Azathioprine in the treatment of thyroid-associated ophthalmopathy (TAO)

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Introduction

Azathioprine (Imuran®):

- Purine analogue
- ↓ purine synthesis
- ↓ synthesis of DNA
- Cytotoxic
- Target rapidly-dividing cells
- Some selectivity for CD4+ lymphocytes
Introduction

Pro-drug

In the liver: 6-mercaptopurine (active metabolite)

Plasma levels are not good indicators of efficacy or toxicity

TPMT (thiopurine methyl-transferase) deficient patients:
- AZA toxicity
- Myelosuppression
- Sepsis
Azathioprine – side effects

Toxicity and possible side-effects

1. **Marrow depression**: May progress for up to 2 weeks after withdrawal.
   - RBC macrocytosis is not uncommon on long-term treatment
   - Macrocytic anaemia may be a problem
2. **Lymphopenia** is usual
3. **Hypersensitivity** (rare)
4. **Dizziness**
5. **Nausea /vomiting/diarrhoea**
6. **Myalgia**
7. **Hypotension**
8. **Abdominal pain**
4. **Colitis**
5. **Pancreatitis, cholestatic jaundice, necrotising liver failure** - rare
5. **Alopecia** (uncommon)
6. **Mutagenic/teratogenic effects**
7. **Lymphoma and other cancers** - long-term risk is <2%
8. **Rash** (Aza→ incorporation of 6-thioguanine (6-TG) into DNA of dividing cells, 6-TG DNA is damaged by UVA)
Drug Interactions

1. **Allopurinol**: ↑effect of azathioprine – extreme caution
2. **Neuromuscular blockers**: azathioprine interferes with the effect
3. **Penicillamine, septrin, indomethacin**: ↑effect of azathioprine

**Not to be combined with other drugs suppressing bone marrow**

**Contraindications**
- Pregnancy/lactating mothers - Contraception is essential for ♀
- Live vaccines should not be used

In liver/renal insufficiency - Reduce dose

**Special Precautions**
- Annual influenza and pneumococcal vaccination
- Non-immune patients exposed to VZV should urgently receive VZV Immunoglobulin if exposed.
EUGOGO recommends the following classification of patients with GO...

1. **Sight-threatening GO**: DON ± exposure keratopathy → immediate medical/surgical intervention

2. **Moderate-to-severe GO (without sight-threatening GO)**:
   - Immunosuppression (if active) – steroids/AZA
   - Surgical intervention (if inactive)

3. **Mild GO** (insufficient to justify immunosuppressive or surgical treatment): lubricants + Selenium

Smoking prevention advice
TAO seen in 50% of patients with Graves' disease
Most patients with active TAO respond well to intra-venous steroids
Minority require second-line agents

Options:
   Cyclosporin
   Rituximab
   Azathioprine

Retrobulbar irradiation
Methods

TAO patients - Responded poorly to conventional treatment

Ix/ TPMT level screening
  FBC, LFT at regular intervals

Management was supervised/monitored by a consultant endocrinologist

Pre and post-treatment Clinical Activity Score (CAS) scores was recorded

Adverse effects were recorded
Results

10 consecutive patients

Previous treatment received:
- IVMP (n=10, 100%)
- Orbital/optic canal decompression (n=2, 20%)
- Orbital radiotherapy (n=4, 40%)
- Selenium 200mg/day (n=10, 100%)

All subjects were females

Mean age at the commencement of AZA: 56 ± 11 years

Mean duration of treatment with AZA: 12 months

Starting dose of AZA: 100mg - 200mg (depending on the patients’ body weight)

Mean CAS score prior to commencement of Azathioprine: 4
Post-treatment CAS: 0 (mean improvement of 4)
While still on Azathioprine...

- 3 – had planned orbital decompressions
- 1 - required orbital radiotherapy
- 1 – Rx with both radiotherapy and orbital decompressions

Majority of the patients tolerated Azathioprine well

Adverse effects:

- Ataxia (1)
- Nausea/gastro-intestinal side effects (2)
- Photosensitive rash (1) - later attributed to a Lichenoid drug reaction due to the Propylthiouracil (PTU)
- Pancreatitis (1) – resolved after stopping AZA

FBC, LFT : no deterioration from pre-treatment levels throughout
AZA is useful adjunct in the management of TAO in some patients

Treatment should be carefully co-managed

Treated individuals should be carefully monitored

Our results appears to be better than published results - small sample

CIRTED trial (n=100): role of radiotherapy and azathioprine as part of a long-term, combination immunosuppressive treatment regime for TAO

Careful case selection + multidisciplinary approach is crucial
References


