Luton and Dunstable Hospital NHS
NHS Foundation Trust

Azathioprine or 6-Mercaptopurine treatment in IBD
Patient Information Leaflet

About Azathioprine and 6-Mercaptopurine

These are immunosuppressant drugs that dampen down the body's immune (defence) system, in order to control ongoing active inflammation. They have been shown to reduce the symptoms of inflammatory bowel disease (IBD) in patients with severe chronic inflammation that have not responded to other simpler medical treatments (e.g. the mesalazines), They are sometimes called steroid sparing agents as they are also used to help prevent the need for recurrent courses of steroids and in those who need to be weaned off from their dependence on high doses of steroids to control their symptoms. 6-Mercaptopurine is a slightly more purified version of Azathioprine, with less side effects, but comes at an increased cost. In those patients that can't tolerate Azathioprine they say 50% are able to tolerate the 6-Mercaptopurine version.

Taking Azathioprine

- It is taken as a tablet that must be swallowed whole with plenty of water.
- The number of tablets will vary depending on your weight and your response to treatment.
- It may take between 6 to 12 weeks before you get a good response, so it is important to keep taking the tablets regularly.

Immunosupressor dosages

Azathioprine = 2 - 2.5mg/kg/day
6-Mercaptopurine = 1 - 1.25mg/kg/day
Initially both tend to be started at half doses.

TPMT Levels

Some centres have access to the measurement of Thiopurine Methyl Transferase genotyping or enzyme levels. About 1 in 300 of the population have no (or very low levels of) TPMT and the drug should be avoided in this group. Similarly heterozygotes with intermediate TPMT levels should receive lower treatment doses (e.g 50% of standard dose regimen).

Unfortunately the measurement of TPMT levels does not replace the need for careful blood (haematochemical) monitoring as only ¼ of cases of myelotoxicity will be due to patients with TPMT mutations. In nearly ¾ of patients who develop neutropenia no reason will have been identified.
Measurement of TPMT levels should be considered for patients prior to starting azathioprine if available locally.

Regular blood tests

In order to assess whether the treatment is working and check for any possible early signs of side effects, you will need regular blood tests while taking this drug.
A sample of blood is taken to test FBC and LFT every 2 weeks for first month, monthly for the next 2 months, then every 3 months. U&E and Creatinine should be repeated 6 monthly. CRP/ESR may be done every 3 months. If satisfactory then you will continue to have the tests every three months for as long as you are taking the drug.

Typically we (as physicians) monitor the following indices;-

Blood Indices	**- Action to be taken**
WBC 2.5-3.5 $x10^9$ /1	- half dose until discussed with specialist team
WBC 1.5-2.5 $x10^9$ /1	- withhold for 1 week + discuss with IBD team
WBC <1.5 $x10^9$ /1	- withhold and if pyrexial admit
Neutrophils <2.0 x 10^9/l	- withhold until discussed with specialist team
Platelets <150 x 10^9/l	- half dose until discussed with specialist team
Amylase > 250	- withhold until discussed with specialist team
>2 fold rise in AST or ALT	- half dose until discussed with specialist team
Rash or oral ulceration	- withhold until discussed with specialist team
MCV> 106fl	- check serum folate and B12 & TSH
	- half dose until discuss with specialist team
Abnormal bruising	- withhold until discussed with specialist team
Severe sore throat	- withhold until discussed with specialist team

Please note that a rapid fall or consistent downward trend in any value should prompt caution and extra vigilance. In case of any doubt stop treatment and refer to the Consultant site for advice. There may also be other tests needed from time to time.

Immunity Status

New guidelines have been released by the ECCO (European Crohn's and Colitis Organisation) and the BSG (British Society of Gastroenterology) recommending that all inflammatory bowel disease (IBD) patients undergo immunological assessment and are up-to-date with their vaccine protocol. Checks will be made on Hepatitis B+C, HIV and TB status.

Possible side effects

30% experience nausea and mild abdominal aches initially
This usually settle within two weeks. Symptoms can sometimes be improved by taking azathioprine / 6-Mercaptopurine with food and splitting the dose so you can take it twice a day, rather than all at once.
Other less common side effects include dizziness, headaches, drowsiness, vomiting, fever, muscle and joint pains, jaundice (yellowing of the skin or eyes), skin rash or hair loss.

Direct Toxicity :
Pancreatitis 3%
Drug induced hepatitis 3%
Bone marrow suppression
Allergic reactions - including nausea + swinging fevers)

Indirect toxicity :
Infections 6% – bacterial and viral (including herpes zoster and simplex, Epstein Barr virus (EBV); Cytomegalovirus (CMV).
Lymphoma - Limited evidence suggests the possibility of a slight increased risk of lymphoma. Kandiel et al (Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and mercaptopurine. GUT 2005; 54 : 1121 – 5) found a relative risk of 4 for the development of lymphoma in patients taking azathioprine, but were unable to distinguish between whether this was the result of the medication, the severity of the underlying inflammatory bowel disease or a combination of the two.
Hepato-splenic Tcell Lymphoma - There have been twenty six cases world wide of hepato-splenic lymphoma in young people on combined thiopurine / infliximab therapy for Crohn's disease is of concern. The relative contribution of each drug is not clear, but AZA is thought to carry a 1:5000 risk.
Cancer - A slight but non significant increase in cervical cancer and an increased risk of non-melanoma skin cancer (similar findings in the immunocompromised transplant population). There are very few case reports of an association between cervical cancer and IBD patients taking azathioprine, although there is more evidence available for patients with rheumatoid arthritis or systemic lupus erythematosus. There are occasional reports of IBD patients on immunosuppressive therapy developing skin tumours (Austin AS, Inflammatory bowel disease, azathioprine and skin cancer : case report and review of the literature. Eur. J. Gastroenterol. Hepatol. 2001; 13 : 193-4).

If ant side effects do occur after starting treatment or increasing the dose, then you should contact your GP, hospital doctor or specialist IBD nurse immediately for further advice, but do not stop taking the medication until you have spoken to one of the above.

Special precautions

- **Azathioprine / 6-Mercaptopurine** should be avoided if you have previously had an allergic reaction to either drug.

- **If you develop an infection, fever, unexplained bruising or bleeding** at any time, report these to your GP or specialist IBD nurse on: 01582 718368.

- **You should avoid sunbathing** due to the known increased risks of sun hypersensitivity rashes (and skin cancer), while you are taking Azathioprine / 6-Mercaptopurine**.** Use a protective high sun factor screen in the summer.

- Avoid in patients with hepatitis B/C or history of TB.

- **Pregnancy** - There is no evidence that azathioprine is teratogenic so the treatment can be continued. In generally azathioprine should not be started during pregnancy. Many gastroenterologists would aim to stop azathioprine treatment in the last trimester so as not to affect the babies immune development.

Taking Azathioprine / 6-Mercaptopurine with other medication

- Azathioprine / 6-Mercaptopurine may interact with some other drugs, so it is important that you tell your GP, hospital doctor, specialist I.B.D nurse and pharmacist about any other tablets or herbal drugs that you are taking. Complications can occur if also taking **allopurinol, warfarin, captopril, antibiotics (trimethoprim and co-trimoxazole), phenytoin, clozapine, digoxin**. If you are purchasing any over-the-counter drugs **please check their safety with your pharmacist**.

- **Allopurinol** slows the breakdown of Azathioprine and 6-Mercaptopurine in the liver leading to high blood levels that could be dangerous. In general if Allopurinol has to be started we recommend cutting the dose down to 25%.

- Azathioprine and 6-Mercaptopurine can inhibit the effects of **Warfarin**

- **You should avoid live vaccinations** while taking Azathioprine / 6-Mercaptopurine**.** Your GP, hospital doctor or specialist IBD nurse will be able to advise you on this. Most vaccinations like the annual flu vaccination are not live vaccines (passive immunisation), therefore you can have these.

Recommendations
The combination of azathioprine and infliximab treatment is superior to azathioprine alone for inducing and maintaining remission and complete steroid withdrawal in steroid dependent patients with active Crohn's disease (Lemann M. et al. Infliximab and azathioprine for steroid dependent Crohn's disease patients - a randomised placebo controlled trial. Gastroenterology 2006; 130 : 1054 – 61). However, clearly this approach carries implications with respect to the increased potential for drug-related toxicity. Dual therapy should be avoided in those patients naive to infectious mononucleosis (EBV).

When can these agents be stopped?
Clear recommendations on optimum duration of therapy cannot be drawn from the available literature. In practice, most physicians tend to continue therapy for at least 3-5 years, and discuss withdrawing azathioprine at this time with the patient. It should be made clear to patients that there is a degree of uncertainty with respect to long-term toxicity if treatment is continued beyond this time frame.

Further information

Further information may be obtained from the manufacturer's information leaflet that comes with the Azathioprine / 6-Mercaptopurine and also from your hospital doctor, GP, specialist nurse or pharmacist

The specialist IBD nurse can be contacted on 01582 718368