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Use of azathioprine during pregnancy and in the postoperative setting in Crohn’s disease: A worldwide survey of experts

Running title: Azathioprine in pregnancy and postoperative Crohn’s disease

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Key Words: azathioprine; mercaptopurine; thiopurines; inflammatory bowel diseases (IBD); Crohn’s disease; postoperative recurrence; pregnancy; survey.

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ABSTRACT

Background:
While thiopurines are considered safe in humans, they are still pregnancy FDA category D drugs. Prevention of postoperative recurrence is a challenge in clinical practice in Crohn’s disease. The ECCO consensus states that thiopurines should be considered in high-risk patients.

Aim:
To perform a worldwide survey for evaluating the extent to which gastroenterologists who are experts in the field of IBD are utilizing thiopurines during pregnancy and in the postoperative setting in Crohn’s disease.

Methods:
This was a Web-based Cross-sectional, statement-based survey, which was conducted among experts who have published at least once in the field of thiopurines in IBD.

Results:
Between December 20, 2009 and April 9, 2010, 175 questionnaires were received. The median number of IBD patients per physician per year was 400 (IQR 25-75th, 188-600) and the total number of IBD patients followed by all responders was 82,379. In a pregnant woman with a history of severe Crohn’s disease in clinical remission after 1 year on azathioprine, 88.6% of experts usually continue azathioprine until delivery and 9.1% of physicians never administrate azathioprine during pregnancy. After ileocecal resection for Crohn’s disease, 39.4% of physicians initiate azathioprine only in high-risk patients, 28% of practitioners
prescribe azathioprine according to endoscopic evaluation, 20% of gastroenterologists systematically initiate azathioprine, and 12.6% have a different attitude.

Conclusions:
Almost 9 out of 10 physicians continue azathioprine throughout pregnancy. About 7 out of 10 physicians prescribe azathioprine in the postoperative setting according to ECCO recommendations, whereas one-fifth of practitioners systematically initiate azathioprine after surgery.
INTRODUCTION

Over the last two decades, treatment of inflammatory bowel diseases (IBD) has greatly evolved, with the more frequent use of immunosuppressants (azathioprine, mercaptopurine, and methotrexate). The thiopurines azathioprine, 6-thioguanine (6-TGN) and mercaptopurine are anti-inflammatory and immunosuppressive drugs that have been available in clinical practice for over half a century. Azathioprine and 6-MP have been shown to be effective for inducing and maintaining clinical remission and fistula closure and for steroid tapering in Crohn’s disease (CD). Thiopurines are now considered standard of care, despite the absence of regulatory approvals.

Because operative resection of the diseased bowel is not curative, postoperative recurrence remains a problem in patients with CD. In a meta-analysis, Peyrin-Biroulet et al. found that purine analogs are more effective than placebo in preventing both clinical and endoscopic postoperative recurrence in CD. Recently, the ECCO (European Crohn's and Colitis Organisation) consensus stated that in patients with a risk factor for early post-operative recurrence (smoking, prior intestinal surgery, penetrating disease behaviour, perianal location and extensive small bowel resection) the drug of choice is azathioprine/mercaptopurine. The frequency and patterns of clinical use of thiopurines for the prevention of postoperative recurrence in CD is unknown.

Azathioprine and mercaptopurine are pregnancy Food and Drug Administration (FDA) category D drugs. Animals studies have demonstrated teratogenicity in mice and rats exposed to azathioprine. In humans, including IBD, multiple case series have not noted an increase in congenital anomalies. Therefore, although thiopurines have FDA rating D, the ECCO consensus recalled that that thiopurines appear to be safe and well tolerated during pregnancy. However, data on the daily use of azathioprine during pregnancy in women with IBD are scarce.
We therefore performed a worldwide survey to evaluate the extent to which gastroenterologists who are experts in the field of IBD are utilizing thiopurines during pregnancy and in the postoperative setting in Crohn’s disease.

MATERIALS AND METHODS

This was a web-based cross-sectional worldwide survey consisting of multiple-choice and open-ended questions. The questionnaire was developed by the Nancy, Saint-Etienne, and Monash University Hospital Departments of Gastroenterology after an exhaustive review of the literature regarding the use of azathioprine in IBD. The questionnaire consisted of two parts. The first part requested information about the responding practitioner and their IBD patients and the second covered the practitioners’ clinical practices (Study questionnaire available as Supplemental document online).

The questionnaire was sent by email to practitioners with expertise in IBD and who have published at least one original article on the use of azathioprine in IBD. In order to locate the email address of the authors, a literature search was conducted using MEDLINE database (U.S. National Library of Medicine, Bethesda, MD, USA) through December 2009, using the following medical subject heading (MeSH) terms: (“Azathioprine”[Title] OR “Mercaptopurine”[Title] OR “Thioguanine”[Title] OR “Thiopurine”[Title]) AND (“Colitis, Ulcerative” OR “Crohn disease” OR “Inflammatory bowel diseases”).

Statistical analysis

All quantitative variables are described as medians and percentiles [Interquartile range (IQR), 25–75th percentile]. All proportions are expressed as percentages with 95% confidence intervals (95% CI). Univariate analysis was performed using the Fischer’s exact test. When considering the continuous variables for dichotomous analysis, optimal cut-off values were
determined using receiver operating characteristic (ROC) analysis, as described by DeLong et al.\textsuperscript{12} All significant items obtained in univariate analyses were integrated into binary logistic regression model for multivariate analysis using a stepwise method. All variables with \( P \)-values of < 0.1 were initially included in the model, and variables with \( P \)-values of < 0.05 were retained in the model. Results were shown as Odds ratios (ORs) and 95% CI. All the reported \( P \)-values were two-sided, and \( P \)-values of < 0.05 were considered statistically significant. Statistical analyses were performed using MedCalc software, version 11.4.1.0 (MedCalc Software, Mariakerke, Belgium).

RESULTS

The literature search found 689 authors who have published at least once on the use of thiopurines in IBD. The questionnaires were first sent to experts on December 20, 2009. In February 2010, 165 questionnaires were received; by April 9, 2010, after the second mailing, we had received a total of 175 questionnaires. Table 1 reports the characteristics of the 175 responding gastroenterologists and their inflammatory bowel disease patients. The median number of IBD patients per physician per year was 400 (IQR 25-75th, 188-600) and the total number of IBD patients followed by all responders was 82,379. A total 21\% of questionnaires were sent from the US and 55\% from Europe, with a total of 25 different countries worldwide (Figure 1).

In a pregnant woman with a history of severe Crohn’s disease in clinical remission after one year on azathioprine, what is your strategy?

In a pregnant woman with a history of severe Crohn’s disease in clinical remission since one year on azathioprine, 88.6\% (n=155) of experts usually continue azathioprine until delivery, 9.1\% (n=16) of physicians never administrate azathioprine during pregnancy, and
2.3% (n=4) of practitioners stop azathioprine treatment only during the third trimester. In multivariate analysis, practitioners who followed more than 100 patients per year were more likely to maintain treatment with azathioprine throughout the pregnancy (OR=8.78; 95% CI, 3.06 to 25.17) while practitioners following less than 100 patients tend to never prescribe azathioprine during pregnancy (OR=13.70; 95% CI, 4.25 to 44.21) (Table 2).

After ileocecal resection for Crohn’s disease, what is your strategy regarding azathioprine?

After ileocecal resection for Crohn’s disease, 39.4% (n=69) of the responders initiate azathioprine only in patients with high-risk of postoperative recurrence, 28.0% (n=49) prescribe azathioprine according to endoscopic evaluation, 20.0% (n=35) systematically initiate azathioprine, and 12.6% (n=22) had a different strategy. The attitudes of these 22 gastroenterologists regarding the use of azathioprine in the postoperative setting are listed in Table 3.

In multivariate analysis, practitioners who follow less than 200 patients per year tend to prescribe azathioprine according to endoscopic evaluation after ileocecal resection for Crohn’s disease (OR=2.56; 95% CI, 1.29 to 5.07). Practitioners were more likely to systematically initiate azathioprine in the postoperative period if the proportion of patients with Crohn's disease in their cohort exceeded 55% (OR=2.73; 95% CI, 1.12 to 6.67), or if they reported having prescribed azathioprine for more than 60% of the patients they follow for Crohn's disease (OR=3.92; 95% CI, 1.73 to 8.90) (Table 2).

DISCUSSION

This is the first survey that evaluated the extent to which gastroenterologists who are experts in the field of IBD are utilizing thiopurines during pregnancy and in the postoperative setting in Crohn’s disease.
Although thiopurines are considered ‘Pregnancy Category D’ drugs by the Food and Drug Administration, the ECCO consensus considers azathioprine safe in pregnant women with no consistent reports of abnormalities of fertility, prematurity, or congenital defects.\(^8\)

Consistently, the American Gastroenterological Association Institute recommends, given on the large experience in transplant recipients\(^13\) and the body of evidence in IBD, the continuation of treatment with azathioprine during pregnancy to keep the mother in remission\(^14\). A flare of disease during pregnancy may be more deleterious to neonatal outcome than any potential risk from the medication\(^14\).

In a prospective, controlled, multicenter study conducted by the Tel Aviv University (Israel), 189 pregnant women on azathioprine who contacted one of seven teratogen information services were compared to a cohort of 230 pregnant women who contacted two of the seven teratogen information services and took nonteratogenic treatments during their pregnancy\(^15\). The aim of this study was to determine whether exposure to azathioprine during pregnancy increases the risk for major malformations and to determine the effect of azathioprine on pregnancy outcome\(^15\). In this study, although the rate of congenital malformations did not differ between the two groups, more cases of prematurity (21\% vs. 5\%, \(P < 0.001\)) and low birth weight (23\% vs. 6\%, \(P < 0.001\)) were noted in the azathioprine group\(^15\). Data from the Danish nationwide cohort study on women who were exposed to azathioprine or mercaptopurine during pregnancy reported relative risk for induced preterm birth of 4.0 (95\% CI 1.5 to 10.8).\(^16\) There was no elevated risk of spontaneous preterm birth, low birth weight at term, and congenital abnormalities.\(^16\) Moreover, this study suggested that adverse birth outcomes were caused by the underlying disease rather than by use of azathioprine or mercaptopurine.\(^16\) Data from the same Danish cohort study on 900 children born to Crohn’s disease women between 1996 and 2004, the relative risk of preterm birth and congenital abnormalities in thiopurine exposed women, was 4.2 (95\% CI 1.4 to 12.5) and 2.9
(95% CI 0.9 to 8.9), respectively. More recently, data from the CESAME study did not show an increased risk of interrupted pregnancies or congenital abnormalities among 204 women who received thiopurines during their pregnancy. In summary, most well conducted studies have shown some excess risk of preterm delivery in pregnant women treated with azathioprine, without warning signals on congenital abnormalities. The fact remains that the safety of using azathioprine during pregnancy is a matter of active debate.

In our survey, almost all experts maintain azathioprine during pregnancy in a pregnant woman with a history of severe Crohn’s disease in clinical remission after one year on this treatment. The number of patients followed per doctor was predictive of their clinical practice with a clear tendency to maintain thiopurine therapy among practitioners following over 100 patients per year.

Postoperative recurrence of Crohn's disease is a common problem in clinical practice. After ileocolonic resection, the recurrence rates of Crohn's disease in the neoterminal ileum are 30% and 80% after 3 months and 1 year of evolution, respectively. The rate of clinical recurrence is around 30% with an incremental annual risk of 10%. After a first Crohn’s disease–related ileocolonic resection, the risk of second surgery is 15 to 45% at three years, reaching 80% at 15 years.

Thiopurines are more effective than mesalamine or imidazole antibiotics alone for preventing both clinical and endoscopic recurrence of Crohn's disease. According to the ECCO consensus, in patients with a risk factor for early postoperative recurrence, the drug of choice is azathioprine/mercaptopurine. A meta-analysis of four controlled trials that enrolled 433 patients evaluated the efficacy of purine analogs in the prevention of postoperative recurrence in Crohn's disease. In the overall analysis, purine analogs were more effective than control arms in preventing both clinical and severe endoscopic recurrences at 1 year (number needed to treat (NNT)=13 and NNT=7, respectively) and for preventing clinical
recurrence at 2 years (NNT=8). It seems very likely that due to reasons stated above, two thirds of the experts who responded to this survey advocate the use of azathioprine before any endoscopic evaluation while only one fifth of them initiate a purine analogs therapy according to an endoscopic evaluation. Interestingly, practitioners who follow less than 200 patients per year await the results of endoscopic assessment before introducing azathioprine, while those that follow a cohort composed primarily of patients with Crohn's disease, are more likely to systematically prescribe azathioprine in the postoperative setting.

Nevertheless, in a recent one year, double-blind, randomized study, in patients with postoperative Crohn’s disease at high risk of clinical recurrence, superiority for azathioprine versus mesalamine could not be demonstrated for therapeutic failure, defined as a CDAI score \( > 200 \) and an increase of \( > 60 \) points from baseline, or study drug discontinuation due to lack of efficacy or intolerable adverse drug reaction.\(^{20}\) In this study, clinical recurrence was significantly less frequent with azathioprine in comparison with mesalamine (\( 0/41 \) (0%) vs. \( 4/37 \) (11%), \( P = 0.031 \)), while study drug discontinuation due to adverse drug reactions only occurred in azathioprine-treated patients (\( 9/41 \) (22%) vs. 0%, \( P = 0.002 \)) which had the effect of leveling the therapeutic failure rate between the two arms.\(^{20}\) Hence, purine analogs appear to represent an attractive option for patients who can tolerate this drug class. Indeed, in an eight-year intercept cohort of previous or present thiopurine-using IBD patients, a quarter of the patients discontinued thiopurines within 3 months, mostly due to adverse events, however, if thiopurine use was successfully initiated in the first months, its use was usually extended over many years.\(^{21}\)

In conclusion, this is the first worldwide IBD expert, statement-based survey that provided information on the extent of use of azathioprine in two clinical situations frequently encountered in clinical practice. During pregnancy, it seems obvious that almost all the experts are unanimous on continued treatment with thiopurines throughout pregnancy.
However, in the postoperative setting, attitudes appear to be less consensual, with two thirds of experts prescribing azathioprine therapy without any postoperative endoscopic evaluation and one third utilizing either an endoscopic–based or an alternative approach.
ACKNOWLEDGEMENTS

We are grateful to all our colleagues who participated in the survey.

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TABLES

Table 1. Characteristics of the 175 responding gastroenterologists and their inflammatory bowel disease patients

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<th>N</th>
<th>Median</th>
<th>IQR, 25-75th</th>
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<td>Year of graduation from medical school</td>
<td>170</td>
<td>1989</td>
<td>1981 to 1996</td>
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<td>What is the number of IBD patients that you follow per year?</td>
<td>172</td>
<td>400</td>
<td>188 to 600</td>
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<td>Among IBD patients followed per year, what is the proportion of patients with Crohn's disease (%)</td>
<td>163</td>
<td>60</td>
<td>50 to 65</td>
</tr>
<tr>
<td>Among IBD patients you have treated with azathioprine, what is the proportion of patients with Crohn’s disease (%)</td>
<td>171</td>
<td>70</td>
<td>60 to 80</td>
</tr>
<tr>
<td>Among patients that you follow for Crohn’s disease, what proportion of those are receiving azathioprine? (%)</td>
<td>173</td>
<td>50</td>
<td>40 to 65</td>
</tr>
<tr>
<td>Among patients that you follow for ulcerative colitis, what proportion of those are receiving azathioprine? (%)</td>
<td>173</td>
<td>30</td>
<td>20 to 40</td>
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</table>

IBD: inflammatory bowel disease; IQR: interquartile range.
Table 2. Predictors of gastroenterologists’ attitudes according to their characteristics, those of their patients, and access to and reimbursement of thiopurine metabolism monitoring tests (non-significant variables in univariate analysis are not shown)

<table>
<thead>
<tr>
<th>In a pregnant woman with a history of severe Crohn’s disease in clinical remission since 1 year on azathioprine, what is your strategy? You stop azathioprine treatment only during the third trimester</th>
<th>P-value, Univariate&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cut-off&lt;sup&gt;b&lt;/sup&gt;</th>
<th>P-value, Multivariate&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Odds ratio</th>
<th>95% CI, Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPMT phenotype (=‘Access and test reimbursed’)</td>
<td>0.03</td>
<td>–</td>
<td>0.27</td>
<td>–</td>
<td>–</td>
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</table>

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<tr>
<th>In a pregnant woman with a history of severe Crohn’s disease in clinical remission since 1 year on azathioprine, what is your strategy? You never administrate azathioprine during pregnancy</th>
<th>P-value, Univariate&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cut-off&lt;sup&gt;b&lt;/sup&gt;</th>
<th>P-value, Multivariate&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Odds ratio</th>
<th>95% CI, Odds ratio</th>
</tr>
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<tr>
<td>Number of IBD patients followed per year? (n)</td>
<td>0.002</td>
<td>≤100</td>
<td>&lt; 0.0001</td>
<td>13.70</td>
<td>4.25 to 44.21</td>
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<tr>
<th>In a pregnant woman with a history of severe Crohn’s disease in clinical remission since 1 year on azathioprine, what is your strategy? You usually continue azathioprine until delivery</th>
<th>P-value, Univariate&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cut-off&lt;sup&gt;b&lt;/sup&gt;</th>
<th>P-value, Multivariate&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Odds ratio</th>
<th>95% CI, Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of IBD patients followed per year? (n)</td>
<td>0.003</td>
<td>&gt;100</td>
<td>0.0001</td>
<td>8.78</td>
<td>3.06 to 25.17</td>
</tr>
<tr>
<td>TPMT phenotype (=‘Access and test reimbursed’)</td>
<td>0.03</td>
<td>–</td>
<td>0.04</td>
<td>3.24</td>
<td>1.05 to 10.05</td>
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<tr>
<th>After ileocecal resection for Crohn’s disease, what is your strategy regarding azathioprine? You prescribe azathioprine according to endoscopic evaluation</th>
<th>P-value, Univariate&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cut-off&lt;sup&gt;b&lt;/sup&gt;</th>
<th>P-value, Multivariate&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Odds ratio</th>
<th>95% CI, Odds ratio</th>
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<tr>
<td>Number of IBD patients followed per year? (n)</td>
<td>0.009</td>
<td>≤200</td>
<td>0.0072</td>
<td>2.56</td>
<td>1.29 to 5.07</td>
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<tr>
<th>After ileocecal resection for Crohn’s disease, what is your strategy regarding azathioprine? You systematically initiate azathioprine</th>
<th>P-value, Univariate&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cut-off&lt;sup&gt;b&lt;/sup&gt;</th>
<th>P-value, Multivariate&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Odds ratio</th>
<th>95% CI, Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of patients with CD among IBD patients (%)</td>
<td>0.01</td>
<td>&gt;55</td>
<td>0.03</td>
<td>2.73</td>
<td>1.12 to 6.67</td>
</tr>
<tr>
<td>Proportion of patients receiving azathioprine among CD patients (%)</td>
<td>0.03</td>
<td>&gt;60</td>
<td>0.001</td>
<td>3.92</td>
<td>1.73 to 8.90</td>
</tr>
</tbody>
</table>

IBD: Inflammatory bowel diseases; CD: Crohn’s disease; TPMT: Thiopurine S-methyltransferase.

<sup>a</sup>Fisher’s exact test
Cut-off defined using the receiver operating characteristic analysis as described by DeLong et al.\textsuperscript{12}

\textsuperscript{c}Binary logistic regression
FIGURE LEGENDS

**Figure 1.** Number of questionnaires received by country
REFERENCES


Characteristics of physicians and patients:

- Country: ......................
- Year of graduation from medical school: ................
- Number of IBD patients followed per year: ..............
- Among patients you have treated with azathioprine, what are the respective proportions of ulcerative colitis and Crohn’s disease? (the sum must equal 100%):
  - Ulcerative colitis = ________%
  - Crohn’s disease = ________%
- Among patients that you follow for UC, what proportion of those are receiving azathioprine? _____%
- Among patients that you follow for CD, what proportion of those are receiving azathioprine? _____%

QUESTION N°1
Do you have access to the following azathioprine pharmacogenomic tests?

- **TPMT genotype**
  - Access and test reimbursed ☐
  - Access but test not reimbursed ☐
  - No access ☐
- **TPMT phenotype**
  - Access and test reimbursed ☐
  - Access but test not reimbursed ☐
  - No access ☐
- **6-TGN dosage**
  - Access and test reimbursed ☐
  - Access but test not reimbursed ☐
  - No access ☐
- **Methylated derivatives dosage**
  - Access and test reimbursed ☐
  - Access but test not reimbursed ☐
  - No access ☐
QUESTION N°2
In a pregnant woman with a history of severe Crohn’ disease in clinical remission since 1 year on azathioprine, what is your strategy:

• You never administrate azathioprine during pregnancy   yes □   no □
• You stop azathioprine treatment only during the third trimester  yes □   no □
• You usually continue azathioprine until delivery    yes □   no □

Question N°3
After ileocecal resection for Crohn’s disease, what is your strategy regarding azathioprine:

• You systematically initiate azathioprine      yes □   no □
• You initiate azathioprine only in patients with high-risk of postoperative recurrence yes □   no □
• You prescribe azathioprine according to endoscopic evaluation yes □   no □
• You have a different attitude (Thank you for giving the details on your attitude):
   ........................................................................................................................................................................
   ........................................................................................................................................................................

THANK YOU!

For Peer Review