ADVANCES IN IBD

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Monitoring and Management of Toxicities in Long-Term Thiopurine Therapy

Kian Keyashian, MD
Assistant Professor of Medicine
Oregon Health Science University
Portland, Oregon

G&H For those who tolerate thiopurine therapy, what is the optimal length of treatment?

KK Thiopurines are slow-acting drugs, taking up to 6 months to reach a therapeutic effect. They can be used by themselves as monotherapy or in combination with other therapies. If they are tolerated as monotherapy and if remission of inflammatory bowel disease (IBD) is achieved, then they are good choices for long-term maintenance therapy. Studies have shown that discontinuing therapy results in relapse even up to 5 years after initiation of therapy. There is no compelling evidence to discontinue thiopurine therapy if the patient is doing well, and there also is no compelling evidence to reduce the dose to avoid toxicity.

G&H Can other agents be introduced in place of thiopurines to maintain remission?

KK Other agents, such as methotrexate, can serve this purpose. Methotrexate likely works by a similar mechanism, although the exact mechanism is not completely known. A few studies have shown that, if patients with Crohn's disease do well on thiopurines, they would be able to transition to methotrexate, which has a slightly different risk profile. Also of interest is that, in some patients with a more aggressive disease, thiopurines can be used in combination with biologic therapy to reduce antibody formation and achieve remission. If the patient achieves symptomatic and endoscopic remission, the thiopurine could potentially be withdrawn after 1 to 2 years of therapy with continuation of biologic therapy.

G&H How is the patient monitored for hepatotoxicity and myelosuppression, and how is the patient managed if these toxicities occur?

KK The hepatotoxicity seems to be partly related to the metabolites of thiopurine, but this is not the only mechanism of hepatotoxicity. In the first 2 to 3 weeks of thiopurine therapy, a hypersensitivity reaction can occur. This more commonly occurs with azathioprine than mercaptopurine use. Cholestatic syndrome is another liver toxicity. Both of these toxicities—the hypersensitivity reaction and the cholestatic syndrome—will be evidenced by abnormal liver enzymes; therefore, closely monitoring liver enzymes would be how to maintain vigilance for emergence of hepatotoxicity.

A third pattern of chronic injury is related to vascular injury. These disorders include nodular regenerative hyperplasia and similar diseases. These patients usually do not present with abnormal liver enzymes, and so it is difficult to monitor for them. Instead, the presenting features include fatigue, nausea, and headaches. Therefore, periodic analysis of liver enzymes and investigation of symptoms such as fatigue and nausea might be the most helpful way to monitor for liver toxicities.

In cases of allergic reaction or cholestatic syndrome, a switch from 1 thiopurine to another may be helpful, and, in fact, stopping therapy has been shown to ameliorate cholestatic syndrome. Hepatotoxicity caused by chronic injury, on the other hand, is irreversible except in the case of peliosis.

As for myelosuppression, all the studies show that the highest risk appears to be within the first 8 weeks

of therapy. Monitoring blood counts during this time is recommended. After this 8-week period, the rates of severe myelosuppression and progression from mild to severe myelosuppression are lower, so it may be reasonable to obtain a complete blood count every 3 months to monitor for myelosuppression. Whether it occurs early or late in the therapeutic cycle, the best way to manage myelosuppression is to reduce the dose or stop thiopurine therapy. Myelosuppression tends to be reversible.

G&H What do we know about the risk of nonmelanoma skin cancer and thiopurine use, and how are patients advised?

KK The observation that thiopurine use may be associated with nonmelanoma skin cancer was first made in patients who had received organ transplants and were receiving thiopurines. Reports of nonmelanoma skin cancer began to emerge in the IBD population in the 1980s. There is some controversy about association, but research has helped us understand the mechanism of injury. There is good evidence that thiopurines are metabolized to highly reactive compounds that can become incorporated into the DNA, resulting in sensitization to ultraviolet light. As a result, thiopurines can generate reactive oxygen species, which can damage DNA and protein.

The current evidence suggests that the risk of nonmelanoma skin cancer is increased in the IBD population regardless of the therapies received. Patients who are older or have had disease longer appear to be at increased risk. Nonmelanoma skin cancer seems to be more common in patients with Crohn's disease, with a 5 to 6 times greater relative risk than that seen in the general population. Meanwhile, ulcerative colitis has a relative risk that is about 2 times higher than that seen in the normal population. Several large cohort studies suggest, however, that thiopurines increase the risk of nonmelanoma skin cancer even further.

The best way to address this risk in the clinical setting would be a multidisciplinary approach that includes a primary care physician, a gastroenterologist, and perhaps a dermatologist. Patients with IBD should be encouraged to apply sunscreen and to minimize sun exposure as much as possible and also to have yearly skin examinations, which can be performed by their primary care physicians. Patients with IBD who are receiving thiopurines should perhaps receive even more aggressive surveillance, with possible involvement of a dermatology service.

Certainly, if nonmelanoma skin cancer is diagnosed in a patient with IBD, the need for continued thiopurine therapy or a change in therapy should be assessed.

G&H Based on the evidence, do you believe that there is a strong link between thiopurine use and lymphoma?

KK In the 1980s, about the time thiopurines were being more closely studied, the risk of lymphoma began to receive significant attention in the form of multiple cohort studies and meta-analyses. Initially, IBD itself was suspected to be a risk factor for lymphoma, but several well-designed, large studies have shown that IBD is not a risk factor.

The general consensus among IBD specialists, based on findings from large studies, is that thiopurines increase the risk of lymphoma, independent of severity of disease. These cases of lymphoma seen in older patients and in men are typically treatable. However, hepatosplenic T-cell lymphoma, which is more aggressive, targets younger patients—those in their 20s. More than 90% of these patients are male. This form of lymphoma may not be responsive to therapy. The risk of hepatosplenic T-cell lymphoma should, therefore, be kept in mind when addressing treatment of IBD in a young man, although the absolute risk of lymphoma in the setting of thiopurine use is still extremely small.

The main point is to minimize the risk of lymphoma as much as possible. In younger men or pediatric patients, methotrexate, which has not been shown to have an association with lymphoma, should be prescribed instead of a thiopurine. Also, if a patient's endoscopy findings look good while the patient is on combination thiopurine and biologic therapy, the thiopurine could be withdrawn after 6 to 12 months to minimize the risk of lymphoma.

G&H Which patients should be monitored for metabolites?

KK I do not find it useful to routinely monitor for metabolites. Monitoring might be done if a change of therapy is being considered. For example, in a patient who continues to have symptoms and evidence of active disease, analysis of the 6-thioguanine (6-TGN) level may help optimize therapy. Monitoring could show that drug levels are subtherapeutic, and an increase in dose might be tried before concluding that thiopurine therapy has failed. Obtaining metabolites might also have a role in investigating hepatotoxicity. For example, a patient on a thiopurine could have an elevated alanine aminotransferase level for a number of reasons, but a high 6-methylmercaptopurine (6-MMP) level has been associated with hepatotoxicity that could be related to the thiopurine therapy.

A problem with monitoring metabolite levels is that findings can be misinterpreted. Also, a number of thiopurine-associated toxicities are unrelated to metabolite levels and might be overlooked if metabolite levels are used to gauge toxicity risk.

G&H What impact does the addition of allopurinol to thiopurine therapy have on the management of IBD?

KK Allopurinol came into use because some hospitalized patients on thiopurines had profound myelosuppression once they were placed on allopurinol. With allopurinol, the concentration of 6-TGN is preferentially increased, and the 6-MMP concentration is markedly decreased. The exact mechanism of action is not fully clear. Numerous studies have shown that this expected change in metabolites occurs. However, I do not think that dual therapy is an option for all patients receiving a thiopurine. The thiopurine dose needs to be reduced by about a third to a fourth. In addition, patients need to adhere to therapeutic monitoring or risk myelosuppression. Complete blood cell counts need to be very closely monitored in these patients. Potential safety issues are another concern, with a few cases of fatal cancers being found in small cohorts.

Researchers at IBD centers have found that splitting the dose of the thiopurine may accomplish the same goal as combination allopurinol and thiopurine, particularly with respect to lessening the risk of hepatotoxicity. So, when we typically give these thiopurines as once-a-day therapy, giving them twice a day in a split dose seems to result in a reduction of 6-MMP levels.

G&H What do we know about the safety of thiopurines in pregnant women?

KK Animal studies have shown that thiopurines result in teratogenicity in animals, so the US Food and Drug Administration has given the class a category B designation, with concern for fetal risk. Some early human studies also showed an association between thiopurine use and low birth weight babies, preterm delivery, and small size for gestational age. The problem with a lot of these earlier studies is they did not consider the actual course of IBD. New studies have shown that very active, uncontrolled disease also can result in these sorts of issues. A recently conducted meta-analysis that looked at birth outcomes in IBD showed no association with thiopurines, low birth weight, congenital abnormalities, or preterm birth. The PIANO registry, a large prospective cohort of pregnant women with IBD headed by Dr Uma Mahadevan at the University of California at San Francisco, also found, via an interval analysis, no increased risk of congenital malformations or other complications in thiopurine-exposed infants. Given these findings, I do not see a reason to withdraw a patient from thiopurine therapy if she becomes pregnant.

G&H If a patient is intolerant to 1 thiopurine, can that patient be switched to another?

KK Studies show that azathioprine can cause intolerance, such as digestive and flulike symptoms, rash, and even pancreatitis. Some clinicians recommend switching the patient from azathioprine to mercaptopurine if intolerance develops—although this should not be attempted in the setting of pancreatitis, in which case thiopurines should be discontinued. Otherwise, azathioprine and mercaptopurine are pretty comparable. Thiopurines are essentially good medications. The key is using them in the right patients and being mindful of the toxicities that could occur when reviewing therapeutic options.

Dr Keyashian has no conflicts of interest to disclose.

Suggested Reading

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