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Drug toxicity in inflammatory bowel disease



"...all medical therapies have toxicity ... The risks are generally outweighed by benefits, as we must appreciate not only the risks of therapy but also the risk of not treating aggressively."

Inflammatory bowel disease (IBD) is a disease characterized by chronic intestinal inflammation; it is a spectrum of disorders with two major subclasses, ulcerative colitis and Crohn's disease. While the pathogenesis of IBD is unclear, it is thought that a combination of environmental triggers (geography, diet, mode of delivery, breastfeeding, smoking), the mucosal innate/adaptive immune systems and genetic predisposition, all play a role in the etiology of IBD [1].

There are over 100 trillion bacteria in the human GI tract and hundreds of pathways that play a role in an exuberant inflammatory response; therefore, there are likely hundreds of therapeutic targets for IBD [2]. Given the diversity of pathways that can lead to inflammation, it is not surprising that inhibiting TNF- α (anti-TNF therapy) is not the panacea, and why broad immunosuppression with corticosteroids still has the greatest success in short-term symptom improvement.

There remain many debated questions regarding treatment of IBD. Should we treat early or late? Should we use a step-up versus top-down approach? Should we use mono or dual therapy [3]? The data suggest that we should treat early, aggressively and with combined therapy with the goal of symptom remission, particularly steroid-free symptom remission. Recent data have further challenged us to push toward mucosal healing and possibly even deep (histologic) remission [4-6]. So if we are more aggressive than ever before in our treatments with endpoints that are stricter than ever, are we asking for problems? Are we perhaps pushing the limits of the risk-to-benefit ratios of our current therapies?

Although steroids provide broad immunosuppression, they have myriad side effects and lead to a significant increase in infections and mortality [7,8]. Though they are not associated with an increase in lymphoma (they are actually used to treat it), their long-term adverse effects are indisputable.

Mesalamines do not have any significant immunosuppressive effects and are overall very safe. Sulfasalazine can cause decrease in sperm motility and can have sulfa-induced side effects, including diarrhea and headache, with reported cases of pancreatitis as well.

There are both idiosyncratic and dosedependent toxicities of thiopurines. It is important to separate the idiosyncratic reactions like pancreatitis, fever and arthralgias/myalgias from the dose-dependent adverse effects like hepatotoxicity and myelosuppression. For the idiosyncratic reactions, these authors are hesitant to use the thiopurine class of drugs in the future unless the reaction was mild or vague by history, as there is no way to predict recurrence. For the dose-dependent toxicities though, there are several strategies to optimize response and minimize toxicity given our understanding of the metabolic pathway of azathioprine and the metabolite levels of 6-TG, 6-MMP and 6-TU that predict best response and least toxicity. Evaluation of thiopurine methyltransferase (TPMT) activity can predict not only the risk of myelosupression when low, but it can also predict the low likelihood of thiopurine success when TPMT activity is very high, as higher TPMT activity predicts less production of the 6-TG metabolite known to lead to therapeutic response. Azathioprine (AZA) is sometimes better tolerated than 6-MP and split dosing (twice daily rather than daily dosing) can attenuate aminotransferase elevation [9,10]. We can also use the



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ratio of 6-TG to 6-MMP to decide when hepatotoxicity (high ratio) is more likely than therapeutic response (low ratio); blocking xanthine oxidase with allopurinol can reverse that ratio and optimize response. There is a four- to fivefold increased risk of non-Hodgkin's lymphoma in those on a thiopurine when compared with IBD controls, but this effect is mostly in the elderly and returns to near baseline risk once the thiopurine has been stopped for several months [11]. There is a slight increased risk of nonmelanoma skin cancer but no substantive risk of melanoma [12].

Cyclosporine has an increased risk of lymphoma in the transplant literature (probably post-transplant lymphoproliferative disorder), but there are no good IBD studies; we also know that lymphoma can regress with drug cessation [11]. Cyclosporine can lower seizure threshold in malnourished patients, cause nephrotoxicity (as can all calcineurin inhibitors) and increase the risk of infection, particularly in those already exposed to corticosteroids and anti-TNF therapies [12].

There is no clear signal of increased lymphoma with the use of methotrexate, but it is an abortaficient and also affects sperm function; therefore, it should be stopped 3–6 months prior to trying to conceive [11]. Other toxicities include hepatic fibrosis with a cumulative lifetime dosing of >1.5–2 g, hypersensitivity pneumonitis and disruption of folate metabolism.

"Inflammatory bowel disease is a disease characterized by chronic intestinal inflammation..."

The use of anti-TNF therapy does increase the risk of infection. In contrast to thiopurines, there is an increased risk of melanoma but no substantively increased risk of non-melanoma skin cancer [13]. There is an increased risk of non-Hodgkin's lymphoma in some studies but not in others; some of these data are hard to interpret given that most patients on anti-TNF therapy in those studies were also exposed to thiopurines that confer their own risk of lymphoma. Most recently, results from the TREAT registry showed that when compared with the general population, there is no increased risk of any malignancy with infliximab [14].

Natalizumab is a nonspecific α_4 integrin blocker that was first approved for MS; though very effective in Crohn's disease, there is a risk of reactivation of the JC virus with subsequent progressive multifocal leukoencephalopathy (PML). However, those who do not have detectable JC virus antibody in the blood should have no increased risk of PML, so this test can be very helpful for risk stratification. Longer duration of exposure to natalizumab can increase risk of PML, so knowing JC virus antibody status and length of exposure to the drug can help us best inform patients of this risk of PML [15]. Newer therapies that block the gutspecific integrin on the leukocyte ($\alpha_4\beta_7$) or its receptor (mucosal addressin cellular adhesion molecule or MAdCAM) should not cause cross the blood-brain barrier and therefore should not cause PML while still providing therapeutic effect.

Although the toxicities described above would make anyone weary, we must also consider the risk of not treating aggressively. Studies have shown fewer Crohn's disease surgeries in the era of greater AZA use [16]. A meta-analysis of 17 studies involving >20,000 patients suggested that thiopurines reduce the need for first resection in Crohn's disease by 40% [17]. And we also have data that the rate of IBD surgeries has decreased in the last six decades, coinciding with better, more aggressive therapy [18].

It is also likely that we can attenuate cancer risk by aggressively treating IBD with the goal of endoscopic and perhaps histologic remission. In recent years, the relative risk of colorectal cancer in UC has nearly disappeared in a European study, possibly due to more aggressive therapy. This decrease was not duplicated in a US study, but the latter probably selected for longer duration and greater severity of disease [19,20]. Finally, the number needed to treat to prevent one hospitalization, relapse or IBD-related surgery is far lower than the number needed to cause one more lymphoma in patients on thiopurine or anti-TNF therapy [11].

In conclusion, all medical therapies have toxicity. The weight of data supports early and aggressive therapy for those with moderate-to-severe disease. The risks are generally outweighed by benefits, as we must appreciate not only the risks of therapy but also the risk of not treating aggressively. To minimize toxicity, it is also important to institute preventive care in IBD patients on immunosuppression including screening for malignancy, metabolic bone disease and infection; providing vaccinations (avoiding live vaccines in those on anti-TNF therapy); and counseling on tobacco cessation. When this is done responsibly, we can best optimize therapy while minimizing risks of treatment.

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