

# Canadian Association of Gastroenterology position statement regarding the use of thiopurines for the treatment of inflammatory bowel disease

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The Canadian Association of Gastroenterology is issuing the present position statement to address concerns resulting from the recent Health Canada warning, “Imuran (azathioprine) or Purinethol (mercaptopurine) – association with a type of blood cancer – hepatosplenic T-cell lymphoma – for health professionals” (Box 1) (1). While the alert does not contain new information, it informs clinicians of updates to the product labelling for azathioprine (Imuran, Triton Pharma Inc, Canada) and 6-mercaptopurine (Purinethol, Teva Canada Ltd, Canada) to include the association with the development of hepatosplenic T cell lymphoma (HSTCL). This serious cancer has been rare in Canada, with Health Canada reports including two cases (one fatal) with mercaptopurine and four cases with azathioprine (three fatal).

Although these agents are not Health Canada-approved for inflammatory bowel disease (IBD), they are frequently administered ‘off-label’ for the treatment of ulcerative colitis (UC) and Crohn disease (CD). Many therapies are used off-label, particularly in pediatric patients (2,3). Other common therapies included in IBD management guidelines, such as corticosteroids (prednisone) and methotrexate, are similarly not authorized for this indication. This does not imply improper or contraindicated use, but rather that clinicians use their professional judgment and the best available evidence to weigh the risk:benefit ratio for an individual patient (3).

The efficacy of thiopurine therapy in IBD is somewhat controversial. The Study of Immunomodulator Naive Patients in Crohn’s Disease (SONIC) (4) and UC SUCCESS (5) trials demonstrated that azathioprine in combination with an anti-tumour necrosis factor-alpha (TNF- $\alpha$ ) agent was superior to either agent alone in CD and UC for induction and maintenance therapy. These same studies suggest that azathioprine monotherapy is an inferior choice for induction and maintenance therapy in both UC and CD (4,5). Furthermore, recent studies have questioned the benefits of introducing thiopurines early in the disease course (6,7). However, in other trials, thiopurine agents have demonstrated benefits for steroid sparing and maintenance of remission (8-10). As a result, recent European and United States guidelines recommend thiopurines with or without anti-TNFs to maintain remission after failure of, or intolerance to, 5-aminosalicylic acid compounds (8-10).

Efficacy must be balanced against safety and tolerability. Immunosuppression can be associated with an increased risk for cancer. Specifically, thiopurines are associated with a small but significant risk of lymphoma (including HSTCL) (8, 11) and nonmelanoma skin cancer (12). Although there is an increased relative risk for lymphoma with thiopurine therapy in IBD patients, the absolute risk is very low (11). Of note, some subgroups, such as elderly patients, may face a much higher absolute risk of thiopurine complications because of a higher baseline risk (13). Thiopurines are also associated with bone

## BOX 1

### Health Canada warning of association of hepatosplenic T cell lymphoma with thiopurine therapy (1)

- Cases of hepatosplenic T cell lymphoma (including fatalities) have been reported in inflammatory bowel disease patients treated with azathioprine (Imuran, Triton Pharma Inc, Canada) or 6-mercaptopurine (Purinethol, Teva Canada Ltd, Canada) monotherapy
- Imuran and Purinethol labels have been updated for hepatosplenic T cell lymphoma and physicians should discuss the currently available information regarding risks and benefits of these treatments with their patients
- Imuran or Purinethol monotherapies are not authorized by Health Canada for the treatment of inflammatory bowel disease

marrow suppression, hepatotoxicity, pancreatitis, allergic reactions and an increased risk for opportunistic infections, especially when used concomitantly with steroids or infliximab (8,9).

The risks associated with thiopurine use, including those highlighted in the Health Canada alert, have been known to clinicians for some time and should be considered in their decision-making process. It is important to discuss both the risks and benefits of thiopurine therapy with patients to avoid uninformed decisions and abrupt discontinuation of therapy. Patients should be cautioned that treatment withdrawal among patients in stable remission on azathioprine has been associated with an increased risk for relapse (14).

Clinicians should conduct routine discussions to ensure that patients are aware of the balance of risk and benefits of therapies as a standard part of care (15). This most recent Health Canada warning reinforces our responsibility to stay current with regard to the risk and benefits of the medications we prescribe. Taking this one step further, it is our duty to communicate these points to our patients. Some suggestions for effective communications to help patients make informed medical decisions include avoiding vague descriptive words (eg, rare, common), using multiple formats (eg, numbers, graphs, pictorial representations), using absolute as opposed to relative numbers, avoiding small percentages (eg, 0.06%, use 6 per 10,000 instead) and individualizing data whenever possible (15).

Management decisions should be individualized. Continuation of therapy should balance the evidence for risk and efficacy against an individual patient’s response to therapy, preferences and risk tolerance. Some patients may have a higher risk tolerance than clinicians would predict (16). Therefore, it is important to have an open, individualized discussion and document this in the patient’s chart. Although events are relatively rare, clinicians must continue to be aware of the risk and counsel patients appropriately.

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