Azathioprine Flowsheet

Patients Name:_____

Approved use: None in dermatology.

Off label use : ___ PV ___ BP ___ Vasculitis
___ Behcets ___ PG ___ DMM
___ Lupus (SLE & DLE) ___ Psoriasis ___ atopic derm

Contraindications:

Absolute: ___ Allergy to Azathioprine
___ Pregnancy or attempting pregnancy
___ Clinically significant active infection

Relative: ___ Concurrent use of allopurinol.
___ Prior tx with alkylating agents: cyclophosphamide, chlorambucil, melphalan, others (high risk of neoplasia)
___ Peds (safety and efficacy in pediatric population not established)

Dosing: ***1mg/kg/day qd or bid (empiric) or by TPMT level (see below)***.
Increase dose by 0.5mg/kg/day after 6-8 wks if necessary. Increase every 4 wks. 2mg/kg/day max dose for most derm purposes.

How supplied: 25mg, 50mg 75mg and 100mg tablets; 100mg vials.
(Doses for transplant pts: 3-5mg/kg/day; rheumatoid arthritis: 1- 2.5mg/kg/day).

BASELINE TPMT Functional Assay*: _____

	BASELINE	2wks	4wks	8wks	12wks	20wks	28wks	36wks	44wks	52wks
CBC/diff/plts	____	____	____	____	____	____	____	____	____	____
LFT's	____		____	____	____	____	____	____	____	____
HCG	____									
SMA-7	____									
PE**	____						____**			____**
IPPD***	____									
U/A										

*TPMT testing is not entirely reliable. It involves testing the activity of TPMT activity in RBC's, which correlates with systemic TPMT activity. The functional enzyme test has been shown to have variabilility between test sites and the kits may contain varying amounts of enzyme inhibitor. Starting at low doses, monitoring for pancytopenia, then increasing the dose is an alternative. If the clinical response is not good, the patient may be a homozygote for high activity and may need an increased dose. Wolverton does not recommend using this assay (Wolverton, Comprehensive Dermatologic Drug Therapy, P.167-168). There are some references that recommend checking before treatment in ALL patients.

TPMT <5.0 U – no treatment with azathioprine.
5-13.7 U – 0.5mg/kg max dose
13.7- 19.0 U – 1.5mg/kg max dose
>19.0 U – 2.5mg/kg max dose

**PE- should focus on lymph node exam, skin cancer exam (SCC's in particular). Repeat every 6 months.
***Strongly consider.

LABS- D/C tx if WBCs <4000, HgB < 10g/dl, plts < 100,000.

Azathioprine Info for Physicians

MOA: 1. Interferes with DNA and RNA synthesis and repair.
2. Decreases T-Cell cell mediated activity.
3. Decreases B-cell antibody production.
4. Decreases both the number and function of Langerhans cells and other antigen presenting cells.

What to expect: Slow acting with therapeutic effect not seen for 6-8 weeks. Metabolites accumulate slowly and maximal immunosuppression is not reached until 8-12 weeks. Don't call a treatment failure before 8-12 weeks. Overall, azathioprine is considered to be a less potent immunosuppressive agent than cyclosporine, cyclophosphamide or chlorambucil.
Bullous diseases: PV, BP, cicatricial pemphigoid. Probably has a steroid sparing effect, but there is some conflicting data. In spite of the conflicting data, it has been used for over 30 years in these diseases, particularly corticosteroid-refractory eye involvement.
Vasculitis: Giant cell arteritis, polyarteritis nodosa, Wegener's granulomatosis, retinal vasculitis and LCV. Gives particularly impressive results with LCV.
Neutrophilic dermatosis: Bechet's- decreases eye problems, arthritis, oral and genital ulcers. Pyoderma gangrenosum- variable success.
SLE: particularly lupus nephritis. Some success in skin lesions of lupus and particularly useful in extensive discoid lesions with palmoplantar involvement.
Dermatomyositis/polymyositis: respiratory and muscular symptoms respond but skin lesion response has not been consistent.
Relapsing polychondritis: particularly useful in treating the eye involvement.
Atopic dermatitis (severe): responds well.
Psoriasis: works. Less commonly used than the other immunosuppressants. Described as the "forgotten alternative" in treating psoriasis.
LP (erosive and generalized): responds and may be a steroid sparing agent.
PMLE: Two case reports of success.
Sarcoid: Lung disease responds; skin lesions – less predictable.

Metabolism: 88% bioavailable; 30% protein bound.

Azathioprine is converted to 6-MP (primarily in erythrocytes). Subsequently, 3 pathways are important:

1. 6-MP → catabolized by TPMT (thiopurinemethyltransferase) → inactive metabolites
2. 6-MP → catabolized by xanthine oxidase → inactive metabolites
3. 6-MP → anabolized by HGPRT → active 6-thioguanine metabolites

Low TPMT activity (path #1) will shift more 6-MP into #3 path thereby increasing the active metabolites and risk of excessive immunosuppression and pancytopenia. 1/300 pts will have this low TMPT activity. 89% of patients are homozygous for high TPMT activity (may need a higher dose of azathioprine), and 11% have intermediate activity . A TPMT activity assay can be done (see flowsheet). Allopurinol may decrease the xanthine oxidase path and again shift more 6-MP into #3 path. If patients are taking allopurinol for gout, decrease the azathioprine dose by 75%.

Patients with Lesch-Nyhan Syndrome have a genetic absence of HGPRT and azathioprine will have NO efficacy (is that not a good useless board question or what?).

S/E:
G.I. side effects: most common (about 10%). Nausea, vomiting, diarrhea. Usually days 1-10 of treatment. Take with food or decrease dose to alleviate.
Pancytopenia- rare. Seen in pts with the low TPMT phenotype (1/300 persons).
Opportunistic infections: seen usually at higher doses.
Hypersensitivity syndrome: rare. Usually develops between 1-4 weeks of starting therapy. Cardiovascular collapse, rashes (many types reported), fever, leukocytosis, nausea, hepatotoxicity, pancreatitis, arthralgias, myalgias, rhabdomyolysis, headaches, renal insufficiency, cough, pneumonitis, erythema nodosum.

Interactions: allopurinol- increases risk of pancytopenia. Captopril/ACE inhibitors- may increase risk of anemia and leukopenia. Warfarin- may need an increase dose of warfarin. Pancuronium- may need an increased dose of this for adequate paralysis. Live virus vaccines, co-trimoxazole (increased risk of hematologic toxicity), rifampicin (transplants possibly rejected), clozapine (increased risk of agranulocytosis).

Azathioprine Consent Form

Azathioprine is a drug that may benefit your medical condition, but like any drug, it may have unwanted side effects. The following is a listing of side effects that may possibly occur as well as an agreement to abide by as a responsible patient.

Initials: **Azathioprine may cause:**

_____1. Gastrointestional: Nausea, vomiting (~12%), diarrhea (1%). Sometimes fever, malaise (feeling bad) and muscle aches accompany these symptoms. Taking after meals helps reduce this side effect. Stop the medicine and call your doctor if you experience these side-effects.
_____2. Hepatotoxicity (liver problems) in <1%.
_____3. Increased susceptibility to infections.
_____4. Fever (<1%)
_____5. Joint aches (<1%)
_____6. Rash (2%)
_____7. Hair loss (<1%)
_____8. Muscle wasting (<1%)
_____9. Teratogenicity (birth defects) if taking while pregnant. I understand I must use effective birth control while taking azathioprine. If I have any questions about effective birth control, I agree to see an OB/GYN physician for counseling.
_____ 10. Taking for prolonged periods of time at high doses may reduce fertility (ability to have children) in both male and female patients.
_____ 11. Increased risk of cancer. The types of cancers are usually non-Hodgkin's lymphomas and squamous cell carcinomas. <u>This risk cannot be determined.</u> This is because most of the data accumulated on azathioprine has been in populations that have an increased risk for malignancies because of their disease (renal transplant patients or rheumatoid arthritis patients). In one completed study of rheumatoid arthritis patients taking high doses (5mg/kg/d) of azathioprine, the rate was 1.8 cases per 1000 patient years compared to 0.8 cases per 1000 patient years in patients not receiving azathioprine.
_____ 12. A rare but life-threatening hepatic veno-occlusive disease (liver blood flow problem) associated with chronic administration of azathioprine has been reported.
_____ 13. A rare azathioprine hypersensitivity syndrome has been described in which people become extremely ill.
_____14. Pancytopenia. This is where your bone marrow stops producing components of your blood such as your blood cells and platelets. This is a rare adverse event and occurs more frequently in people who are genetically predisposed to this effect (an enzyme problem). Blood tests will be done regularly to monitor for this side effect.

_____ 15. I understand I should take this medicine with food or milk.
_____ 16. I will take the medicine exactly as prescribed.
_____ 17. I will keep all follow-up appointments and take all laboratory tests as necessary.
_____ 18. I understand I should use sunscreens, hats, and other protective clothing when in the sun and should avoid prolonged exposure to the sun while on azathioprine.
_____ 19. A more complete listing of all side-effects including the more unusual and rare side-effects may be obtained by requesting the package insert from the pharmacist.

I have read the above 19 items and have been given an opportunity to have any questions answered. Treatment alternatives, including doing nothing, have also been discussed with me. I hereby consent to being placed on azathioprine.

SIGNATURE: _____DATE: _____

PATIENTS NAME_____

PHYSICIANS SIGNATURE_____DATE_____

WITNESS SIGNATURE_____DATE_____