Frequency of use and standards of care for the use of azathioprine and 6-mercaptopurine in the treatment of inflammatory bowel disease: A systematic review of the literature and a survey of Canadian gastroenterologists

Thomas M Wallace BSc, Sander JO Veldhuyzen van Zanten MD PhD FRCPC

OBJECTIVE: To identify the frequency of use and appropriate monitoring guidelines for the adverse effects of azathioprine and 6-mercaptopurine (6-MP) in the therapy of patients with inflammatory bowel disease (IBD).

METHODS: Surveys were sent to all physician members of the Canadian Association of Gastroenterology. Physicians were asked to describe their monitoring practices for IBD patients receiving azathioprine or 6-MP. A systematic literature search was also performed using MEDLINE for articles published in English between 1966 and 1999 using the MeSH terms ‘azathioprine’, ‘6-mercaptopurine’, ‘inflammatory bowel disease’ and ‘drug monitoring’.

RESULTS: Azathioprine and 6-MP were used to treat an average of 7% of patients – a surprisingly low number given the proven efficacy of these agents. All respondents reported monitoring complete blood counts (CBC), while liver enzyme and pancreatic enzyme levels were monitored by 62% and 29% of respondents, respectively. The most commonly reported initial CBC testing frequencies were weekly (42%), monthly (26%) and biweekly (23%). From the literature, it was determined that severe leukopenia (less than 2.10 g/L) occurs in less than 2% of cases and is sometimes associated with serious outcomes, including death. Most cases of severe leukopenia occurred abruptly, early in treatment. Other reported adverse effects and incidences were pancreatitis (3% to 5%), hepatotoxicity (less than 1%) and hypersensitivity (2% to 3%). Data concerning an increased risk of non-Hodgkin's lymphoma were equivocal.

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CONCLUSIONS: Use of azathioprine or 6-MP is low in patients with IBD. A CBC should be performed at weeks 1, 2, 4, 6, 8 and 12, with subsequent testing every eight weeks for the duration of azathioprine or 6-MP treatment. The evidence in support of pancreatic and hepatic monitoring is weak. The risk of non-Hodgkin’s lymphoma is likely low.

Key Words: Azathioprine; Inflammatory bowel disease; 6-Mercaptopurine

Fréquence de prescription de l’azathioprine et de la 6-mercaptopurine et normes de soins relatives à leur utilisation chez les patients atteints d’entéropathies inflammatoires : examen méthodique de la documentation et enquête auprès des gastro-entérologues canadiens

OBJECTIFS : Déterminer la fréquence d’utilisation de l’azathioprine et de la 6-mercaptopurine (6-MP) et dégager des directives concernant la surveillance appropriée des effets indésirables chez les patients atteints d’entéropathies inflammatoires (EI).


RÉSULTATS : Environ 7 % des patients ont été traités à l’azathioprine et à la 6-MP, pourcentage étonnamment faible compte tenu de l’efficacité reconnue de ces agents. Tous les répondants ont indiqué surveiller l’héogramme, tandis 62 % et 29 % d’entre eux respectivement surveillaient la concentration des enzymes hépatiques et des enzymes pancréatiques. La fréquence des contrôles de l’héogramme au départ était répartie comme suit : toutes les semaines (42 %), tous les mois (26 %) et aux deux semaines (23 %). La documentation scientifique, pour sa part, fait état de leucopénie grave (inférieure à 2,10 %) dans moins de 2 % des cas, accompagnée parfois de conséquences graves, dont la mort. La plupart des cas de leucopénie grave sont apparus subitement au début du traitement. Parmi les autres effets indésirables, notons la pancréatite (3 % à 5 %), l’hépatotoxicité (moins de 1 %) et l’hypersensibilité (2 % à 3 %). Les données sur les risques d’oncogénèse non hodgkinien se sont révélées équivoques.

CONCLUSIONS : L’azathioprine et la 6-MP sont peu utilisées chez les patients atteints d’EI. Il faudrait procéder à un contrôle de l’héogramme à la 1re, 2e, 4e, 6e, 8e et 12e semaine de traitement à l’azathioprine et à la 6-MP, puis toutes les huit semaines. Peu de données établissent la nécessité d’un contrôle des enzymes pancréatiques et hépatiques. Quant aux risques de lymphome non hodgkinien, ils semblent plutôt faibles.

The efficacy of the immunosuppressants azathioprine and 6-mercaptopurine (6-MP) has been established in the therapy of Crohn’s disease and, to a lesser extent, ulcerative colitis (1-3). However, potentially serious adverse effects, especially leukopenia, complicate the use of these drugs. To use these drugs safely, effective monitoring must be employed to reduce the frequency and clinical consequences of adverse effects. The use of complete blood counts (CBC) to monitor bone marrow suppression is of particular importance.

Accepted indications for azathioprine in the treatment of Crohn’s disease are moderate to severe inflammatory bowel disease (IBD) refractory to corticosteroids, corticosteroid-dependent disease, fistulating disease and maintenance of remission. For the treatment of ulcerative colitis, azathioprine is indicated for corticosteroid-dependent disease and maintenance of remission. The adverse effects of azathioprine and 6-MP can be divided into allergic type, which are dose-independent reactions, and nonallergic type dose-dependent reactions (4). Allergic type reactions include pancreatitis, fever, rash, arthralgias, malaise, nausea and diarrhea, while nonallergic type reactions include leukopenia, thrombocytopenia, infection, hepatitis and malignancy.

Azathioprine is a prodrug that is rapidly converted to 6-MP by glutathione enzymes present in erythrocytes and other tissues (5). A conversion factor of approximately 0.5 can be used when equating azathioprine doses to 6-MP, considering molecular weights and bioavailability (4). After absorption, 6-MP is either converted to active metabolites, 6-thioguanine nucleotides (6-TGN), or inactivated by one of two pathways. The active metabolites of 6-MP are purine antagonists that inhibit the synthesis of protein, RNA and DNA (6).

A survey of Canadian gastroenterologists was conducted to determine how practising physicians monitor the adverse effects of azathioprine and 6-MP. In addition, the literature was systematically reviewed for articles concerning data on and recommendations for monitoring the adverse effects of azathioprine and 6-MP. Finally, a monitoring schedule is proposed based on the literature review and the survey results.

METHODS

A literature search was performed using MEDLINE for articles published from January 1966 to November 1999 using the MeSH terms 'azathioprine', '6-mercaptopurine', 'inflammatory bowel disease' and 'drug monitoring'. Azathioprine and 6-MP were limited to the subheadings 'adverse effects' and 'toxicity', while IBD was limited to the subheading 'drug therapy'. Titles and abstracts were then screened for articles describing the frequency of adverse effects and guidelines for monitoring IBD patients receiving azathioprine or 6-MP. All selected articles were checked for other relevant references.

A brief survey was developed, pretested and mailed to physician members of the Canadian Association of Gastroenterology (CAG). A profile of survey respondents, including age, practice type, number of IBD patients taking azathioprine and number of years in practice, was obtained. The main section of the survey asked physicians to describe their monitoring practice for IBD patients receiving azathioprine or 6-MP. Specifically, they were asked to describe the
types and frequency of monitoring tests performed. Physicians were also asked about the content of information that they provided to their patients when starting them on azathioprine or 6-MP.

**RESULTS**

Surveys were mailed to 457 members of the CAG who were believed to be practising physicians. For approximately 80% of the surveys, it was unclear whether the member was a practising physician, leaving 377 possible respondents; 240 (63%) surveys were returned. Forty-six of the returned surveys were excluded from analysis. Reasons for exclusion were change of address (n=4), no IBD patients in practice (n=29) or retirement from clinical practice (n=13). A total of 194 completed surveys were analyzed.

The average respondent was 48 years of age (range 28 to 69 years), with 18 years of practice experience (range one to 44 years) and 26 IBD patients (range two to 200 IBD patients) receiving azathioprine or 6-MP. Some respondents (15%) reported the number of patients receiving azathioprine or 6-MP as a percentage of all their IBD patients. From these data, the estimated mean percentage of IBD patients receiving azathioprine or 6-MP was 7% (range 3% to 23%). Forty-five per cent of respondents were affiliated with an academic centre. Of the remaining respondents, 30% had hospital-based solo practices, 12% had hospital-based group practices, 11% had community-based solo practices, 11% had community-based group practices, 12% had hospital-based group practices and 2% had hospital-based solo practices. The majority of physicians – 61% – prescribed azathioprine; 25% prescribed 6-MP; and 14% prescribed both drugs. Starting doses, maximum doses and minimum trial periods for the drug varied considerably among respondents. The most common doses indicated by physicians prescribing azathioprine were a starting dose of 50 mg and a maximum dose of 150 mg with a usual trial period of 24 weeks.

The main objective of the survey was to determine monitoring practices for IBD patients receiving azathioprine or 6-MP. All physicians (100%) indicated that they regularly monitored patients’ CBC, which, for the purposes of this study, was defined to include white blood cell count, automated white blood cell differential, platelet count and hemoglobin. Other monitoring tests mentioned were liver enzyme (62%), pancreatic enzymes (29%) and renal function tests (13%).

Physicians were also asked to describe the schedule that they employed for monitoring tests. Many (42%) reported that they initially performed CBCs on a weekly basis. The second and third most reported initial testing frequencies were monthly (26%) and biweekly (23%), respectively. A flow chart representing the most frequently reported monitoring schedules is presented in Figure 1. Because of the divergence of individual monitoring schedules beyond initial testing, it is not practical to represent all reported schedules. The number of physicians reporting specific initial testing frequencies and the duration that each frequency was employed are reported.

If specific monitoring schedules were not included for liver, pancreatic or renal monitoring, it was assumed that these tests were ordered each time a CBC was indicated. Separate liver monitoring frequencies reported were monthly, every three months, every four months and every six months. Each of these frequencies was specified by approximately 2% of respondents. Separate pancreatic or renal monitoring schedules were only specified by 4% of respondents.

On the issue of informed consent, physicians were asked to report which adverse effects they routinely discussed with IBD patients before prescribing them azathioprine or 6-MP. Adverse effects, and the percentage of physicians indicating each, were bone marrow suppression (86%), pancreatitis (83%), non-Hodgkin’s lymphoma (NHL) (52%), hepatic toxicity (41%), infection (24%), hypersensitivity (23%) and teratogenicity (14%). Physicians were also asked to report the estimated frequency of each adverse effect that they mentioned to their patients. Many (49%) respondents did not report frequencies. Those who did often replied qualitatively (eg, rare, uncommon), while others included a range of percentages for adverse effect frequency.

Physicians were also asked to specify how they informed their patients of adverse effects. Most – 56% – indicated they presented the information only verbally; 35% informed their patients both verbally and with written information;
and 5% used only written information. The most frequently cited patient handouts were the Canadian Crohn’s and Colitis Foundation information pamphlet (7), information from the Compendium of Pharmaceuticals and Specialties (8) and a patient education article (9) concerning the adverse effects of azathioprine and 6-MP. Only 2% of respondents indicated that they required a signed informed consent.

### LITERATURE REVIEW

The MEDLINE search using the MeSH terms ‘azathioprine’, ‘6-mercaptopurine’, ‘inflammatory bowel disease’ and the subheadings described in the ‘Methods’ section yielded 141 articles – 119 when limited to articles published in English. A total of 20 articles discussing the adverse effects bone marrow suppression, hepatotoxicity, pancreatitis, and neoplasm were selected. All articles were checked for relevant references.

To determine an effective monitoring schedule, it is first necessary to understand the incidence, clinical consequences and nature of onset of the adverse effects. Important adverse effects with the potential to be monitored were reviewed, including bone marrow suppression, pancreatitis, hypersensitivity and hepatotoxicity. Although not practically monitored, the risk of neoplasm was also reviewed.

The results of studies reporting leukopenia in terms of low white blood cell counts are summarized in Table 1. Leukopenia can be classified as mild (3.0×10⁹/L to 4.0×10⁹/L), moderate (2.0×10⁹/L to 3.0×10⁹/L) or severe (less than 2.0×10⁹/L) (10). Mild leukopenia is the most common adverse hematological effect. Its occurrence is predictable, and dose-dependent, temporary cessation of therapy or reduction of drug dose is usually sufficient to correct leukopenia. Clinical problems are rarely associated with these mild to moderate leukopenias. It has been shown that a certain degree of leukopenia correlates with efficacy and may be desirable (11). Severe leukopenia, however, was much rarer, occurring in less than 2% of cases (10-14). The consequences of severe leukopenia effects are potentially serious. In a retrospective review of 739 patients, five of nine patients with severe leukopenia were acutely ill. Two deaths occurred among these nine cases, both due to sepsis (10). In a retrospective study of 396 patients with IBD, severe leukopenia that required hospitalization occurred in eight (2%) patients. No patients died, and abnormal counts returned to normal in all cases after withdrawal of 6-MP (13). In a meta-analysis of nine randomized, controlled trials (n=302), only 1.7% of patients had to discontinue azathioprine or 6-MP secondary to leukopenia (15).

### Table 1

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Number of patients</th>
<th>Study design</th>
<th>Standard dose*</th>
<th>Drug discontinued†</th>
<th>White blood cells (×10⁹/L)</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connell et al (10)</td>
<td>739 Retrospective</td>
<td>Azathioprine 2 mg/kg/day</td>
<td>26 (3.5%)</td>
<td>2.0–3.0</td>
<td>19 (2.6)</td>
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<tr>
<td>Bernstein et al (12)</td>
<td>57 Prospective</td>
<td>6-MP 50 mg/day</td>
<td>1 (1.8%)</td>
<td>3.5–4.5</td>
<td>8 (14)</td>
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<td></td>
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<td></td>
<td>2.5–3.5</td>
<td>8 (14)</td>
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<td></td>
<td></td>
<td>&lt;2.5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Colonna and Korelitz (11)</td>
<td>98 Retrospective</td>
<td>6-MP 50 mg/day</td>
<td>0</td>
<td>4.0–4.9</td>
<td>20 (20)</td>
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<td></td>
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<td>3.0–3.9</td>
<td>26 (27)</td>
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<td></td>
<td></td>
<td>&lt;3.0</td>
<td>5 (5)</td>
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<tr>
<td>Present et al (13)</td>
<td>396 Retrospective</td>
<td>6-MP 1.5 mg/kg/day</td>
<td>8 (2.0%)</td>
<td>0.3–2.5</td>
<td>8 (2)</td>
<td></td>
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<tr>
<td>Candy et al (14)</td>
<td>33 Prospective</td>
<td>Azathioprine 2.5 mg/kg/day</td>
<td>0</td>
<td>2.0–4.0</td>
<td>13 (39)</td>
<td></td>
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<td></td>
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<td></td>
<td>&lt;2.0</td>
<td>0</td>
<td></td>
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<tr>
<td>Bouhnik et al (33)</td>
<td>157 Retrospective</td>
<td>Azathioprine 2 mg/kg/day</td>
<td>3 (1.9%)</td>
<td>&lt;3.0</td>
<td>18 (11)</td>
<td></td>
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<tr>
<td>Lobo et al (42)</td>
<td>47 Retrospective</td>
<td>Azathioprine 2 mg/kg/day</td>
<td>0</td>
<td>N/A</td>
<td>5 (11)</td>
<td></td>
</tr>
<tr>
<td>O’Brien et al (48)</td>
<td>78 Retrospective</td>
<td>Azathioprine 1–1.5 mg/kg/day</td>
<td>0</td>
<td>N/A</td>
<td>1 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Singleton et al (49)</td>
<td>59 Prospective</td>
<td>Azathioprine 2.5 mg/kg/day</td>
<td>2 (3.4%)</td>
<td>&lt;4.0</td>
<td>9 (15)</td>
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<td>&lt;2.5</td>
<td>2 (4)</td>
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</tbody>
</table>

*Starting therapeutic dose, which is often adjusted up or down according to response to therapy or development of leukopenia; †Withdrawal of azathioprine or 6-MP because of hematological adverse effects; ‡Only includes patients with leukopenia who required hospitalization.
Adverse effects of azathioprine and 6-MP in the treatment of IBD

From a monitoring viewpoint, the timing and rapidity of the onset of leukopenia are very important. Most severe cases tend to occur early in treatment. Connell et al (10) reported a range of onset for severe leukopenia (less than $2 \times 10^9$/L) of 0.5 to 132 months (mean nine months), with four of nine cases occurring within three months and a further two within a year. Most of these cases (six of nine) occurred abruptly – within one month of a normal blood count. The nature of onset of the two fatalities in this group was not specified separately. For moderate leukopenia ($2 \times 10^9$/L to $3 \times 10^9$/L) the range was one to 76 months (mean 12.5 months), with 16 of 19 cases occurring abruptly. In the remainder of cases, there was a gradual decline over several months that was not initially noticed in early tests. Bernstein et al (12) reported a range of three to 42 months (mean seven months) for moderate leukopenia. In Present et al’s review (13), five of eight cases of severe leukopenia occurred within the first month of 6-MP treatment.

Other, less common, forms of bone marrow suppression in azathioprine and 6-MP therapy include thrombocytopenia and pancytopenia. Connell et al (10) reported six cases of pancytopenia and nine cases of isolated thrombocytopenia in their review. Thrombocytopenia occurs less commonly than leukopenia and usually has no clinical adverse outcomes (10,13).

Several monitoring guidelines have been proposed in the literature using the above information on leukopenia incidence, clinical consequences and nature of onset. A schedule proposed by Present et al (13) stated that a blood count should be obtained weekly for one month, biweekly for the second month, monthly for four months and then bimonthly when stable after six months of treatment. Some authors have recommended less frequent initial testing based on doses of 6-MP 50 mg/day. For example, in a prospective study by Bernstein et al (12), the initial dose of 6-MP was 50 mg/day, and 79% of patients never received more than this amount. Bernstein et al (12) argued that less frequent monitoring is currently necessary, as opposed to when standard doses of 6-MP were 1.5 to 2.0 mg/kg/day. Present et al (13) also noted a correlation between dose and development of leukopenia. They observed that most bone marrow suppression occurred before the standard initial dose of 6-MP was changed from 1.5 mg/kg/day to 50 mg/day, regardless of weight. Connell et al (10) cited lower doses and the unpredictable timing and rapidity of onset in recommending initial monitoring every two weeks for three months followed by blood testing more frequently than once every three months for the remainder of treatment. Tanis (16) proposed similar guidelines.

An alternative to frequent monitoring of a large population is the prospective identification of patients at risk for acute toxicity. Improved understanding of the etiology of bone marrow suppression has led to the development of new tests for the early identification of such patients. Thiopurine methyltransferase (TPMT) is an enzyme in a catabolic pathway that is important in the deactivation of azathioprine and 6-MP. The activity of TPMT shows codominant genetic polymorphism (17). Those with high activity, 90% of the population, are homozygous for wild-type alleles. Approximately 10% are heterozygous with one mutant and one wild-type allele, and have intermediate activity. A small group, approximately 0.3%, are homozygous for two mutant alleles and have little or no TPMT activity (18).

Clinical studies have established an inverse correlation between TPMT activity and accumulation of the active 6-TGN metabolite of azathioprine and 6-MP (19). Those with intermediate TPMT activity appear to be at increased risk for bone marrow suppression with standard, empirical doses of azathioprine or 6-MP (20,21). Low TPMT activity in some patients has been linked to fatal hematological toxicity in response to thiopurine-based therapies (22). Because azathioprine induces TPMT activity in erythrocytes, direct assessment of enzyme activity is difficult. However, it is now possible to identify TPMT genotype using a polymerase chain reaction-based assay to detect mutant alleles (23). In a prospective study, six of 67 (9%) patients with immunosuppressive disease beginning azathioprine therapy were heterozygous for mutant TPMT (24). Of these six patients, five had to discontinue azathioprine therapy within one month because of leukopenia ($0.9 \times 10^9$/L to $2.7 \times 10^9$/L). The sixth patient did not adhere to treatment. Patients with wild-type TPMT alleles received therapy longer than patients with mutant alleles.

Another proposed alternative to CBC monitoring involves periodic measurement of 6-MP metabolite concentrations. This strategy has the potential to both avoid toxicity and improve efficacy by maintaining metabolite levels within a therapeutic window. This therapeutic window has been studied, although it has not yet been defined (25-27). Prospective studies are needed to prove the efficacy of this technique, but it is likely to be more costly than existing blood tests.

As was discussed for bone marrow suppression, the incidence, onset and clinical consequences of pancreatitis, hepatotoxicity and hypersensitivity must be considered to determine the value of monitoring these adverse effects. Pancreatitis has been reported in 3% to 5% of patients, with onset occurring within the first three weeks of therapy (13,28). The symptoms of pancreatitis subsided promptly, usually within two to three days, on withdrawal of azathioprine or 6-MP, and recurred with rechallenge (13,29). Drug discontinuation secondary to pancreatitis was reported in 1.3% of patients in a meta-analysis of nine studies of azathioprine and 6-MP efficacy (15). Pancreatitis was not found to be associated with other adverse effects, such as leukopenia, and there were no complications secondary to pancreatitis. It is recommended that patients with this adverse effect not reuse either azathioprine or 6-MP.

There are few reports of azathioprine- or 6-MP-induced hepatotoxicity in humans, suggesting that this adverse effect is rare (30-32). The evidence favouring azathioprine-induced hepatotoxicity includes improvement of liver function tests after discontinuation or adjustment of azathioprine dose, recurrence of serum enzyme abnormalities after reinsti-
tution of azathioprine therapy and absence of other factors that could have caused liver dysfunction. Also described are clinical features obscuring the issue, including concomitant administration of other potentially hepatotoxic drugs or blood products, absent or incomplete serological data regarding viral infection and possible hepatic involvement by underlying systemic disease (30).

Present et al (13) reported one case (0.3%) of hepatotoxicity in their review of 396 patients and Boulhnik et al (33) reported four cases (2.5%) in a review of 157 patients. Reported cases of hepatotoxicity can be grouped into three syndromes: hypersensitivity, idiosyncratic cholestatic reaction and presumed endothelial cell injury with resultant increased portal pressures, veno-occlusive disease and peliosis hepatitis. The strong association of hepatotoxicity with male sex and human leukocyte antigen suggests a genetic component. Present et al (13) recommended that liver enzymes be obtained every three to four months for the first year and every four to six months thereafter.

Hypersensitivity reactions are also a concern when prescribing and monitoring azathioprine or 6-MP. These reactions have been reported in 2% to 3% of patients (13,15,34). They usually occur early in therapy, with a mean onset of 18±17 days (range one to 45 days). Hypersensitivity reactions are usually fever and gastrointestinal effects, including nausea and vomiting. Gastrointestinal symptoms usually subside with continued use and do not have clinical implications. However, nausea severe enough to discontinue azathioprine or 6-MP therapy has been reported in 1.3% of patients (15). Identification of patients in whom hypersensitivity reactions are likely to occur is difficult. Demographics such as age, sex, drug dosage and known allergies to other drugs did not vary significantly between those who had reactions and those who did not (35).

The risk of malignancy, particularly NHL, has been well documented in transplant recipients receiving immunosuppressive agents (36). This same risk is less clear in patients with IBD receiving azathioprine or 6-MP, although reassuring data do exist. Connell et al (10) did not find a significant excess of malignancy and reported no NHL in a review of 755 IBD patients receiving azathioprine (37). In another review involving 396 patients, only one malignancy—a diffuse histiocytic lymphoma of the brain—had a possible association with 6-MP therapy. Concern persists, however, due in part to other published reports of NHL in IBD patients receiving azathioprine or 6-MP (33,38-40). An increased incidence of lymphoma in IBD without azathioprine or 6-MP treatment has also been reported (41). The effect on hematopoietic cells has also been cited in cases of acute myeloid leukemia and acute lymphoid leukemia after azathioprine or 6-MP therapy in IBD patients (42,43).

DISCUSSION
Our analysis of the monitoring schedules of survey respondents indicates that there are three prevailing monitoring patterns. The most common initial testing frequency is weekly, reported by 38% of respondents; 21% employ initial biweekly testing, while 24% initially test monthly. Because of the relationship between bone marrow suppression and mutations in the TPMT enzyme, and based on data from our literature review that demonstrated that most moderate to severe leukopenia occurs early after starting therapy, initial testing should be done on a weekly or biweekly basis. Subsequent monitoring can be less frequent, but if excessively large intervals (ie, longer than three months) are used, the unpredictable and possibly rapid onset of bone marrow suppression could lead to severe leukopenia and serious clinical effects. For these reasons, after more frequent initial testing, testing frequency can be reduced to monthly and bimonthly testing. We suggest that a CBC be performed at weeks 1, 2, 4, 6, 8 and 12, with subsequent testing every eight weeks for the duration of treatment.

Our survey did not ask physicians about their knowledge of the importance of mutations in the TPMT enzyme or whether they had access to this test. Recent evidence has shown that, in only 27% of patients, myelosuppression in patients with Crohn’s disease during azathioprine therapy was due to a mutation in the TPMT enzyme (44). The unpredictable timing of onset means that monitoring must be conducted on a regular basis for the duration of therapy. Because the majority of cases have an early onset, it makes sense that more frequent monitoring be conducted early on. Monitoring is necessary to control drug dosage properly to prevent mild and moderate leukopenia from progressing to severe leukopenia. Because most cases of severe leukopenia occur abruptly, monitoring may not be able to prevent their occurrence in all patients.

There is little evidence to support the monitoring of other adverse effects of azathioprine or 6-MP therapy. However, as indicated by survey respondents, pancreatitis and hepatotoxicity are abnormalities for which IBD patients receiving azathioprine or 6-MP are routinely tested.

The typical onset and clinical course of azathioprine- or 6-MP-induced pancreatitis do not support monitoring of pancreatic enzymes. The onset of pancreatitis is rapid, which makes the chance of preventing clinical symptoms small. There is also a phenomenon of a transient rise in amylase levels without clinical symptoms, which complicates the interpretation of abnormal results. Finally, the clinical course of pancreatitis is usually mild with a quick resolution of symptoms. For these reasons, measurement of amylase appears to be indicated only if symptoms typical of pancreatitis develop. It is, therefore, important that patients be informed about the possibility of pancreatitis and how it typically presents. Most physicians – 83%—do inform their patients of the risk of pancreatitis.

In spite of its rare and uncertain nature, hepatotoxicity was a concern for at least 62% of the respondents who reported monitoring liver enzymes (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamylate, bilirubin). The evidence in support of hepatic monitoring is weak. However, it seems prudent to check liver enzymes before starting therapy and at least twice a year given the prevailing standard of practice, the associ-
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Physicians should be alert to the sudden onset of fever, rash, gastrointestinal complications and shock, especially within four weeks of initiating azathioprine or 6-MP therapy. Only 23% of physicians mention hypersensitivity reactions to their patients as a possible adverse effect. If the initial dose elicits a febrile or systemic response, cessation of the drug without titration or rechallenge should be considered.

Neoplasia, especially the development of NHL, is a concern to many physicians when prescribing azathioprine or 6-MP. More than half, 52%, of respondents reported mentioning this risk to their patients at the beginning of azathioprine or 6-MP therapy. Most, however, indicated that they stressed that this was a theoretical risk that has rarely been reported in IBD patients. Given the uncertainty, it seems advisable to inform patients of the small possible risk of NHL with the long term use of azathioprine or 6-MP. Recent data indicate that the risk of lymphoma indeed is small in patients with Crohn’s disease taking azathioprine or 6-MP (45,46). The survey also shows that there is room for improvement in informing patients of the risks associated with azathioprine and 6-MP. Perhaps more frequent use of written handouts would be helpful in standardizing information that patients receive.

The efficacy of azathioprine and 6-MP in the treatment of IBD is well established (1,4,47). It was somewhat surprising to find that the average number of IBD patients receiving these agents was only 7% (range 3% to 23%). It is possible that respondents estimated the number of their patients on azathioprine and 6-MP from memory rather than from an actual count of patients currently taking these medications. This makes the actual number of 7% somewhat unreliable, although the difference from the real figure is likely to be small. We did not ask the respondents to document the number of patients who were treated with azathioprine and 6-mercaptopurine. The numbers provided give a reasonably good idea of the number of patients receiving the treatment but are probably not exact. Given the increased evidence of overall benefit of these agents, especially in patients who are corticosteroid dependent or corticosteroid refractory, further research is necessary to determine why use of these agents is so low among Canadian gastroenterologists.

CONCLUSIONS
Azathioprine and 6-MP are efficacious agents for the treatment of Crohn’s disease and ulcerative colitis. These agents were used in an average of 7% of patients—a surprisingly low number given the proven efficacy of these agents. Toxicity is a concern, although it has been shown that the occurrence of severe adverse effects is rare. The severity and incidence of dose-dependent adverse effects are presumably less of a problem now that lower doses of azathioprine and 6-MP are often being used. Bone marrow suppression, particularly leukopenia, is one of the more common adverse effects, with potentially serious clinical consequences. Appropriate monitoring can reduce but not completely eliminate the risk of bone marrow suppression in therapy with azathioprine or 6-MP.

We propose a monitoring guideline based on a systematic review of the literature and the current practice of Canadian gastroenterologists. A CBC should be performed at weeks 1, 2, 4, 6, 8 and 12, with subsequent testing every eight weeks for the duration of treatment. Pancreatic testing should only be conducted in the presence of clinical symptoms. The evidence in support of hepatic monitoring is weak. However, it seems prudent to check liver enzymes at least twice a year. The risk of neoplasm, NHL in particular, is likely low with azathioprine or 6-MP therapy for the treatment of IBD. However, given the uncertainty and serious nature of this adverse effect, it should be discussed with patients. Generally, patients do receive appropriate information from their physicians concerning the risks of azathioprine or 6-MP therapy, although few physicians state explicit adverse effect frequencies. This aspect of patient care could be improved if more physicians were to provide their patients with accurate, written information.

REFERENCES
Wallace and Veldhuyzen van Zanten


