management group. The rates of clinical remission (CDAI score < 150), irrespective of the concomitant therapy, were 84% at month 12, 81% at month 24, and 83% at month 36 in the early azathioprine group and 86% at month 12, 91% at month 24, and 86% at month 36, respectively, in the conventional management group. These differences were not significant. Among those who had a normal perianal examination at

inclusion, 2 patients in the early azathioprine group and 4 patients in the conventional management group developed perianal lesions during follow-up. Perianal surgery was required in 11 patients (2 in the early azathioprine group and 9 in the conventional management group). The cumulative probability of remaining free of a perianal surgical procedure was higher in the early azathioprine group than in the conventional management group (Figure 3). Of note, none of the 11 patients in the early azathioprine group with perianal lesions at inclusion required perianal surgery versus 5 of 16 patients in the conventional management group ($P = .049$). Intestinal resection was performed in 9 patients: 5 in the early azathioprine group and 4 in the conventional management group. There was no difference regarding the cumulative proportion of patients remaining free of intestinal surgery between the 2 groups ($P = .68$) at month 36: $89\% \pm 5\%$ in the early azathioprine group versus $93\% \pm 4\%$ in the conventional management group. Finally, the cumulative proportion of subjects who did not require anti-TNF therapy was not different ($P = .46$) at month 36: $64\% \pm 7\%$ in the early azathioprine group and $71\% \pm 6\%$ in the conventional management group.

The median CDAI score at each 3-month visit fluctuated between 47 and 79 in patients in the early azathioprine group and between 24 and 61 in those in the conventional management group. Concomitant median C-reactive protein values varied between 2 and 9 mg/L in the early azathioprine group and between 4 and 7 mg/L in the conventional management group. There was no significant difference when comparing CDAI scores and C-reactive protein values between the 2 groups at each time point. Median (IQR) IBDQ values in patients in the early azathioprine group versus the conventional management group were as follows: 174 (131-195, $n = 35$) versus 181 (161-199, $n = 40$) at month 12 ($P = .27$), 168 (140-190, $n = 29$) versus 188 (164-205, $n = 31$) at month 24 ($P = .03$), and 183 (166-199, $n = 20$) versus 174 (162-196, $n = 23$) at month 36 ($P = .42$). The total number of days of hospitalization was 263 in the early azathioprine group (median per trimester, 0 [0-0.7]) and 233 in the conventional management group (median per trimester, 0 [0-0.4], $P = .95$). The total number of days out



| No. at risk | | | | |
|-------------|----|----|----|----|
| Early aza. | 65 | 54 | 49 | 35 |
| Conv. m. | 67 | 58 | 46 | 31 |

Figure 3. Kaplan-Meier estimates of the time without CD-related perianal surgery.

of work was 1462 in the early azathioprine group (median per trimester, 0 [0–2.5]) and 1106 in the control group (median per trimester, 0 [0–2.7], $P = .62$).

Safety

Table 3 shows adverse events not related to CD. Intolerance to azathioprine was frequent in both groups, including pancreatitis, flu-like illness, and hepatotoxicity, leading to drug discontinuation in 17 patients in the early azathioprine group (24%) and 4 in the conventional management group (11% of those treated with azathioprine). Azathioprine was switched successfully to mercaptopurine in patients without pancreatitis; only one patient in the control group discontinued therapy because of an adverse event (neutropenia). Methotrexate was well tolerated. Severe cutaneous lesions and anaphylactic reactions were observed in some patients treated with anti-TNF. Eight patients became pregnant; of those, 3 underwent an abortion.

Discussion

This study, performed in adult patients with a high risk of disabling CD, failed to show that early treatment

with azathioprine within 6 months of diagnosis was more effective than conventional management for increasing the duration of remission over the next 36 months. Among the secondary efficacy measures, only the development of fewer perianal complications and less need for perianal surgery was associated with early azathioprine use.

The efficacy of azathioprine for maintenance of remission in patients with CD, albeit modest (number needed to treat of 6), is well established when used at the appropriate dosage (2 to 2.5 mg · kg⁻¹ · day⁻¹) and duration (at least 17 weeks).¹⁶ However, it has been claimed that this effect may be jeopardized if prescribed too late, at a time when irreversible damage has already occurred. This allegation is mainly based on some retrospective studies that suggest a benefit of early introduction of azathioprine in reducing the rates of surgery.^{5,6} In the present study, the median interval between diagnosis and inclusion was only 2 months and patients with severe or complicated disease requiring biologic agents or surgery were excluded. Despite that treatment with azathioprine was initiated before any complication of CD occurred, it did not significantly change the disease course or reduce the occurrence of intestinal complications requiring surgery when compared with the conventional treatment group. It is difficult to compare our data with previous clinical trials on thiopurines^{17–19} or methotrexate^{17,20} in adults with CD because they used different end points and none included newly diagnosed patients. Still, the efficacy of azathioprine monotherapy is probably modest during the early phase of CD or confined to a subset of patients. In the SONIC trial, at week 26, only 30% of patients with a median disease duration of 2.4 years and receiving azathioprine monotherapy achieved corticosteroid-free remission and only 15% had mucosal healing.²¹ In the placebo-controlled AZTEC trial, azathioprine started within the first 8 weeks after diagnosis of CD was not associated with an increased rate of sustained corticosteroid-free remission at week 76 compared with placebo.²² Actually, the only prospective study thus far showing the efficacy of early treatment with thiopurine in children was small and of short duration.⁸ Differences with the AZTEC and RAPID trials may be related to different phenotypes; there is a higher proportion of extensive disease, rapid disease progression, and increased activity in pediatric cases of CD.^{7,23,24}

The only apparent benefit of early treatment with azathioprine was a reduced occurrence of active perianal lesions and less need for perianal surgery. Although their effect is slow and unpredictable, thiopurines have been shown to increase the rate of fistula closure in patients with CD,^{25,26} and in the long-term azathioprine responders have a decreased cumulative rate of perianal surgery compared with controls.²⁷ The beneficial effect of early treatment with azathioprine on perianal disease needs to be confirmed by another study before recommending early initiation of azathioprine therapy in patients with rectal involvement and/or perianal lesions at diagnosis.

Table 3. Adverse Events (Excluding CD-Related Events)

| | Early azathioprine group (n = 71) | Conventional management group (n = 71) |
|--|-----------------------------------|--|
| Drug-related serious adverse events | | |
| Pancreatitis (azathioprine) | 7 (10) | 1 (1) |
| Flu-like illness (azathioprine) | 3 (4) | 0 |
| Pancreatitis-like abdominal pain (azathioprine) | 1 (1) | 0 |
| Other clinical intolerance (azathioprine) | 3 (4) | 1 (1) |
| Cholelithiasis leading to cholecystectomy (azathioprine) | 0 | 1 (1) |
| Elevated liver function tests (azathioprine) | 3 (4) | 1 (1) |
| Neutropenia (mercaptopurine) | 0 | 1 (1) |
| Anaphylactic reaction (infliximab) | 0 | 2 (3) |
| Cutaneous lesions (infliximab, adalimumab) | 2 (3) | 1 (1) |
| Pancreatitis (mesalamine) | 0 | 1 (1) |
| Other serious adverse events | | |
| Gastroduodenal ulcer | 2 (3) | 0 |
| Appendicitis | 1 (1) | 0 |
| Adverse events ^a | | |
| Dental abscess | 1 (1) | 2 (3) |
| Upper respiratory tract infections | 2 (3) | 2 (3) |
| Arthralgia | 0 | 3 (4) |
| Fatigue | 2 (3) | 3 (4) |
| Depression | 4 (6) | 0 |
| Full-term pregnancy | 4 (6) | 1 (1) |
| Abortion | 3 (4) | 0 |

NOTE. Data are expressed as number of events (%). Patients included in this table were patients who were randomized and had more than one visit after randomization (n = 142).

^aAdverse events that occurred in at least 3 patients.

A relatively high proportion of patients (approximately one third) in the conventional arm who were considered at high risk for disabling disease still did not require immunomodulator or biologic therapy during the study. This percentage is higher than the 16% observed in the original study by Beaugerie et al,¹¹ in which patients were followed up for 5 years but also included the most severe cases requiring anti-TNF therapy or surgery at diagnosis. Even though these patients may still develop significant damage over time, this observation underlines the need for better predictors of disease course in CD.

This study had several strengths. It was conducted in a well-characterized group of patients with early CD who had predictors of disabling disease. The end points were related to the whole 3-year study period rather than measured at a particular point in time. Finally, it compared 2 therapeutic strategies relevant to daily clinical practice. This study also had several limitations. First, investigators and patients were aware of the treatment assignment. We believe that our primary and secondary end points, which took into account all significant events and therapeutic changes occurring during each trimester over a 3-year period, still allowed a valid comparison of the 2 therapeutic strategies even unblinded. Second, treatment with azathioprine was associated with a high rate of adverse events, with a need for drug discontinuation in up to one-fourth of the patients. However, this occurred in both groups and azathioprine was immediately replaced by mercaptopurine or methotrexate, allowing most patients in the early azathioprine group to remain on immunomodulator therapy throughout the study. Third, azathioprine was also rapidly started in some patients in the conventional management group, and the difference in the median delay of first azathioprine prescription was only 11 months between the 2 groups. This actually reflects current clinical practice, which is to prescribe immunomodulator and/or biologic therapy promptly in patients with chronic active disease or poor response to corticosteroids. Nevertheless, this 11-month interval is probably long enough to show a difference in clinical activity over a period of 3 years in a selected group of patients with a high risk of progressing disease. It has indeed been shown that the first 3 years are probably the most important in shaping progression of CD, which then tends to decrease and stabilize afterward.¹⁴

In conclusion, our study failed to show that early initiation of azathioprine therapy significantly increases the proportion of trimesters in clinical remission during the first 3 years of CD as compared with conventional management in patients at risk for disabling CD. These results do not support systematic early prescription of azathioprine in adult patients with CD at risk for a disabling course.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of

Gastroenterology at www.gastrojournal.org, and at <http://dx.doi.org/10.1053/j.gastro.2013.04.048>.

References

- Louis E, Collard A, Oger AF, et al. Behaviour of Crohn's disease according to the Vienna classification: changing pattern over the course of the disease. *Gut* 2001;49:777-782.
- Cosnes J, Cattan S, Blain A, et al. Long-term evolution of disease behavior of Crohn's disease. *Inflamm Bowel Dis* 2002;8:244-250.
- Wolters FL, Russel MG, Stockbrugger RW. Systematic review: has disease outcome in Crohn's disease changed during the last four decades? *Aliment Pharmacol Ther* 2004;20:483-496.
- Cosnes J, Nion-Larmurier I, Beaugerie L, et al. Impact of the increasing use of immunosuppressants in Crohn's disease on the need for intestinal surgery. *Gut* 2005;54:237-241.
- Lakatos PL, Golovics PA, David G, et al. Has there been a change in the natural history of Crohn's disease? Surgical rates and medical management in a population-based inception cohort from Western Hungary between 1977-2009. *Am J Gastroenterol* 2012;107:579-588.
- Ramadas AV, Gunesh S, Thomas GA, et al. Natural history of Crohn's disease in a population-based cohort from Cardiff (1986-2003): a study of changes in medical treatment and surgical resection rates. *Gut* 2010;59:1200-1206.
- Vernier-Massouille G, Balde M, Salleron J, et al. Natural history of pediatric Crohn's disease: a population-based cohort study. *Gastroenterology* 2008;135:1106-1113.
- Markowitz J, Grancher K, Kohn N, et al. A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. *Gastroenterology* 2000;119:895-902.
- Kruis W, Katalinic A, Klugmann T, et al. Predictive factors for an uncomplicated long-term course of Crohn's disease: a retrospective analysis. *J Crohns Colitis* 2012 Nov 20. [Epub ahead of print].
- Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet* 2009;374:1617-1625.
- Beaugerie L, Seksik P, Nion-Larmurier I, et al. Predictors of Crohn's disease. *Gastroenterology* 2006;130:650-656.
- Lemann M, Mary JY, Duclos B, et al. Infliximab plus azathioprine for steroid-dependent Crohn's disease patients: a randomized placebo-controlled trial. *Gastroenterology* 2006;130:1054-1061.
- Hodges JL, Lehmann EL. Estimates of location based on rank tests. *Ann Math Stat* 1963;34:598-611.
- Munkholm P, Langholz E, Davidsen M, et al. Disease activity courses in a regional cohort of Crohn's disease patients. *Scand J Gastroenterol* 1995;30:699-706.
- Cosnes J, Seksik P. Computer database for patients with IBD. In: Bayless T, Hanauer S, eds. *Advanced therapy in inflammatory bowel disease*. Volume 1. Shelton: People's Medical Publishing House, 2011:117-124.
- Prefontaine E, Sutherland LR, Macdonald JK, et al. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2009:CD000067.
- Ardizzone S, Bollani S, Manzionna G, et al. Comparison between methotrexate and azathioprine in the treatment of chronic active Crohn's disease: a randomised, investigator-blind study. *Dig Liver Dis* 2003;35:619-627.
- Candy S, Wright J, Gerber M, et al. A controlled double blind study of azathioprine in the management of Crohn's disease. *Gut* 1995;37:674-678.
- Present DH, Korelitz BI, Wisch N, et al. Treatment of Crohn's disease with 6-mercaptopurine. A long-term, randomized, double-blind study. *N Engl J Med* 1980;302:981-987.
- Feagan BG, Fedorak RN, Irvine EJ, et al. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. North American Crohn's Study Group Investigators. *N Engl J Med* 2000;342:1627-1632.

21. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010;362:1383-1395.
22. Panés J, López-SanRomán A, Bermejo F, et al. Early azathioprine therapy is no more effective than placebo for newly diagnosed Crohn's disease. *Gastroenterology* 2013;145:766-774.
23. Newby EA, Croft NM, Green M, et al. Natural history of paediatric inflammatory bowel diseases over a 5-year follow-up: a retrospective review of data from the register of paediatric inflammatory bowel diseases. *J Pediatr Gastroenterol Nutr* 2008;46:539-545.
24. Pigneur B, Seksik P, Viola S, et al. Natural history of Crohn's disease: comparison between childhood- and adult-onset disease. *Inflamm Bowel Dis* 2010;16:953-961.
25. Jeshion WC, Larsen KL, Jawad AF, et al. Azathioprine and 6-mercaptopurine for the treatment of perianal Crohn's disease in children. *J Clin Gastroenterol* 2000;30:294-298.
26. Pearson DC, May GR, Fick GH, et al. Azathioprine and 6-mercaptopurine in Crohn disease. A meta-analysis. *Ann Intern Med* 1995;123:132-142.
27. Camus M, Seksik P, Bourrier A, et al. Long-term outcome of patients with Crohn's disease that responds to azathioprine. *Clin Gastroenterol Hepatol* 2013;11:389-394.

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Acknowledgments

A list of investigators and study centers appears in the Appendix.

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Conflicts of interest

The authors disclose the following: Jacques Cosnes has served as a paid consultant for Abbott Laboratories. David Laharie has received fees for lectures and advisory boards for Abbott Laboratories and MSD. Yoram Bouhnik has served as a paid consultant for Bristol-Myers Squibb, Shire, Sanofi, Norgine Pharma, MSD, Abbott Laboratories, and AstraZeneca and received honoraria from Bristol-Myers Squibb, MSD, Abbott Laboratories, Teva, Ferring, Solvay Pharma, Vifor Pharma, and HAC. Matthieu Allez has received honoraria for consulting or teaching activities from Abbott Laboratories and MSD. Guillaume Savoye received lecture fees from Ferring, Abbott Laboratories, MSD, Vifor, and HAC Pharma. Jean-Frédéric Colombel has served as a paid consultant for Abbott Laboratories, Amgen, Biogen Idec, Boehringer Ingelheim, Bristol-Myers Squibb, Cellerix SL, ChemoCentryx, Centocor, Cosmo Technologies, Elan Pharmaceuticals, Genentech, Giuliani SPA, Given Imaging, GlaxoSmithKline, Immune Pharmaceuticals, Merck, Millennium Pharmaceuticals, Neovacs SA, Ocera Therapeutics (previously Renovia), Pfizer, Prometheus, Sanofi, Schering-Plough, Shire Pharmaceuticals, Synta Pharmaceuticals, Takeda, Teva Pharmaceuticals, Therakos, TxCell, UCB Pharma (previously Celltech Therapeutics), and Wyeth Pharmaceuticals; received speaker's fees from Abbott Laboratories, Centocor, Falk Pharma, Ferring, Given Imaging, Merck, Schering-Plough, Shire Pharmaceuticals, and UCB Pharma; received financial support for research from Abbott Laboratories, Ferring, Schering-Plough, UCB Pharma, and Giuliani SPA; and is a shareholder in Intestinal Biotech Development. The remaining authors disclose no conflicts.

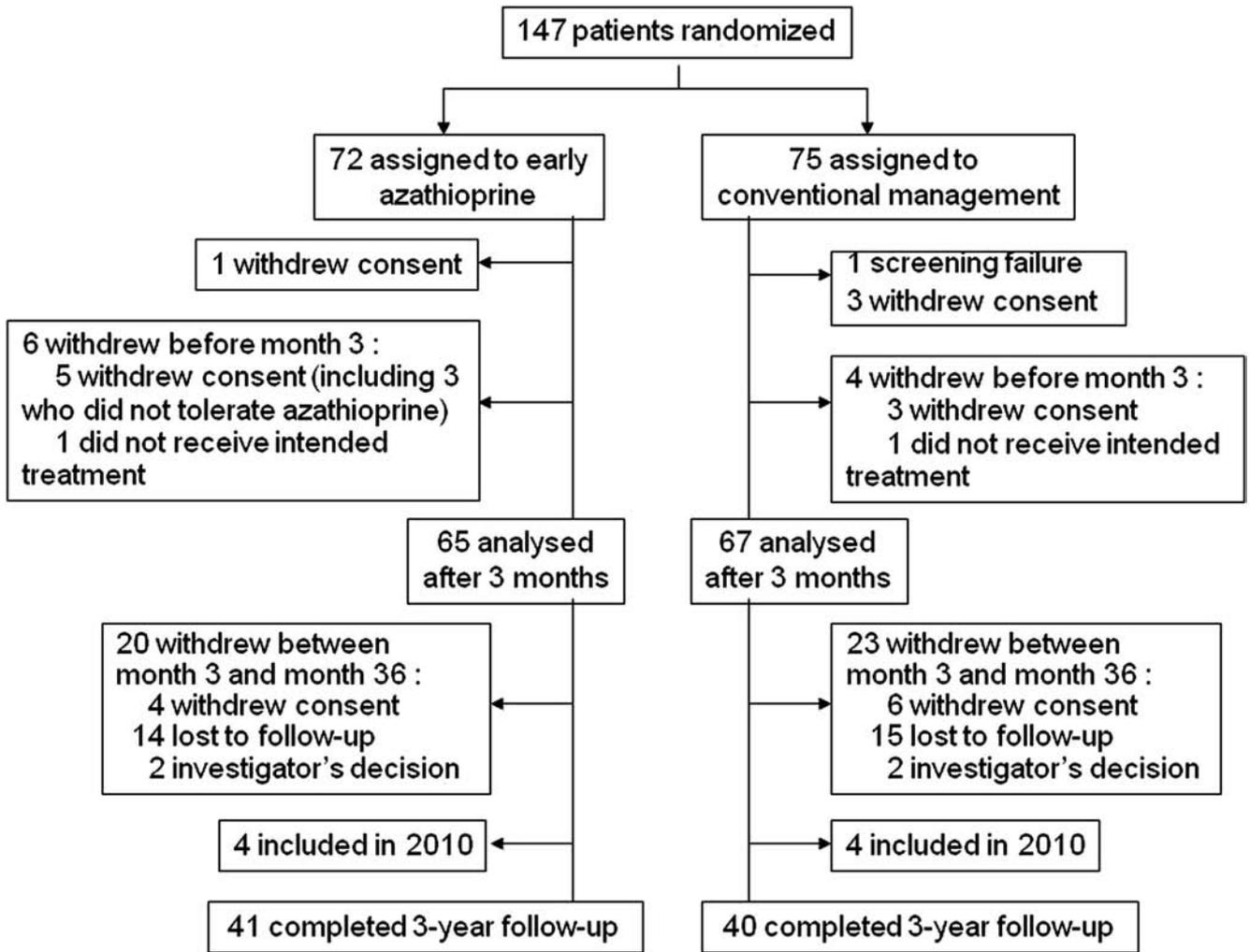
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Appendix. List of Investigators and Study Centers

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Supplementary Figure 1. Trial profile.