Methotrexate: “Lessons from rheumatology”

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Methotrexate (MTX) is an antimetabolite drug that was initially developed as a treatment for cancer in children. Following an extensive and successful period of evaluation for oncological indications, clinicians noted by chance that the drug also possessed anti-inflammatory and immunomodulating properties. These observations were confirmed in early experimental data in rheumatoid arthritis (RA) (1,2). The anti-inflammatory and immunomodulating properties of MTX provide an attractive therapeutic alternative to steroids in chronic inflammatory diseases. Randomized controlled trials have demonstrated clinically important benefits in diseases such as RA, psoriasis, multiple sclerosis and asthma. Recently, MTX has been evaluated in controlled trials for the treatment of inflammatory bowel disease (3,4). The two pivotal trials performed by Feagan et al (3,4) serve as the basis for the appropriate use of MTX in Crohn's disease for both induction and remission. More recently, the use of MTX has been associated with mucosal healing in a small, uncontrolled observational study (5).

In this issue of *The Canadian Journal of Gastroenterology*, Chande et al (pages 553-558) from the University of Western Ontario, London, Ontario, publish the results of a survey sent to Canadian gastroenterologists exploring the use of MTX in the treatment of Crohn's disease. The results of this survey are both fascinating and disappointing. Three main themes emerge from the survey: a significant proportion (one-third) of gastroenterologists do not use MTX; a significant proportion (approximately one-third) who are using MTX are using the drug inappropriately; and there is a lack of understanding in the toxicity associated with MTX.

In the survey, one-third of gastroenterologists never used MTX. This is alarming given that approximately one-half of the patients started on steroids will be either steroid-refractory or steroid-dependent at the end of one year. Many of these patients are started on purine antimetabolites (azathioprine, 6-mercaptopurine). This begs the question “what is happening to patients who fail corticosteroids or purine antimetabolites?” Arguments can be made that MTX should be used as the first-line immunomodulator because of the overall better data for steroid sparing, its faster onset of action compared with the purine antimetabolites and its ‘forced adherence’ when given parenterally. If one subscribes to the notion that Crohn's disease is truly RA of the gut then the rheumatologists would tell us that we should be using more MTX. Certainly, it has become the disease-modifying antirheumatic drug of choice

in rheumatology simply because it is effective, it has a quick onset of action and it has a favourable safety profile.

Even when MTX was being used by gastroenterologists, it was often being given orally and at the wrong dose. A common question arises “why can't I give MTX orally?” The answer is that you can give it orally but not at the doses that are used in Crohn's disease. Although rheumatologists usually use oral MTX, when the dose is pushed into ranges recommended in Crohn's disease, there are significant differences in bioavailability of the oral formulation. Bioavailability after oral dosing ranges from 50% to 90% (6). More recent investigations have shown important interindividual variability in the bioavailability of oral MTX (7). However, parenteral administration ensures a more uniform bioavailability. Therefore, MTX should be given at 25 mg intramuscularly or subcutaneously weekly for 16 weeks, and then 15 mg intramuscularly or subcutaneously weekly for maintenance with the knowledge that one-quarter of patients will need their dose adjusted upward if they fail the 15 mg/week maintenance dose.

Toxicity is common with MTX; however, most adverse reactions are mild and do not lead to the discontinuation of the drug. Minor reactions are common and include gastrointestinal intolerance, nausea, mucositis, headache, rash, central nervous system effects, fatigue, alopecia and minor infections. Major toxicities are rare and consist of pulmonary disease, liver dysfunction and bone marrow suppression. The mechanisms of MTX toxicity remain unclear. Some toxicity, such as gastrointestinal intolerance, mucositis and cytopenia, mimic folate deficiency, while others represent idiosyncratic or immunoallergic reactions.

Hepatotoxicity can be minimized by avoiding administration in patients with significant alcohol consumption (more than seven standard drinks per week), patients with type II diabetes mellitus, obesity, and concurrent liver diseases which may cause steatohepatitis. Hepatotoxicity in patients with Crohn's disease is rare (8). Routine liver biopsy is not recommended and only recommended if transaminases are elevated two times the upper limit of normal more than 50% of the time in a 12-month period or there is a persistent decline in albumin (9).

MTX has been a welcome addition to the treatment of patients with Crohn's disease and its introduction into the treatment paradigm is a testament of the excellent work that has been done in Canada in Crohn's disease. Despite this, many gastroenterologists have failed to accept the utility of this agent and there is sufficient room for education.

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