

A survey of Canadian gastroenterologists about the use of methotrexate in patients with Crohn's disease

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BACKGROUND: Methotrexate (MTX) is effective in remission induction and maintenance in steroid-dependent Crohn's disease (CD), but is often considered to be a second-line immunosuppressive agent, to be used in cases of failure or intolerance to azathioprine (AZA) or 6-mercaptopurine (6-MP). This may be related to concerns about hepatotoxicity, but this adverse effect is rare in monitored CD patients taking MTX. Still, there are no guidelines for monitoring patients with CD on MTX, and physicians must decide based on rheumatological literature about how to monitor their patients.

PURPOSE: To determine the patterns of MTX use in patients with CD by Canadian gastroenterologists, examining the reasons for choosing MTX versus AZA/6-MP, the doses and routes of administration of MTX, and how patients on MTX are monitored, including the use of liver biopsy.

METHODS: A self-report survey was sent to physician members of the Canadian Association of Gastroenterology, with a second mailing three months later to increase response rate.

RESULTS: Of 490 surveys mailed, a 54.9% response rate was achieved. Of adult gastroenterologists, 60.7% stated they never use MTX as a first-line immunosuppressive agent, and 33.3% never use MTX at all. The most common reasons for choosing MTX were a contraindication to the use of AZA/6-MP (43.7%) and patient preference (22.5%). MTX is used intramuscularly in 41.5%, subcutaneously in 31.8%, and orally in 26.7% of patients. The most common dose used for remission induction was 25 mg/week (84.2%; range 7.5 mg/week to 50 mg/week; three responders used more frequent dosing than weekly) and for remission maintenance was 15 mg/week (55.4%; range 7.5 mg/week to 50 mg/week; three responders used more frequent dosing than weekly). Most responders checked a liver profile and complete blood count at baseline and serially. Of those who used MTX, 26.5% routinely performed liver biopsy after an accumulated dose of MTX had been taken (usually 1 g to 2 g), 57.7% sometimes performed liver biopsy, and 16.8% never performed liver biopsy. Of pediatric gastroenterologists, 17.6% never used MTX, but those who used it prescribed it subcutaneously (80.0%) more often than intramuscularly (17.5%) or orally (2.5%).

CONCLUSIONS: MTX was used as a first-line immunosuppressive agent in patients with CD by a minority of Canadian gastroenterologists. When used, there is variability in how MTX is prescribed and monitored. Although hepatotoxicity is rare, liver biopsy was performed frequently and probably often unnecessarily.

Key Words: Crohn's disease; Hepatotoxicity; Immunosuppression; Methotrexate

Enquête auprès de gastroentérologues sur l'utilisation du méthotrexate chez des patients atteints de la maladie de Crohn

CONTEXTE : Le méthotrexate (MT) est efficace pour provoquer et maintenir la rémission de la maladie de Crohn (MC) dépendante de la corticothérapie, mais il est souvent considéré comme un immunodépresseur de deuxième intention, à utiliser dans les cas d'échec du traitement à l'azathioprine (AZA) ou à la 6-mercaptopurine (6-MP) ou d'intolérance à ces médicaments. Cette façon de faire peut être liée aux craintes d'hépatotoxicité, mais l'effet redouté s'est manifesté rarement chez des patients atteints de la MC et traités au MT, ayant fait l'objet de surveillance. Pourtant, il n'existe aucune ligne directrice sur la surveillance des patients souffrant de la MC et traités au MT, et les médecins doivent se référer à la documentation en rhumatologie pour savoir comment surveiller leurs patients.

BUTS : Déterminer les modalités d'emploi du MT chez des patients atteints de la MC, par des gastroentérologues (GE) au Canada; examiner les motifs d'utilisation du MT par rapport à l'AZA ou à la 6-MP; comparer les doses et les voies d'administration du MT; relever les méthodes de surveillance des patients traités au MT, y compris la biopsie du foie.

MÉTHODE : Un premier questionnaire autoadministré a été envoyé aux médecins membres de l'Association canadienne de gastroentérologie, puis un second, trois mois plus tard afin d'obtenir un taux de réponse plus élevé.

RÉSULTATS : Le taux de réponse a été de 54,9 % (490 questionnaires postés). Parmi les GE pour adultes, 60,7 % ont répondu qu'ils n'utilisaient jamais le MT comme immunodépresseur de première intention et 33,3 %, qu'ils ne le prescrivaient jamais. Les principaux motifs de recours au MT étaient une contre-indication à l'AZA ou à la 6-MP (43,7 %) et la préférence du patient (22,5 %). Le MT était administré par voie intramusculaire, sous-cutanée ou orale dans 41,5 %, 31,8 % et 26,7 % des cas, respectivement. La dose la plus fréquente d'induction de la rémission était de 25 mg/semaine (84,2 %; 7,5 – 50 mg/sem.; 3 répondants : administration > 1 fois/sem.) et celle du maintien de la rémission, de 15 mg/semaine (55,4 %; 7,5 – 50 mg/sem.; 3 répondants : administration > 1 fois/sem.). La plupart des répondants ont indiqué qu'ils demandaient des épreuves fonctionnelles du foie et un hémogramme au début du traitement et à différents intervalles par la suite. Parmi ceux qui prescrivaient le MT, 26,5 % pratiquaient systématiquement une biopsie du foie après une dose cumulative de médicament (généralement de 1 à 2 g); 57,7 %, parfois; et 16,8 %, jamais. Parmi les GE pour enfants, 17,6 % n'avaient jamais prescrit de MT, et ceux qui en faisaient usage préféraient, et de loin, la voie sous-cutanée (80,0 %) aux voies intramusculaire (17,5 %) et orale (2,5 %).

CONCLUSIONS : Le MT n'est utilisé comme immunodépresseur de première intention chez les patients atteints de la MC que par une minorité de GE au Canada et, dans les cas où il est prescrit, la posologie et les moyens de surveillance varient passablement. Même si les réactions d'hépatotoxicité sont rares, les biopsies du foie étaient fréquentes et probablement non nécessaires, dans bien des cas.

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Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract. Corticosteroid therapy usually leads to symptomatic improvement in patients with CD (1,2), but a substantial proportion of patients are unable to successfully discontinue steroid treatment or relapse after steroids have been withdrawn (3). In addition, the long-term use of corticosteroids has the potential for significant toxicity, and steroid-sparing agents are an important part of managing patients with CD (4). The thiopurine agents azathioprine (AZA) and 6-mercaptopurine (6-MP) have been shown to be safe and effective in the induction and maintenance of remission in steroid-dependent patients (5-10), but there still exists a substantial failure rate with these drugs (11,12). As a result, other therapies have been investigated as steroid-sparing agents.

Methotrexate (MTX) has been used in the treatment of rheumatic disorders for many years (13,14). More recently, it has been shown to be effective in both the induction (at a dose of 25 mg/week) and maintenance (at a dose of 15 mg/week) of remission in patients with steroid-dependent CD (15,16). Although an intramuscular injection route was used in these studies, it has been shown that a subcutaneous route of administration has similar pharmacokinetics and greater tolerability (17,18). However, an oral route of MTX administration has unpredictable bioavailability in CD and cannot be relied on for therapeutic effect (19,20).

Although there are limited data comparing MTX directly with AZA/6-MP, the efficacy and tolerability is likely similar (21-23). Despite this, MTX is considered by some to be a second-line immunosuppressive agent, to be used in cases of failure or intolerance to AZA/6-MP (24,25). The reasons for this are unclear, but they may relate to concerns about the potential hepatotoxicity of MTX described in patients with rheumatic disease (26,27). However, it has become apparent that, when monitored appropriately, MTX hepatotoxicity in rheumatic diseases is rare except in patients with psoriasis, or when dosed more frequently than weekly (27-29). Similarly, it is now clear that significant MTX hepatotoxicity in CD is rare (30,31). However, it still seems prudent to monitor patients with CD on MTX therapy for potential hepatotoxicity. Unfortunately, no guidelines exist for monitoring these patients and physicians must decide about whether to follow MTX monitoring guidelines established for rheumatoid arthritis (Table 1) (28) or psoriasis (Table 2) (27), or to establish their own monitoring protocols.

The purpose of the present study was to determine the practice patterns of Canadian gastroenterologists when prescribing MTX in patients with CD. We sought to determine practitioners' reasons for choosing MTX versus AZA/6-MP when starting an immunosuppressive agent for the first time, the routes of administration and dosages of MTX used, and how MTX is monitored for hepatotoxicity in patients with CD.

METHODS

Approval was obtained from The Canadian Association of Gastroenterology and the Research Ethics Board at the University of Western Ontario. Surveys were sent on the authors' behalf by the Canadian Association of Gastroenterology to its nontrainee physician members. Enclosed with each survey was a cover letter describing the nature and purpose of the study and offering the option to not participate in the survey, as well as a stamped, self-addressed return envelope. Each envelope was numbered to

TABLE 1
Summary of recommendations for monitoring hepatotoxicity in patients with rheumatoid arthritis receiving methotrexate (MTX)*

At baseline:	CBC, creatinine, AST, ALT, ALP, albumin, bilirubin, hepatitis B and C serology Pretreatment liver biopsy if risk factors for liver disease
Serially:	AST, ALT, albumin
Liver biopsy only if:	5/9 or 6/12 abnormal AST or ALT in 12 months or decreased albumin level (despite dose reduction or temporary discontinuation of MTX and exclusion of other etiologies)
Stop MTX entirely if:	Roenigk grade III B or IV hepatic fibrosis [†] or patient refuses liver biopsy

*Adapted from reference 28; [†]Roenigk grade III B is moderate to severe fibrosis; grade IV is cirrhosis (based on Roenigk et al [40]). ALP Alkaline phosphatase; ALT Alanine aminotransferase; AST Aspartate aminotransferase; CBC Complete blood count

TABLE 2
Summary of recommendations for monitoring patients with psoriasis receiving methotrexate (MTX)*

At baseline:	CBC, urea, creatinine, urinalysis, creatinine clearance, AST, ALT, ALP, albumin, bilirubin, hepatitis A, B and C serology Pretreatment liver biopsy if risk factors for liver disease
Serially:	CBC, urea, creatinine, AST, ALT, ALP, albumin
Liver biopsy:	After every 1.0 g to 1.5 g of MTX taken At 2-4 months of therapy in patients with risk factors for liver disease If liver chemistry is persistently abnormal
Stop MTX entirely if:	Roenigk grade III B or IV hepatic fibrosis [†] or patient refuses liver biopsy

*Adapted from reference 27; [†]Roenigk grade III B is moderate to severe fibrosis, grade IV is cirrhosis (based on Roenigk et al [40]). ALP Alkaline phosphatase; ALT Alanine aminotransferase; AST Aspartate aminotransferase; CBC Complete blood count

anonymously keep track of responders. A second mailing was sent three months later to nonresponders to increase the total number of responses received.

Results were transcribed into a spreadsheet-style database and separated into groups based on specialty (gastroenterology, pediatric gastroenterology, other) for analysis. Incomplete surveys were included in the analysis as much as the responses allowed. Totals and percentages were calculated based on the number of responses to each particular question.

RESULTS

A total of 490 surveys were mailed on our behalf by The Canadian Association of Gastroenterology to its nontrainee physician members. There were 229 returned surveys after the first mailing and 85 after the second mailing, for a total of 314 (64.1% return rate). Of these, 45 were returned blank, leaving 269 of the 490 surveys returned completed (54.9% response rate), which were used for the analysis. Almost all responders practice gastroenterology or pediatric gastroenterology (Table 3).

Gastroenterologists

Overall, 47.4% of responders stated that they had an academic practice, 47.4% a community practice, and 5.2% a combined

TABLE 3
Specialties of all responders to the methotrexate in Crohn's disease survey (n=269)

	n (%)
Gastroenterology	231 (85.9)
Pediatric gastroenterology	17 (6.3)
Internal medicine	3 (1.1)
General surgery	3 (1.1)
Family medicine	1 (0.4)
Pathology	1 (0.4)
Pediatric surgery	1 (0.4)
Did not specify	12 (4.5)

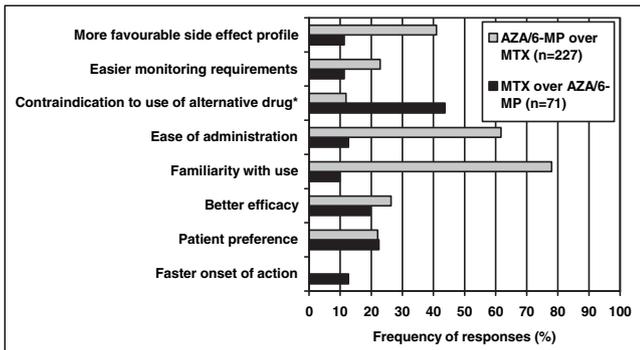


Figure 1) Most important reasons by gastroenterologists for choosing azathioprine/6-mercaptopurine (AZA/6-MP) versus methotrexate (MTX) as a first-line immunosuppressive agent in Crohn's disease. *Contraindication to MTX use for AZA/6-MP group, and contraindication to AZA/6-MP use for MTX group

academic and community practice. The mean number of years in practice was 16.5, and the mean number of patients with CD was 174. Of these, a mean of 33.4% were on MTX or AZA/6-MP.

When selecting an immunosuppressive agent for a patient with CD, 60.7% of responders never used MTX as a first-line agent. Of the 39.3% of responders that used MTX, this drug was chosen as a first-line agent in 16.2% of patients. Only 0.9% of responders always used MTX as a first-line immunosuppressive agent and never used AZA/6-MP first. Of the 99.1% of responders that used AZA/6-MP, this drug was chosen as a first-line agent in 94.5% of patients. The most important reasons for selecting AZA/6-MP versus MTX as a first-line immunosuppressive agent are summarized in Figure 1.

Seventy-six of 231 responders (33.3%) never prescribe MTX. Responders were more likely to never use MTX if they were in a community practice (41.5%) than in an academic practice (21.0%). The number of years in practice did not predict whether a responder ever used MTX (mean 16.2 years in MTX users versus 16.9 years in MTX nonusers). The 153 responders (66.7%) who used MTX prescribed it orally in 26.7% of cases, intramuscularly in 41.5%, and subcutaneously in 31.8%. The most common dose of MTX used for induction of remission was 25 mg weekly and for maintenance of remission was 15 mg weekly (Figures 2 and 3).

Before initiating MTX therapy, most responders routinely checked a patient's liver profile and complete blood count (CBC) (Figure 4). Most responders used MTX in patients with

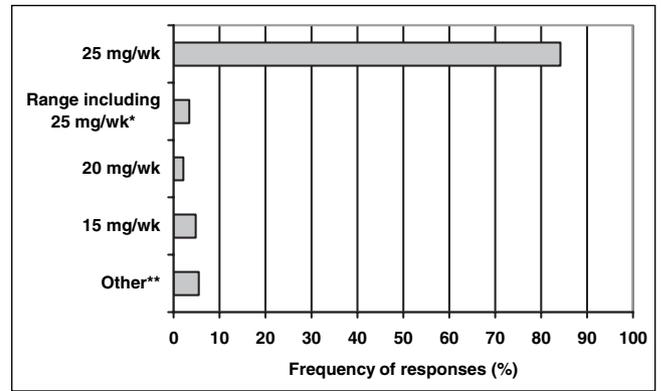


Figure 2) Doses of methotrexate used by gastroenterologists for induction of remission in Crohn's disease (n=146). *Responders gave a dose range that included 25 mg/week; **Range of doses was 7.5 mg/week to 50 mg/week; one responder used 6 mg three times a week; one used 25 mg twice a week; one used 12.5 mg twice a week

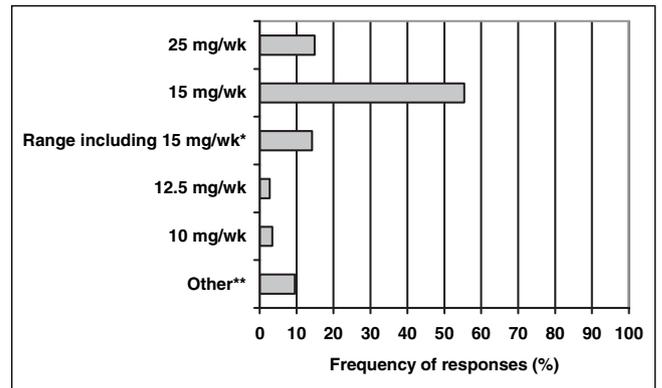


Figure 3) Doses of methotrexate used by gastroenterologists for maintenance of remission in Crohn's disease (n=148). *Responders gave a dose range that included 15 mg/week; **Range of doses was 7.5 mg/week to 50 mg/week, one responder used 3 mg three times a week, one used 15 mg twice a week, and one used 10 mg twice a week

prior alcohol consumption if the liver enzymes and function were normal. In patients with persistently abnormal baseline aspartate aminotransferase (AST) levels, approximately two-thirds considered using MTX depending on the results of other tests. Most responders would not use MTX in a patient with chronic hepatitis B or C infection (Figure 5).

When monitoring a patient on MTX therapy, most responders obtained a liver profile and CBC every four weeks (Figure 6). Thirty-eight of 149 responders (25.5%) always obtained a liver biopsy after a significant total dose of MTX had been taken by a patient. Of these, 24 (63.2%) obtained a liver biopsy after 1 g to 2 g of MTX had been taken, 10 (26.3%) performed biopsy after more than 2 g had been taken, and four (10.5%) did not specify the dose. Eighty-six (57.7%) sometimes obtained liver biopsy. Of these, 46 (53.5%) biopsied the liver in 15% of cases or less, 19 (22.1%) biopsied the liver in greater than 15% of cases, and 21 (24.4%) did not state the percentage of cases in which they biopsy the liver. Twenty-five (16.8%) responders stated that they never obtained a liver biopsy in patients on MTX.

When faced with a situation of a single abnormal AST value in a CD patient well-controlled on MTX, most responders

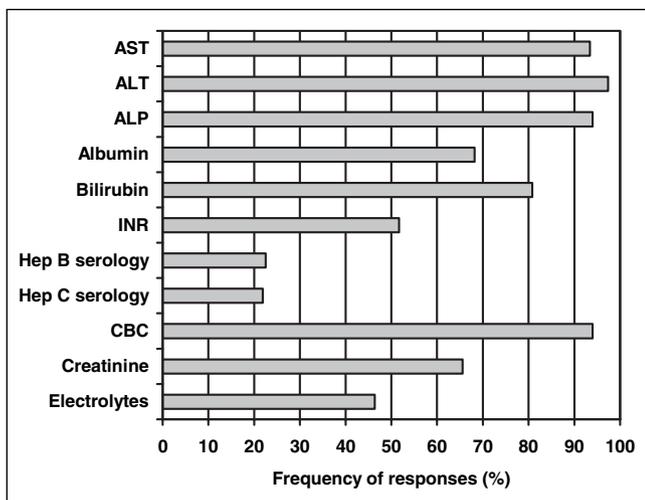


Figure 4) Investigations at baseline before initiating methotrexate therapy for Crohn's disease (n=151). ALP Alkaline phosphatase; ALT Alanine aminotransferase; AST Aspartate aminotransferase; CBC Complete blood count; Hep Hepatitis; INR International normalized ratio

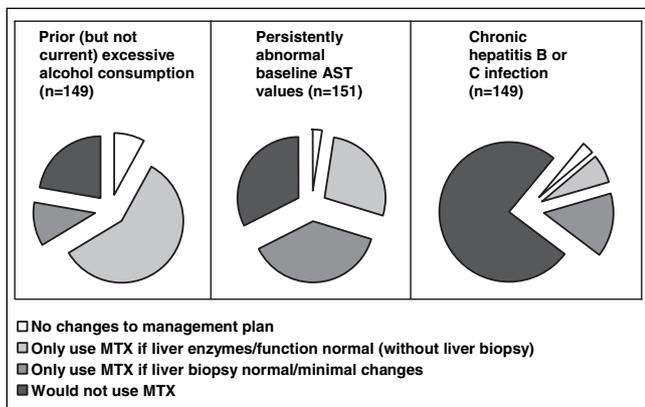


Figure 5) Management of specific clinical situations before initiating methotrexate (MTX) therapy in patients with Crohn's disease. AST Aspartate aminotransferase

simply followed bloodwork and only changed management if the value was persistently abnormal. When asked how they would manage a patient with an AST elevated on six occasions over a one-year period, most responders indicated that they would perform a liver biopsy and base further management on the pathology (Figure 7).

Pediatric gastroenterologists

Seventeen responders stated that their specialty was pediatric gastroenterology. They had a mean number of years in practice of 10.3 and a mean number of patients with CD of 82. Of these, a mean of 41.8% of patients were on immunosuppression. Three (17.6%) of the responders used MTX as a first-line immunosuppressive agent, but none of them used it in more than 5% of cases. The most important reasons for choosing AZA/6-MP over MTX as a first-line immunosuppressive agent were familiarity with use (88.2%) and ease of administration (70.6%). Three (17.6%) never used MTX at all. Overall, when MTX was used, it was prescribed orally in 2.5% of cases, intramuscularly in 17.5% of cases, and subcutaneously in 80% of

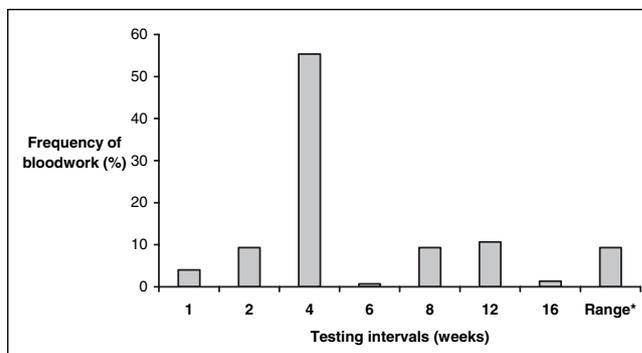


Figure 6) Frequency of bloodwork monitoring by gastroenterologists in Crohn's disease patients on methotrexate (n=150). *Responders gave a range of weeks (eg, every four to eight weeks) in their response

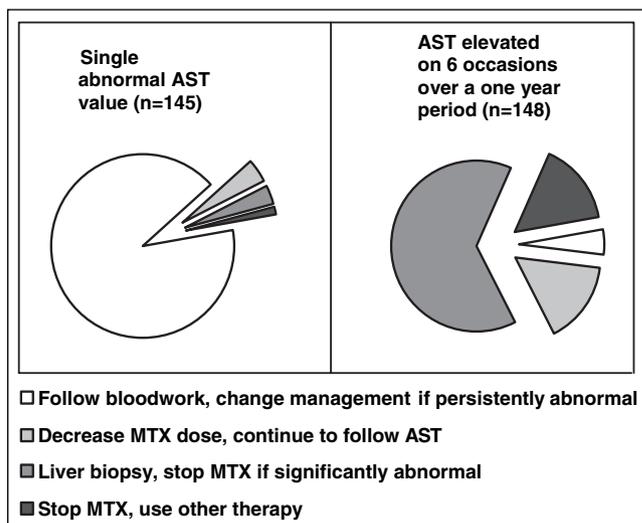


Figure 7) Management of abnormal aspartate aminotransferase (AST) values in Crohn's disease patients on methotrexate (MTX)

cases. A dose of 25 mg/week (range 12.5 mg/week to 20 mg/week) was most commonly used for remission induction, and 15 mg (range 12.5 mg to 25 mg) for remission maintenance. None performed routine liver biopsy, but 75% performed liver biopsy in selected cases.

DISCUSSION

MTX is effective in inducing and maintaining remission in steroid-dependent CD, with similar efficacy to AZA/6-MP (15,16,21-23). Despite this, MTX use in clinical practice is limited (24,25). There are a number of possible reasons for this, and our survey has shed some light on these.

The use of a survey for data collection has inherent weaknesses. The data obtained reflect only those individuals who chose to respond. We used two separate mailings to increase our response rate, but still, just over one-half of our surveys were returned completed. In addition, how individuals answer a survey does not necessarily reflect what actually occurs in their practices. People may over- or underestimate actual numbers and percentages, or respond based on what they believe to be the 'correct' answers to particular questions. Still, a survey can provide a reasonable estimate of practice trends from which generalizations can be made.

AZA/6-MP have been in use for a longer period of time than MTX in CD, and we found that familiarity with use was the most important reason for choosing AZA/6-MP as a first-line immunosuppressive agent. Community-based gastroenterologists (41.5%) were more likely to never use MTX than academic physicians (21.0%). This may represent a referral bias of more resistant cases at an academic centre, or perhaps a greater emphasis on staying up-to-date with current literature by academic physicians. Physicians also get comfortable using a particular regimen of medications as they become experienced with them. However, the mean number of years in practice was similar in physicians who use MTX (16.2 years) and those who never use MTX (16.9 years).

The next most important reason for choosing AZA/6-MP over MTX was ease of administration. Many patients prefer an oral route, making AZA/6-MP a more attractive option. Although MTX is available orally, the pharmacokinetics of oral MTX in CD are variable, and a parenteral route should be used (19,20). However, one-quarter of responders to our survey use oral MTX. Intramuscular and subcutaneous routes have similar pharmacokinetics, but self-injecting via a subcutaneous route is easy and well-tolerated (17,18,32). Despite this, more responders use an intramuscular route than a subcutaneous one when prescribing MTX parenterally.

The third most important reason for choosing AZA/6-MP over MTX was a more favourable side effect profile (41% of responders). Although AZA/6-MP are generally safe, there exist small risks of pancreatitis, allergic reaction, hepatitis, as well as myelosuppression, which may be severe in patients with thiopurine methyltransferase deficiency (33). MTX commonly causes nausea and vomiting, but this can be reduced with concomitant folate use (25). More severe adverse events, including myelosuppression, pneumonitis, and hepatic fibrosis or cirrhosis are rare (25,30,31). However, MTX is contraindicated in pregnancy, and is generally avoided in women of child-bearing age (34).

In circumstances where MTX is chosen as a first-line immunosuppressive agent, the most common reasons were a contraindication to AZA/6-MP use or patient preference. The third most common reason was better efficacy with MTX (19.7%), although a similar proportion of responders (26.4%) believe AZA/6-MP to be more effective. In reality, the efficacy of MTX and AZA/6-MP are similar (21-23).

There was variability in MTX doses used by survey responders. Although the recommended dose for remission induction is 25 mg/week (15,25), some responders use doses as low as 7.5 mg/week and as high as 50 mg/week. Similarly, for remission maintenance, 15 mg/week is the usual dose (although doses up to 25 mg/week are required for some patients) (16,25), but a range of 7.5 mg/week to 50 mg/week was reported by responders. In addition, three responders dose MTX more than once per week, which is associated with a higher risk of hepatotoxicity (29).

When initiating MTX therapy, guidelines (27,28) for both rheumatoid arthritis and psoriasis recommend testing a CBC, liver profile and viral hepatitis serology (Tables 1 and 2). Most responders to our survey check a patient's CBC and liver profile at baseline, but only about one-fifth of responders test hepatitis B or C serology. A pretreatment liver biopsy is recommended in both rheumatoid arthritis and psoriasis in patients with risk factors for liver disease or abnormal transaminases at baseline (27,28), but we found variable management

decisions in similar CD patients who are considered for MTX therapy. Over one-half of responders to our survey would use MTX in a patient with a prior history of alcohol abuse with normal liver enzymes and function without first performing liver biopsy, although almost one-quarter would not use MTX at all in this situation. Most responders would not use MTX in a patient with chronic hepatitis B or C infection, but the small proportion that would consider using it would usually first perform liver biopsy. Management of a patient with a persistently abnormal baseline AST value had a more variable response, with approximately one-third willing to use MTX if other liver blood tests were normal, one-third requiring a liver biopsy first, and one-third not willing to use MTX in this circumstance.

Serial monitoring of AST and ALT is recommended in both rheumatoid arthritis and psoriasis patients on MTX (27,28). All responders to our survey check a liver profile and CBC serially at variable intervals. In patients with rheumatoid arthritis and psoriasis, following the serum albumin as a marker of hepatic dysfunction is recommended (27,28), but in Crohn's disease this test may have less value because a decline in albumin may simply reflect activity of bowel disease. The response to a single abnormal AST in rheumatoid arthritis and psoriasis is to continue to follow this test and possibly reduce the MTX dose (27,28). Almost all responders to our survey adopt a similar approach, although for a few this is enough to trigger a liver biopsy. A persistently abnormal AST in rheumatoid arthritis and psoriasis is a recommendation for liver biopsy and, although we found this to be the case for most responders to our survey, there were still a number of responders who would continue to follow the AST, possibly with a reduction in the MTX dose. In addition, others would stop the MTX entirely and use another therapy without performing liver biopsy at all.

The most intriguing result of our survey related to the use of 'routine' liver biopsies in patients with CD taking MTX. Although most responders sometimes (only in cases of suspected hepatotoxicity) or never perform liver biopsy, one-quarter routinely perform liver biopsy after a total accumulated dose has been taken (usually 1 g to 2 g). This is similar to recommendations for psoriasis but different from rheumatoid arthritis, which do not include the use of routine liver biopsies because the risk of hepatotoxicity from long-term MTX use in rheumatoid arthritis (approximately 1%) is much lower than in psoriasis (approximately 7%) (27,28). The reason for this difference may be due to a higher rate of alcohol consumption in patients with psoriasis than in rheumatoid arthritis (26,27). In CD, it is apparent that hepatotoxicity due to MTX is rare. When it does occur, other risk factors usually play a role, and most authors recommend against the use of routine liver biopsies in patients with CD taking MTX (25,30,31,35). It appears that MTX-induced hepatotoxicity in CD is more similar to rheumatoid arthritis than to psoriasis, and the rheumatoid arthritis guidelines are generally applicable to CD patients. However, these guidelines were published before MTX was proven to be effective in CD, and there is great variation among gastroenterologists related to monitoring CD patients taking MTX.

Although MTX in pediatric CD patients has limited evidence (36-38), almost all pediatric gastroenterologists who responded to our survey use it in this population, and primarily use a parenteral route. Dosages used are similar to adult patients, although many responders gave dose ranges in their answers and perhaps use weight-based dosing. The risk

of hepatotoxicity due to MTX in children with CD is unknown, but is rare in juvenile rheumatoid arthritis (39), and routine liver biopsy is not performed by responders to our survey.

MTX is an effective therapy for patients with steroid-dependent CD; however, AZA/6-MP are used much more often as first-line immunosuppressive agents by Canadian gastroenterologists. There is considerable variability in dosages

and routes of administration used in clinical practice. Hepatotoxicity is rare, but routine liver biopsy after a total accumulated dose is commonly and probably unnecessarily performed. The absence of guidelines about how to best prescribe and monitor MTX in CD may contribute to the variability in how this medication is used; the development of such guidelines may lead to more consistent management of CD patients.

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