

Azathioprine/6-mercaptopurine (6MP):

6MP and **azathioprine** are immunosuppressant therapies that have been used previously for the treatment of certain cancers and leukemias, and for the prevention of rejection of transplanted organs. The mechanism of action of these drugs is down regulation of the inflammatory response in person with inflammatory bowel disease, including Crohn's disease and ulcerative colitis. **6MP** and **azathioprine** while very similar in nature (**azathioprine** is actually metabolized to **6MP** in the liver) are not administered as identical doses and care should be taken that correct amounts are prescribed to the individual patients. It is important to note that effects on disease activity are not immediate and adequate trials of therapy (3-4 months or longer) are required before the full benefit (or lack thereof) can be determined.

Current Indications

- ❑ Medically refractory Crohn's disease and ulcerative colitis or patients: specifically, IBD patients who are either steroid resistant or steroid dependent.
- ❑ Patients with Crohn's disease who require intestinal resection who are at risk for postoperative recurrence
- ❑ Patients with IBD who have extra intestinal manifestations including pyoderma gangrenosum and erythema nodosum.
- ❑ Persons on chronic infliximab therapy who require the addition of immunomodulator for prevention of antibodies to infliximab

Treatment Regimen

Pre **6MP/azathioprine** evaluation:

- ❑ CBC
- ❑ Liver function tests
- ❑ TMPT assay

Treatment protocol

- ❑ **6MP** (brand name Purinethol) is available in 50mg tablets. **Azathioprine** (brand name Imuran) is available in 50mg tablets. **Azathioprine** (brand name Azasan) is available in 25, 75 and 100mg tablets
- ❑ Drug administration is generally once daily, but can be taken in divided doses twice per day. Nausea and heartburn have been reported: by taking the medication at night (or in divided doses) and with plenty of fluid can eliminate or greatly decrease the incidence.
- ❑ Dose range for **6MP** is 1-1.5mg/kg of body weight. Dose range for **azathioprine** is 2-2.5mg/kg body weight.
- ❑ Initial oral dosing of both medications is started at the low end of the range, based on laboratory parameters. Dose of medication is titrated up, based on both

- laboratory and patient response. If TMPT testing is done prior to administration then dosage can be adjusted accordingly.
- ❑ Contraindications to the use of these medications are few. Primarily if patient has been exposed to them in the past and have a history of pancreatitis associated with their use, then repeat use should be avoided.
 - ❑ There is some debate about the safety of use in women who are pregnant. It is our experience and recommendation that **6MP** and **azathioprine** are safe for use during all stages of pregnancy, but this must be discussed at length with the patient and should include the patient's obstetrician in the discussion. **6MP** and **azathioprine** are NOT safe for use during breastfeeding and alternative medications (or avoidance of breastfeeding altogether) must be considered.
 - ❑ Monitoring: labs are drawn at baseline as noted. Repeat CBC and LFT's are done at 2 weeks, then at 2 weeks again. If labs are stable at this point, repeat CBC in 4 weeks. If labs are stable at this point, then CBC is done every 3 months and LFT's done every 6 months. For every increase in dosage, the schedule as outlined here should be repeated. Caution should be observed in patients who have relatively low white counts (i.e. < 6.0) who are increasing their dose of **6MP/azathioprine**, while actively decreasing prednisone dosage. Removal of prednisone from the patient's regimen, in combination with aggressive increase in immunomodulators can result in drastic decrease in WBC.
 - ❑ Testing is available for the active metabolites of 6MP/azathioprine (Prometheus labs, San Diego, CA) . The use of this metabolite testing is helpful to guide the optimum dosing of these medications. 6-thioguanine (6TG) is associated with response and 6-MMP is associated with hepatotoxicity, but they should be used in conjunction with routine testing of LFT's and CBC.

Citation: Sandborn W, Sutherland L, Pearson D, May G, Modigliani R, Prantera C. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. *The Cochrane Database of Systematic Reviews* 1998, Issue 3. Art. No.: CD000545. DOI: 10.1002/14651858.CD000545.