AZATHIOPRINE- IMMUNOSUPPRESSIVE DRUG FOR MYASTHENIA GRAVIS

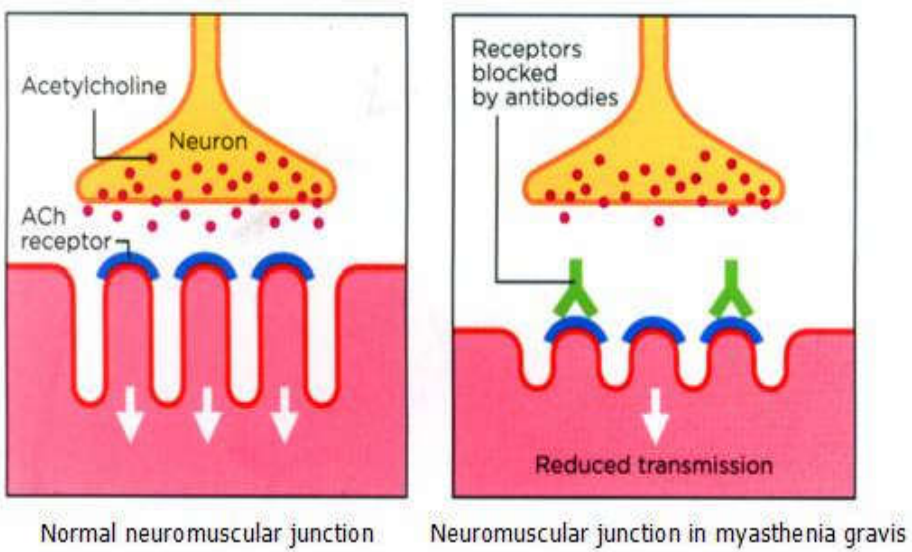
NEUROLOGY DEPARTMENT

CONTENT

- Generalle Information
- Treatment-Immunosuppressants:
  - Azathioprine
- Conclusion

I. General Information

- Myasthenia gravis (MG) is an autoimmune disorder characterized by fluctuating muscle weakness and fatigability on exertion, in which autoantibodies to proteins of the neuromuscular junction (NMJ) are pathogenically relevant



Distribution of weakness

- Ocular 17%
- Ocular and bulbar 13%
  - Mild 2%
  - Moderate/severe 11%
- Ocular and limb 20%
- Generalised 50%
  - Mild 2%
  - Moderate 14%
  - Severe 15%
  - Assisted ventilation 11%
  - Died despite ventilation 8%

Pract Neurol 2015;**15**:199-206 doi:10.1136/practneurol-2015-001126

Clinical guidelines

Myasthenia gravis: Association of British Neurologists' management guidelines

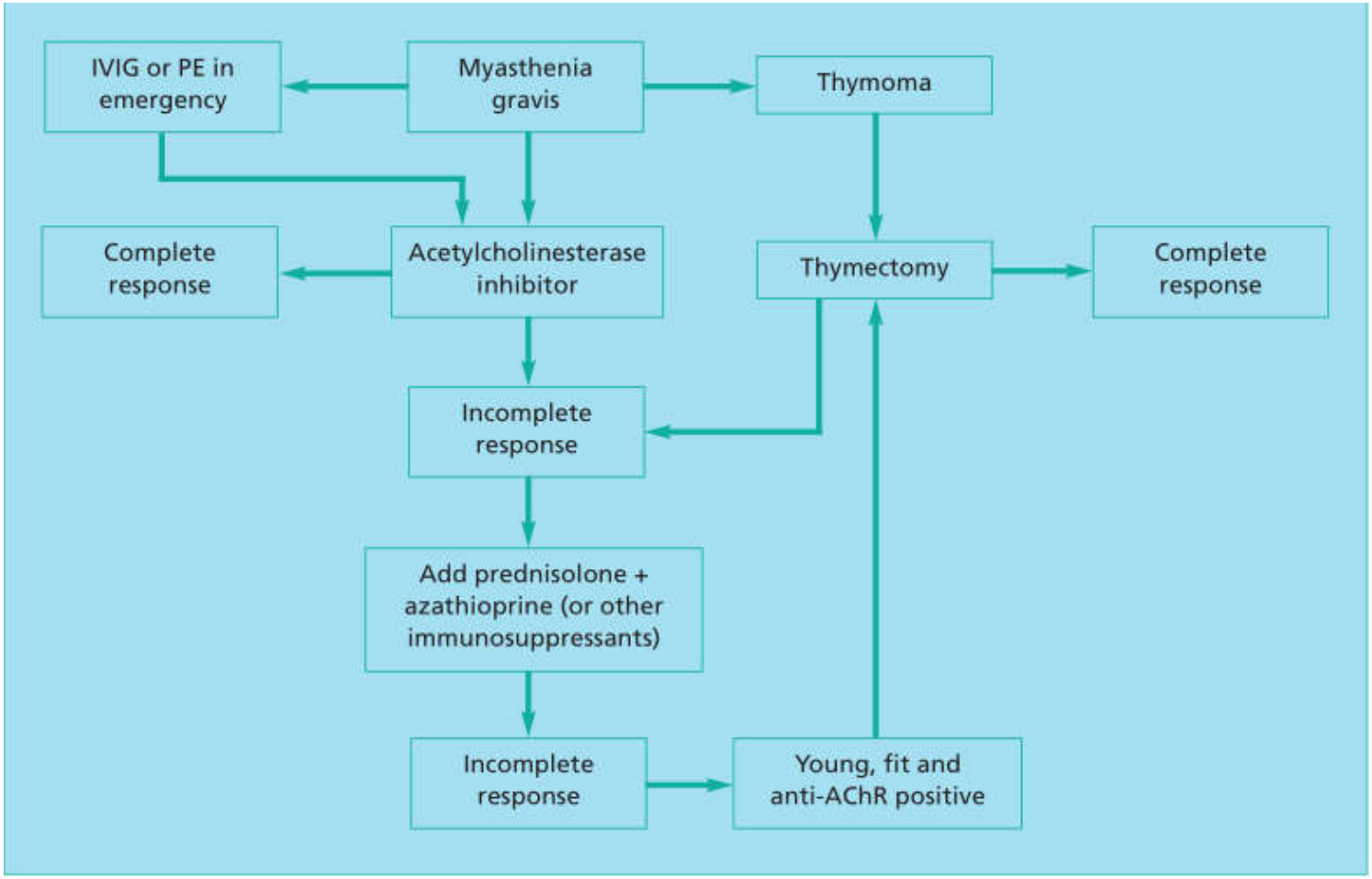
Jon Sussman[1], Maria E Farrugia[2], Paul Maddison[3], Marguerite Hill[4], M Isabel Leite[5], David Hilton-Jones[5]

1 Start pyridostigmine following protocol.

2. ACh-R antibody seropositive and aged under 45 years: consider thymectomy.

3. If symptomatic despite pyridostigmine, start prednisolone (generally given on alternate days.

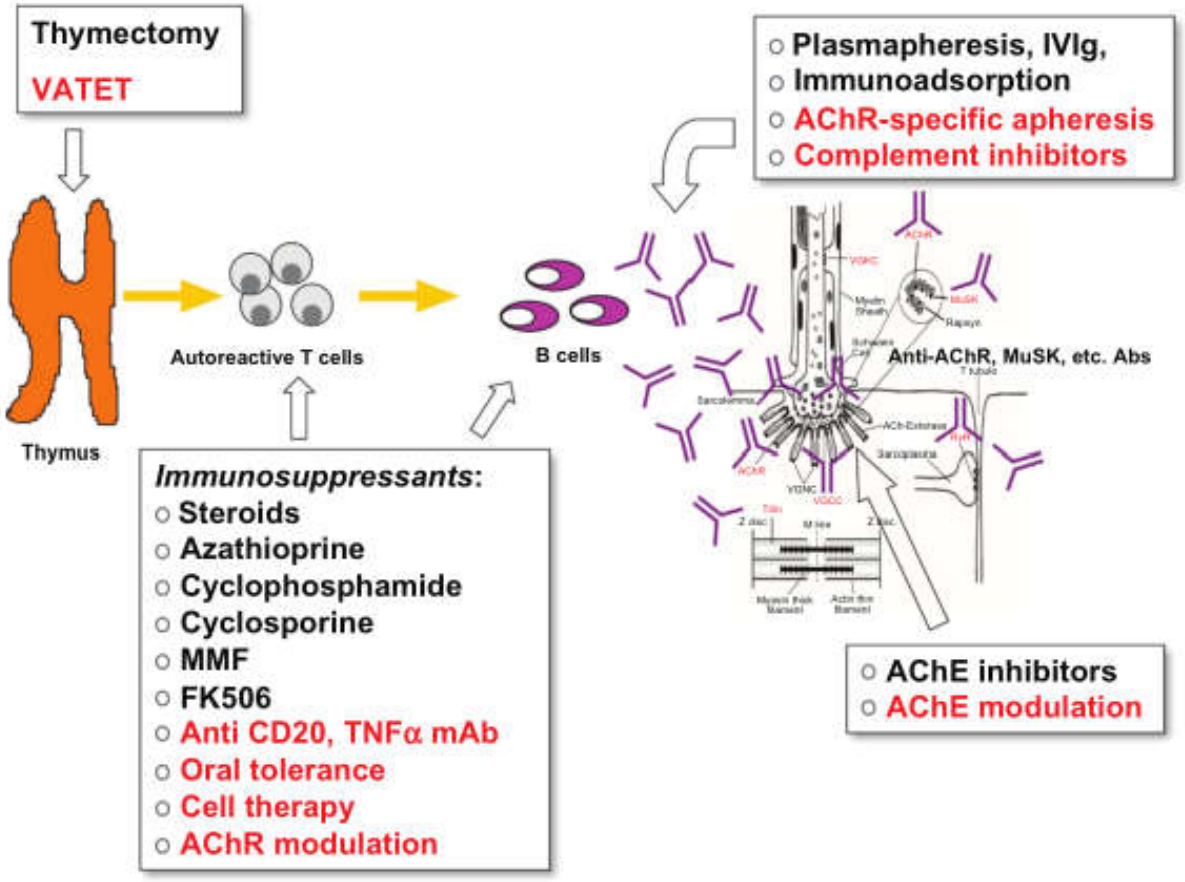
4. If relapse occurs on prednisolone withdrawal at a dose of 7.5–10 mg/day (or 15–20 mg alternate days) or greater, introduce immunosuppression. Immunosuppression may also be used for patients with corticosteroid-related side effects on low-dose prednisolone.


IVIG or PE in emergency
Myasthenia gravis
Thymoma
Complete response
Acetylcholinesterase inhibitor
Thymectomy
Complete response
Incomplete response
Add prednisolone + azathioprine (or other immunosuppressants)
Incomplete response
Young, fit and anti-AChR positive

Treatment	Mode of action	Evidence class*	Serious adverse events	Recommendation
Symptomatic				
Pyridostigmine	Inhibits acetylcholinesterase	Class III	Cholinergic crisis	First line
Short-term immunosuppression				
Prednisolone	Inhibits T-cell activation and impairs function of cells from the monocyte/macrophage lineage	Class II	Cushingoid features, diabetes, hypertension, osteoporosis, psychiatric disorders	First line
Long-term immunosuppression				
Azathioprine	Purine antagonist that inhibits DNA synthesis and cell proliferation	Class I	Haematopoietic suppression, hepatotoxicity, malignancy, pancreatitis	First line
Ciclosporin	Calcineurin-mediated inhibition of T-cell interleukin-2 production	Class I	Hypertension, malignancy, nephrotoxicity	To be considered in patients intolerant of or unresponsive to azathioprine, methotrexate, mycophenolate mofetil or tacrolimus
Cyclophosphamide	DNA-alkylating agent that blocks cell proliferation	Class I	Bladder toxicity, haematopoietic suppression, infertility, malignancy, opportunistic infections	To be considered in patients intolerant of or unresponsive to azathioprine, methotrexate, mycophenolate mofetil, tacrolimus or ciclosporin
Methotrexate	Folate antagonist that inhibits *de novo* synthesis of purines and pyrimidines	Class II	Haematopoietic suppression, hepatotoxicity, pneumonitis	Second line in patients intolerant of or unresponsive to azathioprine
Mycophenolate mofetil	Inhibits T-cell proliferation by blocking purine synthesis	Class I	Haematopoietic suppression, hepatotoxicity, opportunistic infections, progressive multifocal leukoencephalopathy	Third line in patients intolerant of or unresponsive to azathioprine, methotrexate or tacrolimus
Rituximab	Chimeric monoclonal antibody against the B-cell surface marker CD20	Class IV	Neutropaenia, opportunistic infections, progressive multifocal leukoencephalopathy	To be considered only in patients with severe refractory MG unresponsive to other treatments
Tacrolimus	Calcineurin-mediated inhibition of T-cell interleukin 2 production	Class I	Hyperglycaemia, hypertension, malignancy, nephrotoxicity	Third line in patients intolerant of or unresponsive to azathioprine, methotrexate or mycophenolate mofetil

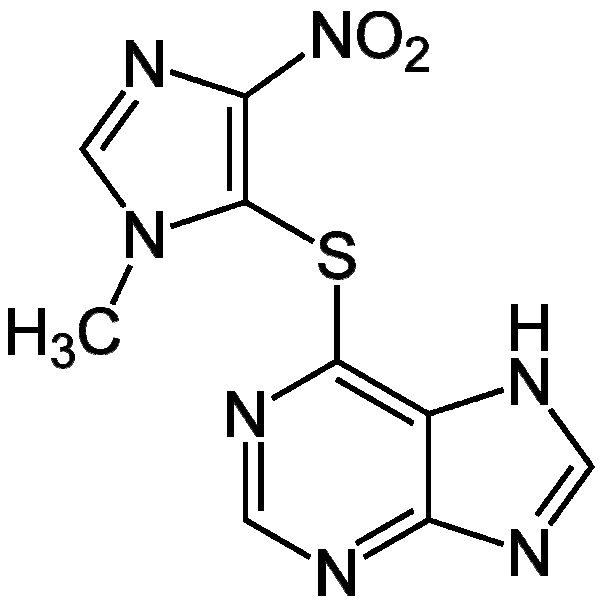
Treatment	Mode of action	Evidence class*	Serious adverse events	Recommendation
Rapid short-term immunomodulation				
Immunoglobulin	Interference of signalling via Fc receptors, neutralisation of activated complement, suppression of idiotypic antibodies, modulation of proinflammatory cytokines	Class I	Aseptic meningitis, solute-induced renal failure, thrombotic complications, volume overload	First line
Plasma exchange	Removes circulating antibodies, cytokines, immune complexes, and other inflammatory mediators	Class I	Air embolism, disturbances in acid-base homeostasis, hypocalcaemia, hypotension, infection, pneumothorax, thrombosis, volume overload	First line
Long-term immunomodulation				
Thymectomy	Disrupts B-cells producing anti-AChR antibodies	Class II	General risks of surgery	Always indicated in patients with a thymoma; in non-thymomatous anti-AChR antibody-positive patients, to be considered if MG is not controlled adequately with medical treatment

*Evidence Class I - randomised controlled trials available; Class II - controlled trials without randomisation or randomised trials with small patient number; Class III - uncontrolled trials; Class IV - case series


Thymectomy
VATET
Thymus
Autoreactive T cells
B cells
Plasmapheresis, IVIg,
Immunoadsorption
AChR-specific apheresis
Complement inhibitors
Anti-AChR, MuSK, etc. Abs
AChE inhibitors
AChE modulation
Immunosuppressants:
Steroids
Azathioprine
Cyclophosphamide
Cyclosporine
MMF
FK506
Anti CD20, TNFα mAb
Oral tolerance
Cell therapy
AChR modulation

II.AZATHIOPRINE

- Azathioprine, a prodrug of 6-mercaptopurine (6-MP), interferes in purine nucleotide synthesis and metabolism which makes it an effective inhibitor of lymphocyte proliferation



Pract Neurol 2015;**15**:199-206 doi:10.1136/practneurol-2015-001126

Clinical guidelines

Myasthenia gravis: Association of British Neurologists' management guidelines

Jon Sussman[1], Maria E Farrugia[2], Paul Maddison[3], Marguerite Hill[4], M Isabel Leite[5], David Hilton-Jones[5]

- Azathioprine is the first-line agent
- Azathioprine is slow to achieve maximum effect

Table 1. Table 1. Time to Clinical Effect of Therapies for Myasthenia Gravis

Medscape® www.medscape.com

Treatment	Time to Clinical Effect
Pyridostigmine	10–15 minutes
Plasmapheresis	1–14 days
IVIg	1–4 weeks
Prednisone	2–8 weeks
Mycophenolate mofetil	2–6 months
Cyclosporine	2–6 months
Azathioprine	3–18 months

A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis

J. Palace, BM, DM, J. Newsom-Davis, MD, FRS, B. Lecky, MD, FRCP and Myasthenia Gravis Study Group

+ SHOW AFFILIATIONS

Address correspondence and reprint requests to Dr. Jackie Palace, Department of Clinical Neurology, Radcliffe Infirmary, Woodstock Road, Oxford, OX2 6HE, UK.

doi: http://dx.doi.org/10.1212/WNL.50.6.1778
Neurology June 1998 vol. 50 no. 6 1778-1783

A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis

J. Palace, BM, DM, J. Newsom-Davis, MD, FRS, B. Lecky, MD, FRCP and Myasthenia Gravis Study Group

+ SHOW AFFILIATIONS

Address correspondence and reprint requests to Dr. Jackie Palace, Department of Clinical Neurology, Radcliffe Infirmary, Woodstock Road, Oxford, OX2 6HE, UK.

doi: http://dx.doi.org/10.1212/WNL.50.6.1778

Neurology June 1998 vol. 50 no. 6 1778-1783

- The prednisolone dose and clinical outcome were compared in a multicenter randomized double-blind study of 34 MG patients who were followed up for mgkg); the other group received prednisolone on alternate days plus placebo (PRED + PLAC).
- Initial high-dose prednisolone (1.5 mgkg on alternate days) was tapered at remission to the minimal dose required to maintain remission. 3 years.
- One group (PRED + AZA) received prednisolone (on alternate days) plus azathioprine (2.5

- The prednisolone dose did not differ significantly between the two groups at 1 year (median values: PRED + AZA, 37.5 mg on alternate days; PRED + PLAC, 45 mg on alternate days) but was reduced at 2 and 3 years in the PRED + MA group (median value at 3 years: PRED + AZA, 0 mg on alternate days; PRED + PLAC, 40 mg 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 a sharp rise in the anti-acetylcholine receptor (AChR) titers in the PRED + PLAC group at 2 years. Incidence of side effects was slightly less in the PRED + MA group.
- **Azathioprine as an adjunct to alternate day prednisolone in the treatment of antibody-positive generalized MG reduces the maintenance dose of prednisolone and is associated with fewer treatment failures, longer remissions, and fewer side effects.**

Postgrad Med J (1990) **66**, 102 – 105

Long term treatment of myasthenia gravis with azathioprine

V. Fonseca and C.W.H. Havard

Royal Free Hospital, Pond Street, London NW3 2QG, UK.

Summary: Twenty-seven patients with myasthenia gravis have been treated with azathioprine in conjunction with pyridostigmine and prednisolone for a total of 138 patient years. Side effects necessitated discontinuation of treatment in only four patients. Treatment with azathioprine was associated with marked clinical improvement in all the remaining 23 patients, resulting in reduction in the dose of pyridostigmine and prednisolone. The number of hospital admissions as well as the number of episodes of respiratory failure were markedly reduced.

Table II Effect of azathioprine in 23 patients with myasthenia gravis

		Pre-azathioprine	*Post-azathioprine (current status)*
Clinical grade	1a	0	4
	1b	0	11
	2	0	8
	3	10	0
	4	13	0
Hospital admission in last year		40	1
Median (range) dose of pyridostigmine mg/day		600 (180–1200)	240 (0–900)
Median (range) dose of prednisolone mg/day		15 (0–20)	5 (0–20)

Original investigations

Journal of Neurology

© Springer-Verlag 1988

J Neurol (1988) 235:449–453

Azathioprine as a single drug or in combination with steroids in the treatment of myasthenia gravis

R. Mantegazza[1], C. Antozzi[1], D. Peluchetti[2], A. Sghirlanzoni[2], and F. Cornelio[1]

Departments of [1]Neuromuscular Diseases and [2]Neurology, Istituto Neurologico "C. Besta", Via Celoria 11, I-20133 Milan, Italy

Azathioprine (Aza) has been used alone or in combination with steroids for two groups of myasthenic patients. Positive responses were noted in **75% of patients** on Aza alone and in 70% receiving the combined regimen. The clinical course of the two groups differed in terms of respiratory crisis and need for plasma exchange. With an appropriate Aza administration schedule side-effects were not a limiting factor to its use. **Aza treatment induced a reduction in anti-AchR-antibody level** that was correlated with clinical improvement and greatly decreased the need for steroids.

Toxicities of Immunosuppressive Medications-Azathioprine

- Nausea and vomiting in about 22% of patients
- Pancreatitis and hepatotoxicity have also been reported and these symptoms occur within the first 3-6 months
- Leucopenia and thrombocytopenia
- Malignancies are known to occur in azathioprine treated patients but the exact incidence is unknown: lymphoma, squamous cell carcinomas of the skin, Kaposi's sarcoma, in situ carcinomas of the cervix, carcinomas of the vulva and perineum, hepatobiliary carcinoma, and mesenchymal tumors

Conclusion

- Azathioprine still remains the first choice for longterm immunosuppressive therapy. However, it is important to point out that there are only very limited data from controlled studies on the efficacy of azathioprine.
- A significant disadvantage of azathioprine is the delayed onset of action. Commonly, azathioprine is therefore started combined with prednisolone to achieve a rapid therapeutic effect.

REFERENCE

- *Myasthenia gravis: Association of British Neurologists' management Guidelines-Jon* Sussman, Maria E Farrugia, Paul Maddison, Marguerite Hill, M Isabel Leite, David Hilton-Jones
- *Autoimmune myasthenia gravis: emerging clinical and biological Heterogeneity-Matthew* N Meriggioli, MD 1 and Donald B Sanders, MD
- *Diagnosis and management of myasthenia gravis*-Sivakumar Sathasivam MRCP (UK), LLM, PhD- Progress in Neurology and Psychiatry January/February 2014
- *Toxicities of Immunosuppressive Treatment of Autoimmune Neurologic Diseases*- Enrico C. Lallana and Camilo E. Fadul *


Thank You