



New Medicine Assessment

Azathioprine for treatment of Myasthenia Gravis

Recommendation:

Amber 1 (with Shared Care)

- Suitable for prescribing in primary care following recommendation or initiation by a specialist.
- Minimal monitoring required.
- Patient may need a regular review, but this would not exceed that required for other medicines routinely prescribed in primary care.
- Full prior agreement about patient's on-going care must be reached under the shared care agreement.

Primary care prescribers are advised not to take on prescribing of these medicines unless they have been adequately informed by letter of their responsibilities with regards monitoring, side effects and interactions and are happy to take on the prescribing responsibility. A copy of locally approved shared care guidelines should accompany this letter which outlines these responsibilities. Primary care prescribers should then tell secondary care of their intentions as soon as possible by letter so that arrangements can be made for the transfer of care

Summary of supporting evidence

- Use of azathioprine is supported by the Association of British Neurologists' management guidelines for myasthenia gravis and the International Consensus Guidance for the Management of Myasthenia Gravis.
- Use appears widespread with neighbouring organisations having shared care protocols for the drug.
- Relatively inexpensive drug costing around £64.22 per year's treatment.
- Savings can be made by reduced dosing of corticosteroid drugs which azathioprine will allow.
- Clinical studies, although small and low in number, support the use of azathioprine in myasthenia gravis.
- During the first 8 weeks of therapy, complete blood counts, including platelets, should be performed weekly or more frequently if high dosage is used or if severe renal and/or hepatic disorder is present. The blood count frequency may be reduced later in therapy, but it is suggested that complete blood counts are repeated monthly, or at least at intervals of not longer than 3 months.

Details of Review

Name of medicine (generic & brand name): **Azathioprine**

Strength(s) and form(s): 25mg and 50mg tablets

Dose and administration:

From BNF:¹

Initially 0.5–1 mg/kg daily, then increased to 2–2.5 mg/kg daily, dose is increased over 3–4 weeks, azathioprine is usually started at the same time as the corticosteroid and allows a lower maintenance dose of the corticosteroid to be used, oral administration preferable, if not possible then can be given by intravenous injection (intravenous solution very irritant) or by intravenous infusion.

Association of British Neurologists' management guidelines²

Immunosuppression with azathioprine

Azathioprine is the first-line agent. Thiopurine methyltransferase (TMPT) should be measured in view of the association between TMPT deficiency and myelosuppression with azathioprine. TMPT deficiency is not a contraindication to using azathioprine but may reduce the dose required. Patients with very low TMPT activity should not take azathioprine.

Azathioprine should be increased over 1 month to a maintenance dose of 2.5 mg/kg. Blood tests should be monitored weekly (full blood count, urea and electrolytes, liver function tests) as the dose is titrated upwards. The dose may need to be modified in light of side effects or changes in blood tests. We recommend using local shared-care protocols.

Azathioprine is slow to achieve maximum effect. The target is to achieve a maintenance dose of prednisolone of below 20 mg on alternate days after 2 years. Failure to achieve efficacy may be a consequence of inadequate dosing. Not all patients respond to azathioprine. Corticosteroids should be withdrawn using the protocol described.

Myasthenia gravis may relapse on corticosteroid withdrawal. This may be a consequence of a slow response to azathioprine or using too low a dose. The lowest effective corticosteroid dose before relapse is the maintenance dose. If this is above 20 mg on alternate days, this is considered a relapse and requires action.

From Surrey Prescribing Clinical Network SCG:³

In generalised myasthenia gravis azathioprine is usually started at a dose of 0.5–1 mg/kg daily, which is increased over 3–4 weeks to 2–2.5 mg/kg daily or less if TMPT (thiopurine methyltransferase) is low. Azathioprine is usually started at the same time as the corticosteroid and allows a lower maintenance dose of corticosteroid.

In some individuals nausea may be a problem upon initiating therapy and one may consider starting at a lower dose of 50mg. The dose should then be gradually increased in 50mg increments every 2 weeks to 2 – 2.5 mg/kg daily, if tolerated.

BNF therapeutic class / mode of action:

Immune system and malignant disease – immunosuppressants / antimetabolites

Licensed indication(s)⁴

Azathioprine is used as an immunosuppressant antimetabolite either alone or, more commonly, in combination with other agents (usually corticosteroids) and procedures which influence the immune response. Therapeutic effect may be evident only after weeks or months and can include a steroid-sparing effect, thereby reducing the toxicity associated with high dosage and prolonged usage of corticosteroids.

It is also used in combination with corticosteroids and/or other immunosuppressive agents and procedures, is indicated to enhance the survival of organ transplants, such as renal transplants, cardiac transplants, and hepatic transplants; and to reduce the corticosteroid requirements of renal transplant recipients.

Either alone or more usually in combination with corticosteroids and/or other drugs and procedures, has been used with clinical benefit (which may include reduction of dosage or discontinuation of corticosteroids) in a proportion of patients suffering from the following:

- severe rheumatoid arthritis;
- systemic lupus erythematosus;
- dermatomyositis and polymyositis;
- auto-immune chronic active hepatitis;
- pemphigus vulgaris;
- polyarteritis nodosa;
- auto-immune haemolytic anaemia;
- chronic refractory idiopathic thrombocytopenic purpura

Proposed use (if different from, or in addition to, licensed indication above):

Generalised Myasthenia Gravis – off label use

Course and cost:

On-going course.

If we assume the average weight of an adult male patient to be 83.9kg⁵ at the maximum daily maintenance dose of 2.5mg/kg = 209.75mg. A dose of 200mg is likely to be given i.e. 4x 50mg tablets / day.

Drug Tariff Price (October 2019)⁶

- Azathioprine 25mg tablets x 28 = £1.71
- Azathioprine 50mg tablets x 56 = £2.47

Cost of 28 days treatment = 112 x 50mg tablets = £4.94

Annual cost = 13 x £4.94 = £64.22

Current standard of care/comparator therapies:

Anticholinesterases e.g. Pyridostigmine

Corticosteroids e.g. Prednisolone - azathioprine is used as a corticosteroid sparing medicine

Relevant NICE guidance: None

Myasthenia gravis: Association of British Neurologists' management guidelines 2015⁷

Background and context

Myasthenia gravis is an autoimmune disease of the neuromuscular junction for which many therapies were developed before the age of evidence based medicine. The basic principles of treatment are well known and the Association of British Neurologists' management guidelines⁵ were developed to account for evidence based practice where available and established best practice where evidence is unavailable. Azathioprine has been used in the treatment of myasthenia gravis for many years in the UK and is accepted as best practice.

These guidelines recommend the use of pyridostigmine as first line therapy, with the addition of prednisolone if the patient remains symptomatic. A prednisolone dose above 15-20mg on alternate days is probably too high for long term use and is an indication to introduce immunosuppression with azathioprine, as are intolerable corticosteroid side effects.

Thiopurine methyltransferase (TMPT) should be measured in view of the association between TMPT deficiency and myelosuppression with azathioprine. TMPT deficiency is not a contraindication to using azathioprine but may reduce the dose required.

The onset of action of azathioprine is slow – it takes around 4 – 12 months before a therapeutic response is seen and up to 24 months for a maximal effect. Azathioprine is often started at the same time as prednisolone to allow the corticosteroid to be tapered over time to the lowest possible dose.⁸

Not all patients respond to azathioprine.

Summary of evidence

As a result of the relative rarity of myasthenia gravis there are limited randomised controlled trials.

Summary of efficacy data in proposed use:

A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis, Palace J et al; 1998⁹

Summary

This was a multicentre, randomised, double blind study of 34 myasthenia gravis patients who were followed up for 3 years.

One group received prednisolone (on alternate days) plus azathioprine (2.5mg/kg) (n=15), the other group received prednisolone on alternate days plus placebo (n= 19). Initial high dose prednisolone (1.5mg/kg on alternate days) was tapered at remission to the minimum dose required to maintain remission. Both groups were on optimal anticholinesterase (pyridostigmine bromide) medication at entry.

10 patients in the Pred + Plac group and 8 patients in the Pred + Aza group completed the 36 month trial

Outcome measurements

1. Maintenance dose of prednisolone
2. Number of patients experiencing treatment failure, defined as either no remission achieved in the 3 year follow up period or clinical relapse after initial remission and necessitating an increase in prednisolone dosage. If a single patient had two or more relapses, this was recorded as one treatment failure.
3. Duration of initial remission (or time to relapse from remission). Remission was defined as the absence of symptoms or symptoms that were infrequent or sufficiently mild that they did not interfere with normal activities.

Results

The prednisolone dose did not differ significantly between the two groups at year 1 (median values: Pred + Aza 37.5mg on alternate days; Pred + Plac 45mg on alternate days) but was reduced at 2 and 3 years in the Pred +Aza group (median value at 3 year; Pred +Aza, 0mg on alternate days; Pred + Plac, 40mg on alternate days; p=0.02).

Relapses and failures to remit over the 3 years were more frequent in the Pred + Plac group. There was also a sharp rise in the anti-acetylcholine receptor (AChR) titres in the Pred + Plac group at 2 years.

Incidence of side effects was slightly less in the Pred +Aza group.

Conclusion

Azathioprine as an adjunct to alternate day prednisolone in the treatment of antibody positive generalised myasthenia gravis reduces the maintenance dose of prednisolone and is associated with fewer treatment failures, longer remissions and fewer side effects.

A randomised clinical trial comparing prednisone and azathioprine in myasthenia gravis. Results of the second interim analysis, Myasthenia Gravis Study Group¹⁰

The study compared the long term effects of prednisone and azathioprine in patients with myasthenia gravis, who were randomly allocated between these two treatment groups. 41 patients with generalised myasthenia gravis were randomly given either prednisone or azathioprine. The main goal was to record the time to the occurrence of the first episode of deterioration.

During a mean follow-up of 30 months, 21 patients showed deterioration, 12 in the prednisone group and nine in the azathioprine group ($p = 0.40$). No difference was observed between the two groups in muscular score and functional grade, assessed at the end of each treatment year, or in tolerance. Treatment failure occurred in 17 patients, 12 in the prednisone group and five in the azathioprine group ($p = 0.02$); even after adjustment for imbalances in prognostic features, the failure rate remained 2.8 times higher in the prednisone group than in the azathioprine group ($p = 0.5$).

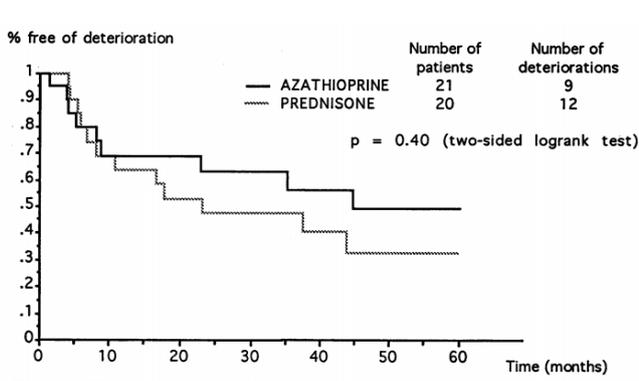


Figure 1 Time to occurrence of clinical deterioration according to randomisation.

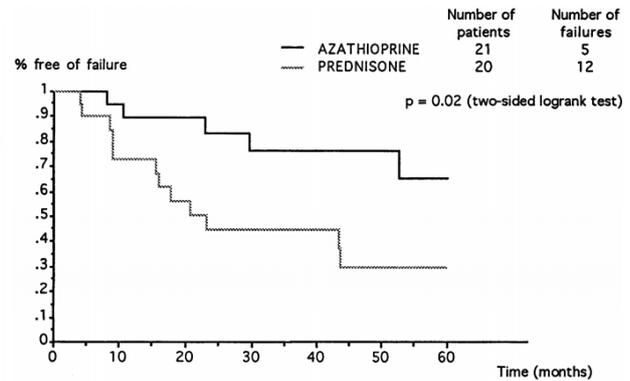


Figure 2 Time to occurrence of treatment failure according to randomisation.

These findings indicate that azathioprine increases treatment response compared with prednisone, although no difference in the duration of improvement was demonstrated. Nevertheless, it appears that the most severe forms of the disease, often resistant to prednisone or azathioprine alone, could benefit from the combination of both drugs.

Consensus guidelines, etc.

Myasthenia gravis: A review of available treatment approaches (Review Article) Gilhaus NE et al (2011)¹¹

Azathioprine is the other well-established first-choice immunoactive drug used for myasthenia gravis. This drug is often used in combination with prednisolone. Formal scientific evidence for its effect in myasthenia gravis is lacking, but a controlled trial (as detailed above) showing the superiority of the combination prednisolone—azathioprine over prednisolone alone is much cited.⁹ Azathioprine is regarded as safe and with few side effects, also during long-term treatment. The clinical effect of azathioprine is slow to appear. Improvement should not be expected to appear until after 3–6 months, and full effect of the drug first occurs after 1-2 years. This is a reason why azathioprine is usually combined with other immunoactive treatments, such as prednisolone, and especially in the initial phase. Marked improvement on azathioprine is reported in 70–90% of myasthenia gravis patients in open series.

International Consensus Guidance for the Management of Myasthenia Gravis; Sanders DB et al (2016)¹²

A panel of 15 international experts was convened to develop formal consensus based guidelines for the management of Myasthenia gravis. Guidance statements were developed for symptomatic and immunosuppressive treatments which included the following conclusions:

- Pyridostigmine bromide is the oral drug of choice for the symptomatic treatment of myasthenia gravis.
- The benefit of immunosuppression in generalised myasthenia gravis is generally accepted. Corticosteroids are the most commonly used agents. However, because of unacceptable adverse effects, corticosteroids are frequently used in combination with another immunosuppressive agent, the most common being azathioprine or mycophenolate mofetil.
- Combination therapy with corticosteroids is more effective than corticosteroids alone, with longer remissions and fewer side effects.

Summary of safety data:

For this product there is no modern clinical documentation that can be used as support for determining the frequency of undesirable effects. Undesirable effects may vary in their incidence depending on the indication.

	Very common	Common	Uncommon	Rare	Very rare
Infections and infestations	Viral, fungal and bacterial infections (in transplant patients in combination with other immunosuppressants)		Viral, fungal and bacterial infections (in other indications)		
Neoplasms benign and malignant (including cysts and polyps)				neoplasms including lymphoproliferative disorders, skin cancers (melanomas and non-melanomas), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ, acute myeloid leukaemia and myelodysplasia	

Blood and lymphatic system disorders	Depression of bone marrow function; leucopenia.	Thrombocytopenia.	Anaemia.	Agranulocytosis, pancytopenia, aplastic anaemia, megaloblastic anaemia, erythroid hypoplasia	
Respiratory, thoracic and mediastinal disorders					Reversible pneumonitis.
Gastrointestinal disorders			Pancreatitis.	Colitis, diverticulitis and bowel perforation reported in transplant population, severe diarrhoea in inflammatory bowel disease population.	
Hepato-biliary disorders			Cholestasis and degeneration of liver function tests.	Life-threatening hepatic damage.	
Skin and subcutaneous tissue disorders				Alopecia, photosensitivity	
Immune system disorders			Hypersensitivity reactions		Stevens-Johnson syndrome and toxic epidermal necrolysis.

The following convention has been utilised for the classification of frequency: Very common, $\geq 1/10$; common, $\geq 1/100$ and $< 1/10$; uncommon, $\geq 1/1000$ and $< 1/100$; rare, $\geq 1/10000$ and $< 1/1000$; very rare, $< 1/10000$

Monitoring

There are potential hazards in the use of Azathioprine. It should be prescribed only if the patient can be adequately monitored for toxic effects throughout the duration of therapy.

It is suggested that during the first 8 weeks of therapy, complete blood counts, including platelets, should be performed weekly or more frequently if high dosage is used or if severe renal and/or hepatic disorder is present. The blood count frequency may be reduced later in therapy, but it is suggested that complete blood counts are repeated monthly, or at least at intervals of not longer than 3 months.

Patients receiving Azathioprine should be instructed to report immediately any evidence of infection, unexpected bruising or bleeding or other manifestations of bone marrow depression.

There are individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) who may be unusually sensitive to the myelosuppressive effect of azathioprine and prone to developing rapid bone marrow depression following the initiation of treatment with Azathioprine. This problem could be exacerbated by co-administration with drugs that inhibit TPMT, such as olsalazine, mesalazine or sulfasalazine. Also it has been reported that decreased TPMT activity increases the risk of secondary leukaemias and myelodysplasia in individuals receiving 6-mercaptopurine (the active metabolite of azathioprine) in combination with other cytotoxics. Patients with very low TPMT activity should not take azathioprine.

The Myasthenia Gravis Study Group recorded adverse events during the trial comparing prednisolone and azathioprine as follows:

Total side effects observed in the prednisone group and in the azathioprine group

	<i>Prednisone (n = 20)</i>	<i>Azathioprine (n = 21)</i>	
	<i>Number of patients with at least one side effect</i>		<i>p value (Fisher's test)</i>
	<i>16 (80 %)</i>	<i>12 (57 %)</i>	<i>0.18</i>
Side effects			
Cushingoid features	11	3	0.009
Bacterial infection	10	4	0.05
Viral infection	0	4	0.11
Fungal infection*	3	3	1.00
Systemic hypertension†	2	1	0.61
Diabetes	2	0	0.23
Osteoporosis	6	2	0.13
Psychiatric disorders‡	1	0	0.49
Hair loss	4	2	0.41
Polymorphonuclear cell	1	3	0.61
ASAT or ALAT increase	0	4	0.11
Alkaline phosphatase increase	0	1	1.00
Total	40	27	

*Buccal or cutaneous infections.

†Defined by diastolic blood pressure above 100 mm Hg.

‡Psychotic episode.

Strengths and limitations of the evidence:**Strengths**

- Reflects best practice
- Supported by professional organisation guidelines
- Azathioprine use allows reduction in corticosteroid dose

Limitations

- Lack of RCTs due to relative rarity of condition
- Small patient numbers in studies available
- 'Off label' indication

Summary of evidence on cost effectiveness:

At a maximal dose of 200mg

Cost of 28 days treatment = 112 x 50mg tablets = £4.94

Annual cost = 13 x £4.94 = £64.22

Prescribing and risk management issues:

Monitoring required: It is suggested that during the first 8 weeks of therapy, complete blood counts, including platelets, should be performed weekly or more frequently if high dosage is used or if severe renal and/or hepatic disorder is present. The blood count frequency may be reduced later in therapy, but it is suggested that complete blood counts are repeated monthly, or at least at intervals of not longer than 3 months.

References

¹ BNF 76 September 2018-March 2019

<https://bnf.nice.org.uk/drug/azathioprine.html#indicationsAndDoses>

² Sussman J, et al. Pract Neurol 2015;15:199–206. doi:10.1136/practneurol-2015-001126

- ³ Surrey Prescribing Clinical Network Shared Care Prescribing Guideline: Azathioprine for the treatment of neurological conditions (myasthenia gravis, inflammatory neuropathies etc), November 2015 Approved by: Frimley Interface Prescribing Committee
<https://www.fhft.nhs.uk/media/2405/azathioprine-in-neurology-shared-care.docx>
- ⁴ SPC Imuran Tablets 50mg <https://www.medicines.org.uk/emc/product/3823/smpc>
- ⁵ Average weight of a man <https://www.onaverage.co.uk/body-averages/average-weight-of-a-man>
- ⁶ NHS Electronic Drug Tariff October 2019 <http://www.drugtariff.nhsbsa.nhs.uk/#/00738682-DD/DD00738121/Part%20VIII%20products%20A>
- ⁷ Myasthenia gravis: Association of British Neurologists' management guidelines : BMJ: Practical Neurology Vol 15, Issue 3 <https://pn.bmj.com/content/15/3/199>
- ⁸ Mayers PL et al; Myasthenia gravis management, Clinical pharmacist Vol 4, Nov 2012
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<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC489815/pdf/jnnpsyc00484-0015.pdf>
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<https://www.hindawi.com/journals/ad/2011/847393/>
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