Clinical Usage of Azathioprine and 6-Mercaptopurine.

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Abstract:

Azathioprine (AZA) is a purine antimetabolite. It is a prodrug of 6-mercaptopurine (6-MP); both are widely used drugs for IBD. Sustained leukopenia (that may cause malignancy), acute pancreatitis, and allergy are the most common complications. 6-MP and AZA can take up to 3 months or longer. Leukopenic patients were more likely to respond, more likely to have their dose of steroids reduced, and more likely to be adequately treated for complications of IBD. By using newer technologies, clinicians can determine the safe / therapeutic dose of these agents. The clinical usage of AZA and 6-MP include: inflammatory bowel disease, refractory sprue, autoimmune hepatitis, primary sclerosing cholangitis, minimal change nephrotic syndrome, IgA nephropathy, Myesthina gravis, Henoch-Schonlein purpura, rheumatoid arthritis, sarcoidosis, acute lymphoblastic leukemia, refractory anemia with excess of blasts, liver, lung, renal, and pancreas transplantation, and some dermatologic disorders (e.g., eczema, pemphigus, etc.).

Key Words: Azathioprine, 6-Mercaptopurine.
Introduction:

Azathioprine (AZA) is a purine antimetabolite. It is a prodrug of 6-mercaptopurine (6-MP) containing an imidazole group attached to the sulfur atom at the 6-position of the purine ring. 6-MP and AZA are now two of the most widely used drugs for IBD because of their efficacy in both inducing and maintaining remission and their favorable adverse event profile. Data from 3 studies conducted by investigators at Lenox Hill hospital confirmed the safety of short and long-term 6-MP (with the exception of an increased risk of malignancy in patients with sustained leukopenia [WBC < 4000/mm³ for at least 3 weeks] 16,22,38. Approximately 8% of patients on 6-MP or AZA will develop acute pancreatitis and 1% will develop allergy characterized by fever, rash, and abdominal pain. About 10% will develop leukopenia and thus need to have doses adjusted downward. 6-MP and AZA can take up to 3 months or longer to reach efficacy, creating a clinical dilemma in nonresponding patients. Are patients who fail to respond being inadequately dosed or have they simply not taken the drug long enough to have an opportunity to respond? In previous years, clinicians have escalated the dose until mild leukopenia (WBC < 5000/mm³) was induced. As compared to patients without leukopenia, leukopenic patients were more likely to respond, more likely to have their dose of steroids reduced, and more likely to be adequately treated for complications of IBD. However, this "crude" measure of drug level is not an acceptable practice because not everyone who is dosed adequately will become leukopenic, and toxic doses could be given before leukopenia develops.

Strategies for Monitoring Treatment:

Technology is now available that allows for more accurate dosing of 6-MP and AZA. The technology also offers clinicians the opportunity to find the very narrow window between efficacy and toxicity for these medications. The end products of the metabolic pathways for these immunosuppressants and an important metabolizing enzyme have become very useful in managing patients with IBD. AZA is converted to 6-MP during the first pass of this drug through the liver. 6-MP is further metabolized to 6-thioguanine (6-TG), the active metabolite that can be measured in blood. 6-TG levels greater than 235 pmols / 8×10⁸ cells have been shown to correlate with response to 6-MP. Achkar and colleagues from the Cleveland clinic foundation proposed that 6-TG levels greater than 260 pmols / 8×10⁸ cells should be the preferred cutoff for therapeutic effectiveness. Moreover, these investigators demonstrated that 6-TG levels were more strongly associated with response than either immunosuppressant dose or WBC less than 5000/mm³.

6-MP is inactivated by 2 pathways: metabolism by xanthine oxidize and by thiopurine methyltransferase (TPMT). Xanthine oxidize metabolizes 6-MP to the inactive
thiouric acid. Patients on allopurinol, a xanthine oxidize inhibitor, should be given immunosuppressants with caution, probably at very low doses. Measuring 6-TG levels would be extremely helpful in such patients. Milk contains xanthine oxidize and patients whose 6-TG levels are low despite relatively high doses of the medication should be advised to minimize milk consumption. 6-MP also metabolized to the inactive 6-methylmercaptopurine (6-MMP) by TPMT. 6-MMP levels greater than 5700 pmol / 8×10^8 cells have been associated with hepatotoxicity, but transient hypertransaminasemia is seen only in a minority of patients. Immunosuppressive medications need not be discontinued if patients are found to have very high levels of 6-MMP and normal liver function tests, but careful monitoring of liver function is essential.

Dubinski and colleagues from Cedars-Sinai Medical Center presented their work on 6-TG in the treatment of patients with active Crohn’s disease who are found to have very high levels of 6-MMP. These patients have an abnormal metabolism of 6-MP such that too much of the inactive 6-MMP is produced while production of 6-TG is insufficient in order to have a therapeutic effect. Providing 6-TG directly to 9 patients with IBD (6 with Crohn’s disease and 3 with ulcerative colitis), Dubinski showed a response in 7 and remission in 6. One patient developed leukopenia and none developed or had recurrence of hepatotoxicity. Alternatively, TPMT activity can be diminished when 5-aminosalicylic acid (5-ASA) products are administered. Markowitz and colleagues from the North Shore long Island Jewish Health System showed that 2 patients with high 6-MMP and low 6-TG could have their metabolite profile improved by co-administering 5-ASA.

Metabolite levels need not be checked in every patient. There are 2 populations, however, for which monitoring metabolite levels could prove extremely important in improving patient care and outcome: 1) Metabolite levels should be checked in patients who fail to respond to immunosuppressive therapy to distinguish the true nonresponders from those who are inadequately dosed and from patients who are not adherent to their medication regimens. Therapy can be changed or abandoned based on the results. 2) Monitoring metabolite levels would be helpful for patients whose remission is being maintained by 6-MP or AZA. The chances of remission being maintained are likely to be greatest when 6-TG levels are within the therapeutic range.

Studies for determining levels of TPMT are also available commercially. TPMT is absent in 1 in 300 individuals and, because of the risk of severe toxicity, immunosuppressive therapy should be avoided in them. Eleven percent of the population has lower-than-normal levels and should therefore have immunosuppressants administered at doses lower than what would be given normally. TPMT levels should be checked in all patients being considered for administration of high-
dose oral (6-MP 1.5 mg/kg/day or AZA 2.5 mg/kg/day) or intravenous immunosuppressive therapy. Mahadevan and colleagues from the Mayo Clinic showed that intravenous AZA given to 9 patients with severely active ulcerative colitis enabled 5 of these patients to avoid colectomy and 3 to achieve remission. All such patients should have TPMT levels measured prior to administration of intravenous AZA.

The clinical usage of AZA and 6-MP:

1- Inflammatory bowel disease (I.B.D):
AZA and 6-MP are effective drugs in the management of steroid dependent and chronic active inflammatory bowel disease. They are also well tolerated on the long term. In patients with ulcerative colitis (U.C.) AZA has no effect in achieving remission when given in combination with Prednisolone. However, it lowers the proportion of relapses. In a 12-month pilot study was shown that treatment with AZA/Prednisolone appears to be more effective and safe compared to mycophenolate mofetil (MMF)/ Prednisolone in patients with chronic active colitis. MMF might be an alternative treatment for patient with contraindications to AZA.

Although the effectiveness of 6-MP or AZA in treating severe U.C. has been in several adult studies, but reported pediatric experiences are rare. In a review of 200 medical records of patients with active U.C. was shown the safety of 6-MP or AZA use in the treatment of pediatric patients with U.C. Side effects were minimal and reversible. 90% of 20 patients tolerated the therapy well. The results also show that 75% of 16 patients with U.C. will benefit from the use of 6-MP or AZA after initial discontinuation of corticosteroid therapy. Although 6-MP or AZA may not prevent further relapses, medical management of these flares may be less intense and may not require long term corticosteroid use.

The studies that are based on using the MEDLINE data base (1966-Dec. 1997), abstracts from major gastrointestinal research meetings and references from published articles and reviews, showed that AZA and 6-MP are effective therapy for inducing remission in active Crohn's disease. The odds ratio of response increases after 17 weeks of therapy or more, suggesting that there is a minimum length of time for a trial of AZA or 6-MP therapy.

Adverse events were more common among patients on therapy. High doses of steroids at the beginning of AZA therapy may be associated with higher remission rate at one year.

In another five randomized double-blind placebo-controlled trials of AZA therapy AZA was effective in maintaining remission of Crohn's disease and there was evidence for a steroid-sparing effect.

In clinical experience with combination treatment using Tacrolimus and either AZA or 6-MP in patients with Crohn's disease perianal fistula seen at the Mayo Clinic from 1996-1998, researchers concluded this combination therapy may be effective treatment for perianal fistulae although higher initial
Tacrolimus doses, increase the risk of nephrotoxicity without improving clinical response\textsuperscript{39}. We must pay attention that discontinuation of 6-MP, while Crohn’s disease is in remission, leads to higher relapse rates and continuation of 6MP reduces the likelihood of relapse\textsuperscript{14}. Also low-dose, weekly, subcutaneous methotrexate can induce remission in some pediatric patients with Crohn’s disease who fail to adequately respond to other immunomodulator medications including 6-MP\textsuperscript{30}.

2. Refractory Sprue:
Vaidya and et al. reported a patient with life-threatening refractory sprue who was dependent on high dose of corticosteroids to prevent severe diarrhea, malabsorption and villous atrophy. AZA allowed tapering of steroids to lower doses, while maintaining remission in histology and in objective measures of malabsorption. Of course, immunosuppressive therapy isn’t without risks, particularly in patients with associated hypoglobulinemia\textsuperscript{49}.

3. Autoimmune hepatitis:
Prednisolone alone or in combination with AZA is the treatment of choice for severe type 1 autoimmune hepatitis. The combination regimen is preferred, especially in the elderly, because of a lower incidence of corticosteroid related complications. Only patients with sustained severe laboratory abnormalities, bridging necrosis or multilobular necrosis on histological assessment, and /or incapacitating symptoms, have absolute indications for treatment based on controlled clinical trials. The institution of therapy must be individualized in other patients, based mainly on symptoms and disease behavior. Serum aspartate aminotransferase and gamma-globulin level are the most useful indices to monitor during therapy. Liver tissue examination is the best method of evaluating completeness of response. Most patients enter remission, but relapse occurs in 50 to 86% after drug withdrawal. Maintenance therapy with low dose of Prednisolone or AZA can be used long term in patients who have relapsed repeatedly. Inability to achieve remission after 3 years, deterioration during therapy and drug toxicity are unsatisfactory responses that warrant alternative strategies\textsuperscript{4}.

4. Primary sclerosing cholangitis (P.S.C):
Schram and et al. in university hospital in Mainz in Germany, administered AZA/ Prednisolone/ ursodeoxycholic acid (UDCA) to 15 patients with PSC. After a median observation period of 41 months, liver enzyme levels declined significantly in all patients. Six of 10 patients with follow-up liver biopsies showed histologic improvement. significant radiographic deterioration was seen in only 1 of 10 patients who had ERCP. In 7 patients previously treated with UDCA alone, liver enzyme levels declined significantly only after immunosuppressive therapy was added\textsuperscript{44}. So they concluded combined immunosuppressive therapy may alter the progression of P.S.C.
5. Minimal change nephrotic syndrome:
Long-term AZA therapy as an alternative treatment to cyclophosphamide and steroid-sparing agent, was presented by Tanaka and et al.47

6. IgA nephropathy:
Although a 6-month course of steroid in IgA nephropathy patients has shown that these drugs are effective in reducing of the risk of renal function deterioration and proteinuria, but this effect seemed to decrease in the long term. So Locatelli and et al. administered AZA in combination with Prednisolone and methyl Prednisolone pulses. They hope to take significant benefit in their prospective randomized multicentric trial during 5 years follow-up of 346 patients 21.

7. Myasthenia gravis (MG):
Rippling muscles in patient with MG are improved by AZA 27.

8. Henoch-Schonlein Purpura (H.S.P.):
Early treatment with Prednisolone and AZA in severe H.S.P. nephritis, prevents progression of chronic changes and improves disease outcome 9.

9. Rheumatoid Arthritis (RA):
AZA appears to have a statistically significant benefit on the disease activity in joints of patients with RA, but methotrexate (MTX) is more effective in compared to AZA in retarding radiologic progression in patients 13,43,52. Also AZA is an effective and well tolerated steroid-sparing agent for juvenile rheumatoid arthritis refractory to NSAIDs or disease modifying drugs 26.

10. Dermatologic disease:
AZA is used in severe atopic eczema, pemphigus, plaque psoriasis and chronic active dermatitis as a steroid-sparing agent or as monotherapy 41,45. Also AZA in combination with acitretin is used for treatment of psoriatic erythroderma and bullous pemphigoid 39.

11. Sarcoidosis:
AZA may be effective as a steroid-sparing agent in long-term therapy of sarcoidosis, but some prospective studies are necessary to give the definitive answer 18,28.

12. Acute Lymphoblastic leukemia (ALL):
6-MP is used in treatment of ALL in pediatric age group but significant proportion of pediatric patients aren't compliant with pill taking. The timing of administration of 6-MP in children with ALL may be crucial in some patients. Evening administration of 6-MP is associated with a lower risk of relapse 25.

13. Refractory anemia with excess of blasts (RAEB):
Triple therapy with cyclophosphamide (CTx), MTX and 6-MP seems to be a useful alternative in patients with RAEB and increase survival in patients, but this finding must be confirmed in further prospective studies 29.

14. Liver Transplantation:
Quadriple Tacrolimus based induction therapy (Tacrolimus, AZA, ALG, Prednisolone) doesn't
significantly improve outcome after liver transplantation in comparison with standard induction with Tacrolimus and steroids.34

15. Pancreas transplantation:
Mycophenolate mofetil (MMF) like AZA can be used in pancreas transplantation. As a single center experience, patients treated with MMF required less frequent and less intensive treatment for acute rejection.40

16. Lung Transplantation:
AZA is used in lung transplantation, but many researches have shown that MMF therapy is more effective in preventing rejection episodes in patients early after transplantation than therapy with AZA.53

17. Renal transplantation:
Although AZA is administered for prevention of acute and chronic rejection after renal transplantation but MMF is more effective than AZA.2,3,7,10,12,32,51. MMF usage in patient with history of previous tuberculosis is indicated while on isoniazide prophylaxis.51

Tips:
* Long lasting leukopenia while on Azathioprine or 6-MP increase risk of malignancy.
* These two drugs can be used in treatment of:
  1. IBD
  2. Autoimmune hepatitis
  3. Rheumatoid arthritis
  4. Sarcoidosis
  5. Primary sclerosing cholangitis
  6. Acute lymphoblastic leukemia
* Pancreatitis occurs in up to 8% of patients on azathioprine or 6-MP.
* Milk can reduce efficacy of 6-MP.

References


