

## Azathioprine Withdrawal in Patients With Crohn's Disease Maintained on Prolonged Remission: A High Risk of Relapse

XAVIER TRETON,\* YORAM BOUHNİK,\* JEAN-YVES MARY,† JEAN-FRÉDÉRIC COLOMBEL,§ BERNARD DUCLOS,|| JEAN-CLAUDE SOULE,¶ ERIC LEREBOURS,# JACQUES COSNES,\*\* MARC LEMANN,†† and the GROUPE D'ETUDE THÉRAPEUTIQUE DES AFFECTIONS INFLAMMATOIRES DU TUBE DIGESTIF (GETAID)

\*Hôpital Beaujon, Pôle des Maladies de l'Appareil Digestif, †INSERM U717, Université Paris 7, Paris, France; §Hôpital Claude Huriez, CHU de Lille, France; ||Hôpital Hautepierre, CHU de Strasbourg, France; ¶Hôpital Bichat, CHU Bichat-Beaujon, Paris, France; #Hôpital Charles Nicolle, CHU de Rouen, France; \*\*Hôpital Saint-Antoine, Université Paris 6, Paris, France; and the ††Hôpital Saint-Louis, CHU Lariboisière-Saint-Louis, Paris, France

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**Background & Aims:** Azathioprine (AZA) withdrawal in Crohn's disease after long-term remission under treatment is controversial. In a Groupe d'Etude Thérapeutique des Affections Inflammatoires du tube Digestif randomized, double-blind, placebo-controlled trial, the hypothesis that AZA withdrawal was not inferior to AZA continuation in patients in prolonged clinical remission could not be shown. **Methods:** A cohort of 66 patients in prolonged remission while being treated with AZA who stopped AZA, during or at the end of the randomized controlled trial, underwent long-term follow-up evaluation. The primary end point was clinical relapse. Prognostic factors of relapse were looked for through a proportional hazards model. **Results:** Median durations of AZA therapy and of clinical remission were 68.4 months (interquartile range, 52.8–85.2 mo) and 63.6 months (interquartile range, 48.0–55.7 mo), respectively. The median follow-up time after AZA interruption was 54.5 months; 32 of 66 patients had a relapse. The cumulative probabilities  $\pm$  SE of relapse at 1, 3, and 5 years were  $14.0\% \pm 4.3\%$ ,  $52.8\% \pm 7.1\%$ , and  $62.7\% \pm 7.2\%$ , respectively. C-reactive protein concentration of 20 mg/L or greater (risk, 58.6; 95% confidence interval, 7.5–457;  $P = .002$ ), hemoglobin level less than 12 g/dL (risk, 4.8; 95% confidence interval, 1.7–13.7;  $P = .04$ ), and neutrophil count  $4 \times 10^9/L$  or greater (risk, 3.2; 95% confidence interval, 1.6–6.3;  $P = .003$ ) were associated independently with an increased risk of relapse. Among the 32 relapsing patients, 23 were retreated by AZA alone, all but 1 up to successful remission. **Conclusions:** Our results confirm that AZA withdrawal is associated with a high risk of relapse, whatever the duration of remission under this treatment. These data suggest that if AZA is well tolerated, it should not be interrupted.

Azathioprine (AZA), and its active metabolite 6-mercaptopurine, are at present the more frequently used immunosuppressive agents in Crohn's disease (CD). AZA has been shown, in clinical trials<sup>1–4</sup> and 2 meta-analyses,<sup>5,6</sup> to be effective in the maintenance of remission of CD, mostly in steroid-dependent patients.

Despite 3 decades of experience with AZA, the optimal duration of this treatment, for the patients maintained on prolonged remission, is still a matter of discussion.<sup>7</sup> A previous retrospective observational study from 2 centers of the Groupe d'Etude Thérapeutique des Affections Inflammatoires du tube Digestif has suggested that voluntary withdrawal from AZA after 4 years of successful remission might provide equal protection from relapse as continuing maintenance of AZA therapy after this time.<sup>8</sup> More recently, a multicenter, randomized, double-blind, controlled withdrawal trial was conducted by the Groupe d'Etude Thérapeutique des Affections Inflammatoires du tube Digestif<sup>9</sup> in 83 patients in clinical remission induced by continuous treatment with AZA for at least 42 months. In this noninferiority trial, the 18-month relapse rate was 8% in the group of 40 patients maintained on AZA as compared with 21% in the group of 43 patients on placebo. The hypothesis that AZA withdrawal was not inferior to AZA continuation could not be shown ( $P = .154$ ). However, 79% of patients remained in remission 18 months after AZA withdrawal. Thus, from a clinical point of view, the question of whether we should or should not interrupt AZA therapy after 42 months of clinical remission remains a debate.

Therefore, to evaluate the relapse risk after AZA withdrawal on a longer term, we extended the follow-up period of all patients who stopped AZA treatment in remission either according to randomization in the previously published trial<sup>9</sup> or after the end of this trial.

### Methods

#### Patients

The studied cohort was composed of a subgroup of patients included in the AZA withdrawal trial between October 1995 and November 1999 in 11 centers in France and 1 center in Belgium. Thus, selection criteria were those used for the AZA withdrawal trial: age older than 18 years; continuous AZA treatment for at least 42 months; no clinical relapse during the preceding 42 months; no treatment with oral steroids ( $>10$  mg/d), artificial nutrition, or other immunosuppressive drug; and no biological agent during the same period. We excluded

**Abbreviations used in this paper:** AZA, azathioprine; CD, Crohn's disease, CRP, C-reactive protein; IQR, interquartile range.

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patients with CD limited to the perianal area and patients treated with AZA for prevention of postoperative recurrence. In addition, patients should have stopped AZA treatment while in clinical remission, either at the time of their inclusion into the AZA withdrawal trial as a result of randomization in the placebo arm, or at the end of their participation in the AZA withdrawal trial after having continued AZA treatment for 18 months because of inclusion in the AZA arm. At this time, physicians did not know the results of the double-blind study, and they were free to prescribe the treatment of their choice.

**Data Collection**

Patients were followed up from the time of AZA withdrawal up to June 2003. Data were collected using case report forms for those recruited at the beginning of the AZA withdrawal trial, and using medical records and direct patient contact, if required, for all patients after their withdrawal from the AZA withdrawal trial. The following data were collected: date of AZA withdrawal, cause of withdrawal (randomization, personal or medical decision, adverse effect, other), therapeutic modification, smoking habits, and biologic values at AZA interruption (C-reactive protein [CRP] concentration, erythrocyte sedimentation rate, leukocyte counts, hemoglobin level and mean corpuscular volume, platelet count). After AZA withdrawal, data on the time of relapse, subsequent treatments, and occurrence of a new remission were collected. Relapse after AZA withdrawal was defined as an increase of clinical activity of CD (Harvey-Bradshaw<sup>10</sup> index  $\geq 4$  points) leading to re-treatment with steroid, immunosuppressant (excluding aminosalicylates), nutritional support, or requiring CD-related surgery. Remission after relapse and re-treatment by AZA was defined by a Harvey-Bradshaw index of 3 points or less without any steroid treatment or immunosuppressive agent in the past 3 months and without surgery.

**Statistical Analysis**

Time-to-relapse rate as a function of time after AZA withdrawal was estimated using the Kaplan-Meier<sup>11</sup> method. Time-to-relapse curves were compared between the group of patients included in the cohort at the beginning of the AZA withdrawal trial and the group of patients included at the end of this trial through log-rank test.<sup>12</sup> The influence of the following variables evaluated at AZA withdrawal on time-to-relapse was examined using the Cox proportional hazards model<sup>13</sup>: sex, age, smoking habits, disease site, duration of disease, duration of remission on AZA treatment, and duration of AZA treatment, previous treatment, and biological parameters. Continuous variables were categorized as follows.<sup>14,15</sup> Each variable was first divided into 3 categories at approximately the 33rd and 67th percentiles. If the relative relapse rates were not substantially different in 2 adjacent categories, they were grouped together. If no clear pattern was observed, the median was used as a cut-off point. In addition, previously suggested limits, such as 20 mg/L for CRP level, were tested.<sup>9,16</sup> The proportional hazards model was used first to study the influence of each factor on time-to-relapse, then to identify independent prognostic factors. For the latter, a multivariate analysis was applied using a stepwise procedure using a likelihood ratio test<sup>17</sup> of those variables having a *P* value of less than .20 in the univariate analysis. In the multivariate analysis, a *P* value of less than .05 was considered as the level of significance. According to independent prognos-

tic factors found in the multivariate analysis, a simple prognostic classification was derived by rounding and adding the coefficients of pejorative prognostic factors in the proportional hazards model. Relapse rates are presented as estimate with standard error (SE), follow-up times as median (interquartile range [IQR]), and hazard ratio as estimate with 95% confidence interval.

In addition, the time-to-remission after relapse among those re-treated by AZA was estimated using the Kaplan-Meier method.<sup>11</sup>

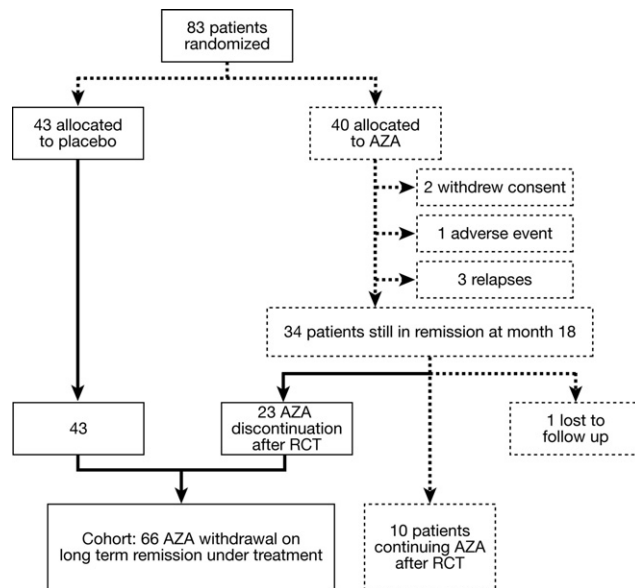
All analyses were performed using SPSS software (SPSS, Inc, Chicago, IL).<sup>18</sup>

**Results**

**Study Population**

The constitution of the cohort is described in Figure 1. Forty-three patients were included in the cohort at the time of their inclusion in the AZA withdrawal trial as a result of randomized assignment to AZA withdrawal (thus they were assigned to the placebo arm). Among the 34 patients who were still in remission on AZA treatment at the end of their participation in the AZA withdrawal trial, 23 stopped AZA treatment and were included in the cohort at this time, 11 patients were treated again with AZA following the decision of their physician (9 of 11 patients were followed up only in 2 of the 12 centers). In this subgroup, 1 patient relapsed at month 43, 1 patient was lost to follow-up evaluation a few weeks after withdrawal from the trial, and 9 patients remained in prolonged remission leading to a median follow-up period of 47 months (IQR, 35-70 mo; n = 10, including the patient lost to follow-up evaluation).

Therefore, the cohort consisted of 66 patients who had stopped AZA while they were on prolonged remission under this treatment. None of the 66 patients were taking steroids (even at a dose  $\leq 10$  mg/d) at the time of AZA cessation. The median durations of AZA therapy and clinical remission were 68.4 months (IQR, 52.8-85.2 mo) and 63.6 months (IQR,



**Figure 1.** Flow-chart of the cohort (dotted lines refer to our previous randomized controlled trial; solid lines refers to the present study).

**Table 1.** Characteristics of the Study Population at Inclusion in the Follow-Up Cohort

Characteristic	Study cohort (N = 66)
Age, y	37 (29–47)
Male, n (%)	29 (44)
Never smoker, n (%)	26 (39)
Nonsmoker (never + ex-smoker who stopped for at least 1 y)	29 (44)
Current smoker, n (%)	27 (41)
Disease site, n (%)	
Small bowel only	5 (8)
Colon only	28 (42)
Both	33 (50)
Active perianal lesions, n (%)	9 (14)
Previous segmental resection, n (%)	28 (42)
Duration of disease, y <sup>a</sup>	10.2 (7.3–15.2)
Duration of remission, y <sup>a</sup>	5.3 (4.0–6.4)
Duration of azathioprine, y <sup>a</sup>	5.7 (4.4–7.1)
Azathioprine dose, mg/kg body weight/d <sup>a</sup>	1.7 (1.4–1.9)
CDAI <sup>a</sup>	37 (8–80) n = 64
CRP level, mg/L <sup>a</sup>	4.0 (3.0–5.0) n = 61
Hemoglobin level, g/dL <sup>a</sup>	13.6 (13.9–14.4) n = 63
Leukocyte count, 10 <sup>9</sup> /L <sup>a</sup>	6.7 (4.7–7.9) n = 63
Neutrophil count, 10 <sup>9</sup> /L <sup>a</sup>	4.4 (3.1–5.7) n = 63
Platelets count, 10 <sup>9</sup> /L	262 (227–297) n = 63

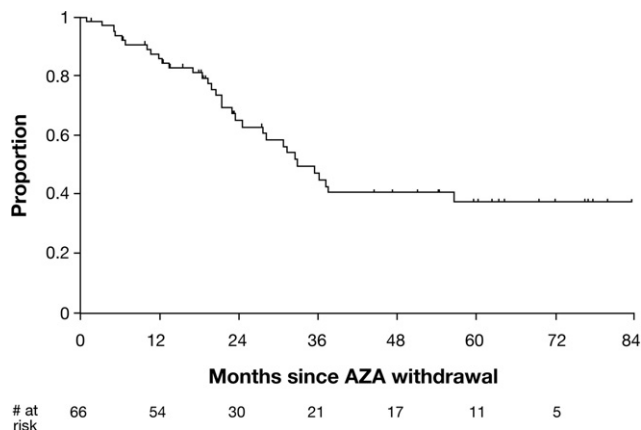
CDAI, Crohn’s disease activity index.  
<sup>a</sup>Median and interquartile range shown.

48.0–55.7 mo), respectively. Characteristics of the study population are listed in Table 1.

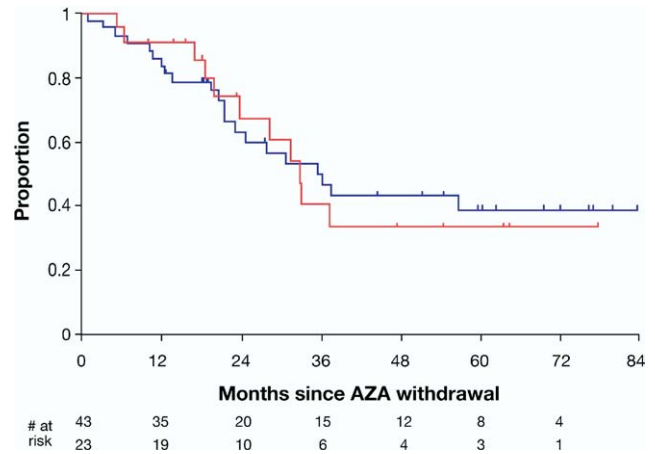
**Outcome After Azathioprine Withdrawal**

The median follow-up time after AZA interruption was 54.5 months (IQR, 20.4–69.6 mo). Thirty-two of the 66 patients had a clinical relapse. The probability of remaining in remission is described as a function of time since AZA withdrawal in Figure 2. The cumulative probabilities of relapse at 1, 3, and 5 years were 14.0% ± 4.3%, 52.8% ± 7.1%, and 62.7% ± 7.2%, respectively.

The time-to-relapse curves of the group of 43 patients who stopped AZA at the inclusion in the AZA withdrawal trial, after a median duration of AZA treatment of 62 months, and the 1



**Figure 2.** Cumulative probability of remaining in remission after AZA withdrawal in 66 patients.



**Figure 3.** Cumulative probability of remaining in remission after AZA withdrawal according to the time of AZA interruption, at inclusion in the AZA withdrawal trial (n = 43, small blue line) versus at the end of the trial (n = 23, red line).

of 23 patients who interrupted it at the end of their participation in the AZA withdrawal trial, after a median duration of AZA treatment of 80 months, were similar (P = .92) (Figure 3).

In univariate analysis, a neutrophil count of 4.0 10<sup>9</sup>/L or higher, a platelet count of 235 10<sup>9</sup>/L or higher, a CRP level of 20 mg/L or higher, a hemoglobin level of 12 g/dL or lower, and a duration of AZA treatment less than 48 months were associated with a high relapse risk. Surprisingly, the nonsmoking status (including never smokers and previous smokers who stopped >1 year ago) was found as a relapse risk factor. Total white blood cell count was not associated with relapse (white blood cell count, ≥6700/mL vs <6700/mL; hazard ratio, 1.9; IQR, 0.9–4.0; P = .069).

In multivariate analysis, a CRP level of 20 mg/L or higher, a neutrophil count of 4.0 10<sup>9</sup>/L or higher, and a low hemoglobin level (<12 g/dL) were independent factors associated with a higher risk of relapse (Table 2). Prognosis classification of relapse derived from these independent factors is reported in Table 3. Time-to-relapse curves according to prognostic classification are presented in Figure 4. The remission rate 5 years after AZA withdrawal was 61% in the subgroup of 25 patients presenting with none of the relapse risk factors.

A model including nonsmoking status, CRP level, hemoglobin level, and neutrophil level was found to be more effective to predict relapse than the model presented in Table 3. However, this model was not retained because of its lack of clinical significance.

**Table 2.** Multivariate Analysis of Variables Associated With a Higher Risk of Relapse After AZA Withdrawal in 60 Patients

Variable	Group at risk vs baseline group	Hazard ratio (95% CI)	P
CRP level, mg/L	≥20 vs <20	58.6 (7.5–457)	.002
Neutrophil count, 10 <sup>9</sup> /L	≥4.0 vs <4.0	3.2 (1.6–6.3)	.003
Hemoglobin level, g/dL	≥12 vs <12	4.8 (1.7–13.7)	.04

NOTE. Percentages or medians and IQRs shown. CI, confidence interval.

**Table 3.** Prognostic Classification of Relapse According to Neutrophil Counts ( $\geq 4.0 \times 10^9/L$ ), Hemoglobin Level ( $< 12 \text{ g/dL}$ ), and CRP Level ( $\geq 20 \text{ mg/L}$ ) at Inclusion in the Follow-Up Cohort

Variables	Number of relapses/number of patients	Hazard ratio (95% CI)	Relapse rate $\pm$ SE, %	
			at 2 y	at 5 y
No prognostic factors	7/25	1	15 $\pm$ 8	39 $\pm$ 12
Only neutrophil counts	19/29	4.2 (1.7–10.1)	44 $\pm$ 10	85 $\pm$ 8
At least one prognostic factor except neutrophil count	5/6	19.5 (5.5–69.2)	83 $\pm$ 15	—

CI, confidence interval.

### Efficacy of a Second Treatment With Azathioprine

Twenty-three of the 32 relapsing patients were retreated with AZA alone or in association with a transient course of steroids. Among them, 22 were put into remission (without steroids) again. The patient who did not respond to AZA alone had dominant anoperineal symptoms (perineal fistula appeared after inclusion in the cohort). The median duration of remission obtained with a second course of AZA, in the 22 of 23 successfully re-treated patients, was 28 months (IQR, 17–45 mo). Among the 9 relapsing patients who were not re-treated with AZA alone, 1 patient was re-treated with AZA associated with infliximab, and 8 patients did not receive AZA but underwent surgery for intestinal stenosis ( $n = 4$ ) or were treated with infliximab ( $n = 1$ ) or methotrexate ( $n = 3$ ).

### Toxicity

During the post-randomized controlled trial follow-up evaluation, adverse events occurred in 5 of the 66 patients. Two patients receiving AZA died: one from breast cancer, and the other, who received AZA in association with infliximab, from a disseminated varicella. Three patients had a moderate leukopenia, responsive to a decrease of the daily dose of AZA.

### Discussion

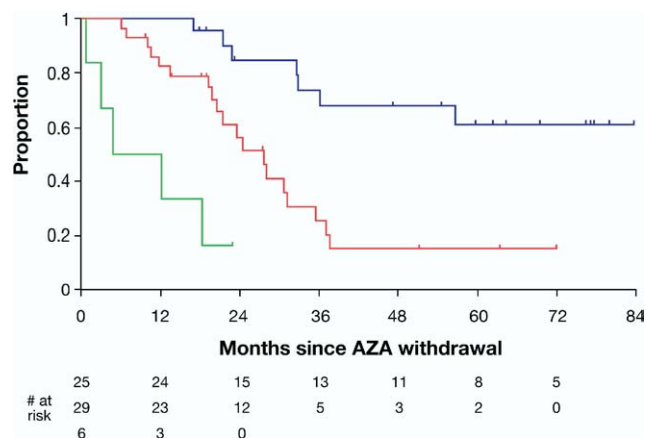
Whether or not AZA can be stopped in CD is an important question. Our study described the outcome of a large homogeneous cohort of patients with CD who have stopped

AZA therapy after a period of remission over 42 months, extending the follow-up period of a previous AZA withdrawal trial. Our study was not a randomized controlled trial, but a descriptive cohort with less degree of scientific evidence. It had the major advantage of a prolonged follow-up period, which is more suitable for a chronic disease than the 18 months of follow-up evaluation of the previous AZA withdrawal trial. Moreover, a usual limitation of such cohort studies is the absence of control on treatment modifications. This drawback appeared to be modest in our study because we showed (Figure 3) that the time-to-relapse curves were quite similar ( $P = .92$ ) for patients with controlled AZA withdrawal conditions (at AZA withdrawal trial randomization) and patients with uncontrolled AZA withdrawal conditions (after AZA withdrawal trial). Our results provide a clear-cut answer: AZA withdrawal is associated with a high risk of relapse in the long term.

Two retrospective surveys reported relapse rates after AZA or 6-mercaptopurine withdrawal from 66%<sup>19</sup> to 85%,<sup>20</sup> respectively, at 3 years. In these studies, the duration of treatment before its interruption was not correlated to the probability of staying in remission after drug withdrawal. In our study, when comparing the group of patients who stopped AZA at randomization in the AZA withdrawal trial (median duration of AZA treatment, 62 mo) with patients who stopped AZA at the end of the AZA withdrawal trial, 18 months later (median duration of AZA treatment, 80 mo), clearly no difference was shown ( $P = .92$ ) between the 2 time-to-relapse curves. Another study<sup>21</sup> reported the outcome of 29 patients in remission under continuous treatment with AZA for 2 years or more, randomized for continuation or withdrawal of AZA. At 1 year after randomization, the remission rate in each group was 85% and 47%, respectively ( $P = .043$ ).<sup>21</sup> This study showed a favorable trend in favor of AZA continuation but had several limitations: a small sample size, a short median of remission period under AZA (37 mo), and a restricted follow-up time after randomization.

In a recent European study including 1176 patients with inflammatory bowel diseases treated with AZA, continuation of AZA beyond 3 to 4 years seemed beneficial, except in patients in complete remission without steroids.<sup>22</sup> This result is contradictory to ours, but the median time of follow-up evaluation after AZA withdrawal in patients treated for more than 4 years was not given in this publication.

The demonstrated high risk of relapse after cessation of an efficient AZA therapy encourages its long-term use. Because most patients affected by CD are young, the potential risks of a prolonged treatment must be discussed. The absence of classic toxicities related to AZA in our study is caused mainly by the selection of patients already tolerant of AZA for 4 years. In studies initiating AZA or 6-mercaptopurine, approximately 10%



**Figure 4.** Relapse predicting classification according to the presence of risk factors after AZA withdrawal in 66 patients (small blue line, no risk factor,  $n = 25$ ; intermediate red line, hemoglobin  $< 12 \text{ g/dL}$  and no other risk factor,  $n = 29$ ; large green line, others,  $n = 6$ ).

to 20% of patients are unable to tolerate the drug because of nonspecific symptoms<sup>23</sup> such as hypersensitivity (including pancreatitis)<sup>24</sup> or bone marrow suppression,<sup>25</sup> which can occur after more than 10 years of treatment. Regular monitoring of blood counts, platelet levels, and liver tests is mandatory to detect delayed bone marrow toxicity and liver toxicity, as recently shown for focal nodular hyperplasia.<sup>26</sup> Another worry with prolonged duration of immunosuppressive treatment is the risk of malignancy,<sup>27</sup> and particularly lymphoma.<sup>28</sup> A recent meta-analysis including 6 studies found that the pooled relative risk of lymphoma in inflammatory bowel disease patients was 4.18 (95% confidence interval, 2.07–7.51).<sup>29</sup> This increasing risk could be owing to the medications, but also to the severity of the underlying disease. Dayharsh et al<sup>30</sup> have reported in a large survey that the bulk of lymphomas in AZA-treated patients (6 of 1200) occur during the first 3 years of treatment, and when associated with AZA it was mainly an Epstein-Barr virus-associated lymphoma. These results suggest that prolonged therapy may not provide a higher risk of lymphoma than shorter treatments. However, biases cannot be excluded and a French survey including more than 20,000 inflammatory bowel disease patients specifically dedicated to evaluate the risk of lymphoma associated with immunosuppressant therapy is ongoing.<sup>31</sup> In our cohort, which included patients from their inclusion in the randomized trial up to the end of their follow-up evaluation, 2 deaths among the 83 patients occurred (2.4%). Of note, the 2 deaths possibly were related to the AZA therapy: one during the randomized controlled trial period, caused by a myelodysplastic syndrome in a 32-year-old man who had received AZA for 68 months, and another during the follow-up period, caused by disseminated varicella in a 35-year-old man who had received combined treatment with AZA and infliximab. Although the role of AZA in the occurrence of this infection cannot be ruled out, a role of infliximab also is possible.<sup>32</sup> Recent surveys have pointed out the increased risk of infections<sup>33</sup> and cervical dysplasia<sup>34</sup> in association with combination treatments (eg, steroids and immunosuppressant, or immunosuppressant and biotherapy). Our results emphasize the importance of careful monitoring of patients treated with AZA, especially when used in association with other treatments.

We found 3 biologic independent predictive factors of relapse after AZA withdrawal (ie, high CRP level, low hemoglobin level, and neutrophil count equal to or higher than  $4.0 \times 10^9/L$ ). Two of these factors (hemoglobin and CRP levels) were found previously in our AZA withdrawal trial. We confirmed the value of biological inflammation markers for the prediction of relapse, as shown in other studies in CD patients with inactive disease under treatment.<sup>16,35</sup> Surprisingly, tobacco was found to be protective of relapse. Because it has been shown that the deleterious effect of tobacco disappeared within 1 year of cessation,<sup>36</sup> the population was divided into *smokers* (including current smokers and previous smokers who stopped within <1 year) and *nonsmokers* (including never-smokers and previous smokers who stopped for at least 1 year). The paradoxical protective effect of smoking in our population is difficult to explain because in most previous studies tobacco has been associated with a poor outcome in CD.<sup>37</sup> One putative explanation might be a more pronounced and prolonged effect of AZA in smokers as compared with nonsmokers.<sup>37</sup>

In patients without any risk factor of relapse, the 5-year relapse rate was about 40%. Time to relapse also was delayed

because all these patients were still in remission 18 months after AZA withdrawal. This result may have important practical implications because it suggests that in such low-risk patients, AZA interruption can be reasonably proposed for a period of time (eg, for pregnancy and breastfeeding). In this situation, the decision to stop or continue AZA is made on an individual basis because studies gave contradictory results about the safety of AZA during pregnancy.<sup>38</sup> The delayed time to relapse in a subgroup of patients also could explain apparently contradictory results reported in other studies without sufficient follow-up evaluation.<sup>8,22</sup> In contrast, the presence of at least one risk factor for relapse at AZA withdrawal conferred a poor outcome and should discourage drug cessation, even temporarily.

Another important finding in our study is the efficacy of a second course of AZA in patients (22 of 23) who relapsed after cessation of this drug. A previous retrospective study performed by 2 centers of our group also has suggested that when a relapse occurs after stopping an effective AZA course, resuming the drug results in an 80% success rate.<sup>39</sup> However, these observational data did not specify the duration of the remissions re-obtained by re-treatment with AZA.

Our study had 2 weaknesses. First, the definition of relapse was based on the Crohn's disease activity index score during the randomized controlled trial but on the Harvey-Bradshaw score during the follow-up evaluation because this simplified index offered the possibility to be calculated retrospectively. However, these 2 activity index scores have been shown to be highly correlated.<sup>40</sup> In addition, the definition of relapse in our study decreased the weakness of a retrospective evaluation based only on the Harvey-Bradshaw index. In fact, relapse was assessed by the association of a Harvey-Bradshaw index of 4 or higher with the introduction of a major treatment. Moreover, relapse was defined using the same items by the principal investigator during the retrospective analysis of patient medical records. The physician of each patient was not implicated in data collection in this follow-up study, to avoid a center effect in the definition of relapse. Second, endoscopy was not performed systematically before AZA withdrawal in our study. Consequently, the predictive value of mucosal healing cannot be deduced. In our AZA withdrawal trial,<sup>9</sup> the presence of residual lesions at endoscopy was not predictive of relapse, but only 54% of the patients were evaluated at baseline. This result contrasted with the one reported in another study suggesting that mucosal healing induced by infliximab could improve the outcome of patients.<sup>41</sup>

In conclusion, we found that even after a long duration of clinical remission under AZA, withdrawal of this drug is associated with a high risk of relapse. However, interruption of AZA can be reasonably considered, at least temporarily, in a selected group of patients having no predictive factor of relapse.

## References

1. O'Donoghue DP, Dawson AM, Powell-Tuck J, et al. Double-blind withdrawal trial of azathioprine as maintenance treatment for Crohn's disease. *Lancet* 1978;2:955–957.
2. 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.
3. 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.

4. 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.
5. 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.
6. Pearson DC, May GR, Fick G, et al. Azathioprine for maintaining remission of Crohn's disease. *Cochrane Database Syst Rev* 2000;CD000067.
7. Modigliani R. Immunosuppressors for inflammatory bowel disease: how long is long enough? *Inflamm Bowel Dis* 2000;6:158, 251-257.
8. Bouhnik Y, Lemann M, Mary JY, et al. Long-term follow-up of patients with Crohn's disease treated with azathioprine or 6-mercaptopurine. *Lancet* 1996;347:215-219.
9. Lemann M, Mary JY, Colombel JF, et al. A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. *Gastroenterology* 2005;128:1812-1818.
10. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. *Lancet* 1980;1:514.
11. Kaplan EL, Meier P. Nonparametric estimation for incomplete observations. *J Am Stat Assoc* 1958;53:457-481.
12. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemotherapy Rep* 1966;50:163-170.
13. Cox DR. Regression models and life-tables (with discussions), series B. *J R Statist Soc* 1972;34:184-192.
14. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. *Br J Cancer* 1977;35:1-39.
15. Byar D. Identification of prognostic factors. In: Byse ME, Staquet MJ, Sylvester RJ, eds. *Cancer clinical trials, methods and practice*. Oxford, UK: Oxford Medical Publications, 1988:423-443.
16. Consigny Y, Modigliani R, Colombel JF, et al. A simple biological score for predicting low risk of short-term relapse in Crohn's disease. *Inflamm Bowel Dis* 2006;12:551-557.
17. Cox DR, Oakes D. *Analysis of survival data*. London: Chapman and Hall, 1984:91.
18. SPSS. *Statistical package for social science, syntax reference guide*. Chicago: SPSS Inc., 1994.
19. Fraser AG, Orchard TR, Jewell DP. The efficacy of azathioprine for the treatment of inflammatory bowel disease: a 30 year review. *Gut* 2002;50:485-489.
20. Kim PS, Zlatanic J, Korelitz BI, et al. Optimum duration of treatment with 6-mercaptopurine for Crohn's disease. *Am J Gastroenterol* 1999;94:3254-3257.
21. Vilien M, Dahlerup JF, Munck LK, et al. Randomized controlled azathioprine withdrawal after more than two years treatment in Crohn's disease: increased relapse rate the following year. *Aliment Pharmacol Ther* 2004;19:1147-1152.
22. Holtmann MH, Krummenauer F, Claas C, et al. Long-term effectiveness of azathioprine in IBD beyond 4 years: a European multicenter study in 1176 patients. *Dig Dis Sci* 2006;51:1516-1524.
23. Present DH, Meltzer SJ, Krumholz MP, et al. 6-Mercaptopurine in the management of inflammatory bowel disease: short- and long-term toxicity. *Ann Intern Med* 1989;111:641-649.
24. Weersma RK, Peters FT, Oostenbrug LE, et al. Increased incidence of azathioprine-induced pancreatitis in Crohn's disease compared with other diseases. *Aliment Pharmacol Ther* 2004;20:843-850.
25. Connell WR, Kamm MA, Ritchie JK, et al. Bone marrow toxicity caused by azathioprine in inflammatory bowel disease: 27 years of experience. *Gut* 1993;34:1081-1085.
26. Vernier-Massouille G, Cosnes J, Lemann M, et al. Nodular regenerative hyperplasia in patients with inflammatory bowel disease treated with azathioprine. *Gut* 2007;56:1404-1409.
27. Fraser AG, Orchard TR, Robinson EM, et al. Long-term risk of malignancy after treatment of inflammatory bowel disease with azathioprine. *Aliment Pharmacol Ther* 2002;16:1225-1232.
28. Loftus EV Jr, Tremaine WJ, Habermann TM, et al. Risk of lymphoma in inflammatory bowel disease. *Am J Gastroenterol* 2000;95:2308-2312.
29. Kandiel A, Fraser AG, Korelitz BI, et al. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. *Gut* 2005;54:1121-1125.
30. Dayharsh GA, Loftus EV Jr, Sandborn WJ, et al. Epstein-Barr virus-positive lymphoma in patients with inflammatory bowel disease treated with azathioprine or 6-mercaptopurine. *Gastroenterology* 2002;122:72-77.
31. Beaugerie L, Carrat F, Bouvier A. Cohorte nationale CESAME: données démographiques et médicales 2004-2005 pour 20919 patients. *Gastroenterol Clin Biol* 2006;29:A154.
32. Tougeron D, Mauillon J, Tranvouez JL. [Severe varicella infection during treatment with infliximab for Crohn's disease]. *Gastroenterol Clin Biol* 2006;30:1410-1413.
33. Toruner MLJ, Harmsen WS, Zinsmeister AR, et al. Risk factors for opportunistic infections in patients with inflammatory bowel disease. *Gastroenterology* 2008;134:929-936.
34. Kane S, Khatibi B, Reddy D. Higher incidence of abnormal pap smears in women with inflammatory bowel disease. *Am J Gastroenterol* 2008;103:631-636.
35. Brignola C, Campieri M, Bazzocchi G, et al. A laboratory index for predicting relapse in asymptomatic patients with Crohn's disease. *Gastroenterology* 1986;91:1490-1494.
36. Cosnes J, Beaugerie L, Carbonnel F, et al. Smoking cessation and the course of Crohn's disease: an intervention study. *Gastroenterology* 2001;120:1093-1099.
37. Cosnes J, Carbonnel F, Beaugerie L, et al. Effects of cigarette smoking on the long-term course of Crohn's disease. *Gastroenterology* 1996;110:424-431.
38. Friedman S. Medical therapy and birth outcomes in women with Crohn's disease: what should we tell our patients? *Am J Gastroenterol* 2007;102:1414-1416.
39. Nachury M, Lemann M, Cosnes J, et al. Efficacy of a second course of azathioprine in patients with Crohn's disease relapsing after azathioprine withdrawal. *Gastroenterology* 2003;124:T1381.
40. Vermaire S, Schreiber S, Sandborn WJ, et al. Determination of Harvey-Bradshaw index (HBI), definitions for response and remission using the CDAI data from PRECISE 1 and PRECISE 2. *Gastroenterology* 2007;132(Suppl 2):1280.
41. Rutgeerts P, Diamond RH, Bala M, et al. Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. *Gastrointest Endosc* 2006;63:433-442, 464.

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Address requests for reprints to: Xavier Treton, MD, Hôpital Beaujon, Service de Gastroentérologie et Assistance Nutritive, PMAD, 100 Boulevard du Général Leclerc, 92110 Clichy, France. e-mail: [xavier.treton@bjn.aphp.fr](mailto:xavier.treton@bjn.aphp.fr); fax: (33) 1-40-87-45-74.

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