allergenic glove', since such gloves still contain latex and may not be used by latex-sensitised individuals, and will not prevent the development of latex allergies in those as yet unaffected workers.

It is essential that the problem of latex allergy in hospitals should be addressed as a matter of urgency by the authorities and hospital administration in order to contain the problem. Although the provision of a completely powder-free environment may be initially more expensive, the long-term savings in terms of loss of staff, morbidity, loss of productivity, and litigation far outweigh the short-term gains of purchasing cheap quality powdered gloves.

Professor Neil White performed occupational assessments on several of the patients. The authors acknowledge the financial support of Regent Medical (UK) and Laboratory Specialities (South Africa), and permission from the Medical Superintendent of Groote Schuur Hospital to publish this report.

Dr M Isaacs of the Groote Schuur Hospital Biostatistics Department performed the statistical analysis of the data.

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HIGH-DOSE IMMUNOSUPPRESSIVE THERAPY IN GENERALISED MYASTHENIA GRAVIS — A 2-YEAR FOLLOW-UP STUDY

J M Heckmann, E B LeePan, R W Eastman

Background. Immunosuppressive (IS) therapy is increasingly advocated in the treatment of myasthenia gravis (MG). This study assessed whether early 'high-dose' IS therapy in new patients with generalised MG (GMG) altered the outcome and reduced the morbidity of GMG.

Methods. Patients with GMG were treated with 'high-dose' IS therapy (prednisone ≤ 1 mg/kg, azathioprine 2 - 3 mg/kg) and followed up for 2 years. Prednisone and azathioprine were initiated on diagnosis. Outcome measures were compared with those of controls previously treated at our clinic with 'low-dose' IS therapy. The primary outcome measure was the number of patients in remission at 1 and 2 years. Secondary outcomes included the MG scores (MGS) after 1 and 2 years, as well as the number of plasma exchanges (P/E), hospital and intensive care unit (ICU) admissions required for decompensated MG.

Findings. At 1 and 2 years there were significant improvements in the MGS of patients treated with 'high-dose' IS therapy compared with those of controls; 50% of these patients were in remission after 2 years compared with less than 16% of controls. The number of hospital and ICU admissions had also dropped significantly in the first year of patients receiving 'high-dose' IS treatment.

Conclusion. Early 'high-dose' IS therapy using azathioprine and prednisone in GMG resulted in a significant increase in the number of patients in remission and reduced morbidity at 1 and 2 years.

S Afr Med J 2001; 91: 765-770.

Myasthenia gravis (MG) is an autoimmune disorder mediated by immunoglobulin G (IgG) antibodies to the muscle acetylcholine receptor (AChR).[1] This results in a reduction in the number of effective AChRs, impaired neuromuscular transmission, and therefore clinically in fatiguable muscle weakness.[1] Autoantibodies against the AChR can be detected in

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the sera of 85 - 90% of patients with generalised weakness.[2] Reduction in the number of functional end-plate receptors resulting from the deleterious effects of the AChR antibodies[3] is due to complement-mediated lysis,[4] increased receptor degradation,[5] and pharmacological block[6] of the AChR. Plasma exchange (P/E), which lowers the serum level of antibodies, produces clinical improvement.[7] The factors that trigger the initial loss of self-tolerance and therefore the autoimmune response, are not known.

The world-wide prevalence of MG has been estimated to be 5 - 10 per 100 000.[8] Groote Schuur Hospital treats approximately 12 - 18 new cases per year, referred mainly from the Western Cape. Patients with generalised MG (GMG) and positive AChR antibodies can be classified into three main subgroups.[8] About 60% present with symptoms from puberty to age 40 years (early-onset MG (EOMG)), and the majority of this group show hyperplasia of the thymic medulla[1,9] for which a thymectomy is recommended. Secondly, less than 20% present with late-onset disease (> 40 years), and thirdly about 10% have an associated thymoma.[9,10] A further 10 - 15% of patients with GMG will have no AChR antibodies detectable in their sera (seronegative MG).[9,10] However, pathogenic antibodies have been implicated in these patients, probably binding to the neuromuscular junction at a site distinct from the AChR,[11] and these patients also respond to P/E.[1]

Before 1996 there was no standard protocol in our clinic as to how to treat GMG; the mainstay of treatment was the anticholinesterases. Prednisone, the principal immunosuppressant, was used sparingly. It was our impression that very few of our patients were going into remission, and that many of them still had chronic active disease, even requiring hospital and intensive care unit (ICU) admission, many years after the initial presentation.

Before corticosteroids were introduced, GMG was treated with anticholinesterases as well as thymectomy in appropriate (EOMG and thymoma) patients; the disease mortality rate was 30% and ultimately only 13% of patients went into remission.[12] Between 1960 and 1980 corticosteroids were used to treat GMG and the mortality rate started to fall (14%), but the remission rate was essentially unchanged (6%, mean follow-up 12 years, $N = 476$).[12]

Azathioprine had been used in Germany since 1969 in doses ranging from 2 to 2.5 mg/kg and found to be effective as a single treatment in GMG.[13,14] Over recent years azathioprine has been used as IS therapy in GMG and, based largely on retrospective uncontrolled studies, the usefulness of high-dose azathioprine (2 - 3 mg/kg) as a steroid-sparing agent, is generally advised in texts.[8,15] In 1993 a randomised non-blind trial of azathioprine versus prednisone after 4 months of initial prednisone, showed more treatment failures in the prednisone group.[16] There was no difference in the functional outcome between the two treatment groups, but more than one-third of the patients had a prolonged disease duration before the study, which may have influenced their immunosuppressive responsiveness. In practice, patients are often reluctantly put onto low doses of azathioprine as an add-on second-line IS agent when prednisone has failed, often many years after symptom onset. This reluctance may stem from the delay in the therapeutic response to azathioprine which is only evident after a few months, whereas with prednisone it is much sooner.

A prospective study was initiated to determine whether high doses of IS drugs (prednisone plus azathioprine) early in the course of GMG would influence the clinical outcome and morbidity over a 2-year treatment period.

PATIENTS AND METHODS

The diagnosis of MG was based on clinical evidence of fatiguable weakness, supported by a positive anticholinesterase test (edrophonium chloride) and/or an AChR antibody assay. The anti-AChR antibody radio-immunoassay performed by the University of Cape Town clinical immunology laboratory, is dependent on AChRs extracted from a human cell line (TE671 cells) and labelling it with ^{125}I-labelled α-bungarotoxin.[2] Repetitive nerve stimulation was performed in selected patients.

The patients were objectively evaluated for fatiguable weakness by scoring 13 categories including ocular and bulbar muscles, vital capacity as a measure of respiratory muscle function, and proximal upper and lower limb fatiguability. The MG score (MGS) was adapted from that published by Tindall *et al.*[17] (Table I).

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Outcome measures were compared with historical controls, namely patients previously treated at our clinic with IS therapy for similar durations. Only those who had been initiated on IS therapy ('low-dose') within 2 years of symptom onset were included. 'Low-dose' refers most often to prednisone alone or in some cases to a low-dose prednisone/azathioprine combination. The records of patients attending the MG clinic from 1986 to 1996 provided control data on the number of

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4. Chewing	Normal	Fatigue after solids	Only soft foods	Gastric tube
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6. Head lifting(s) *	> 120	> 30 - 120	> 0 - 30	0
7. Outstretching right arm (s)†	> 180	> 90 - 180	> 10 - 90	< 10
8. Outstretching left arm (s)†				
9. VC (litres)				
Male	> 3.5	> 2.5 - 3.5	> 1.5 - 2.5	< 1.5
Female	> 2.5	> 1.8 - 2.5	> 1.2 - 1.8	< 1.2
10. Elevating right leg (s)‡	> 100	> 30 - 100	> 0 - 30	0
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As previously, thymectomies were performed in those patients with EOMG and suspected thymoma.

Statistical analysis

The MGS, mean drug doses, duration of symptoms and duration of exposure to IS therapy at time of evaluation between the two groups were compared using the Student's *t*-test (I-tailed). Chi-squared analyses (df = 1) were performed for the primary and secondary outcome comparisons. A *P*-value > 0.05 was considered not significant (NS).

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We present the 1- and 2-year follow-up results of patients exposed to 'high-dose', and controls exposed to 'low-dose', IS therapy for similar periods from time of symptom onset. The types of MG and age of onset in both the study and control groups were comparable (Tables II and III). Thymectomies were performed in all EOMG controls at a mean of 1.38 (SD ± 1.22) years from symptom onset, and in 7 of the 'high-dose' group at 1.73 (SD ± 1.37) years (*P* = NS).

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Patients were classified as defaulters if, in the preceding 6 months, they had discontinued their treatment for 2 weeks or more.

Treatment protocol

Once the diagnosis of GMG was confirmed, anticholinesterases and IS therapy were started. A test dose of azathioprine (50 mg) was given to assess tolerance. The dose was increased to approximately 1 - 1.5 mg/kg and the white cell count (WCC) was monitored fortnightly for 4 weeks. If the WCC fell below 3×10^9/l, or the lymphocytes below 0.8×10^9/l, azathioprine was discontinued for a few days and re-introduced at a slightly lower dose.[15] If the blood count was stable, azathioprine was increased to a maintenance level of 2.5 - 3 mg/kg and blood counts were checked at intervals.

Prednisone was started at a low dose (15 - 20 mg) with 5 mg increments every 1 - 4 weeks until the patient was either asymptomatic, side-effects had intervened, or a dose of 1 mg/kg was reached. If the patient became asymptomatic, anticholinesterases were reduced and stopped, prednisone was slowly withdrawn and azathioprine was continued on the lowest dose that maintained the blood count at the minimum safe levels. (In those patients who received alternate-day prednisone throughout the treatment period, only 50% of their mean dose was used for the calculation.)

As previously, thymectomies were performed in those patients with EOMG and suspected thymoma.

Statistical analysis

The MGS, mean drug doses, duration of symptoms and duration of exposure to IS therapy at time of evaluation between the two groups were compared using the Student's *t*-test (I-tailed). Chi-squared analyses (df = 1) were performed for the primary and secondary outcome comparisons. A *P*-value > 0.05 was considered not significant (NS).

RESULTS

We present the 1- and 2-year follow-up results of patients exposed to 'high-dose', and controls exposed to 'low-dose', IS therapy for similar periods from time of symptom onset. The types of MG and age of onset in both the study and control groups were comparable (Tables II and III). Thymectomies were performed in all EOMG controls at a mean of 1.38 (SD ± 1.22) years from symptom onset, and in 7 of the 'high-dose' group at 1.73 (SD ± 1.37) years (*P* = NS).

Table II. 'High-dose' immunosuppressive therapy versus 'low-dose' therapy in controls evaluated after 1 year*

	'High-dose' (N = 17)	Controls (N = 6)	P-value‡
Type of MG			
EOMG	59% (10)	67% (4)	$P\chi^2$ = NS
Thymoma	6% (1)	0	
Late-onset MG	18% (3)	33% (2)	
Seronegative	6% (1)	0	
Mean time (yrs) between onset of symptoms and IS therapy (SD)	0.79 (0.66)	0.67 (0.52)	NS
MGS at entry (SD)	15.27 (6.30)	ND	
MGS at 1 year (SD)	1.79 (2.57)	12.17 (4.71)	0.001
Remissions (%)	53% (CI ± 23.8)	16% (CI ± 29.8)	0.009

IS = immunosuppressive; MGS = MG score; SD = standard deviation from sample mean; CI = 95% confidence interval.
* All subjects received IS therapy within 2 years of symptom onset. Age at symptom onset was comparable between high-dose patients and controls (P = NS).
† Controls were evaluated after a mean of 0.97 (SD 0.08) years of low-dose IS therapy.
‡ P-value of t-test (1-tailed). Chi-test ($P\chi^2$) was performed with df = 1.

Table III. 'High-dose' immunosuppressive therapy versus 'low-dose' therapy in controls evaluated after 2 years*

	High dose (N = 10)	Controls (N = 8)	P-value
Type of MG (%)			
EOMG	60% (6)	75% (6)	$P\chi^2$ = NS
Thymoma	10% (1)	0	
Late-onset MG	20% (1)	25% (2)	
Seronegative	10% (1)	0	
Mean time (yrs) between onset of symptoms and IS therapy (SD)	0.76 (0.61)	0.49 (0.49)	NS
MGS at entry (SD)	16.30 (5.77)	ND	
MGS at 2 years (SD)	1.22 (1.48)	7.13 (4.73)‡	0.001
Remissions (%)	50% (CI = 31.6)	13%§ (CI = 23.4)	0.06

IS = immunosuppressive; MGS = MG score; SD = standard deviation from sample mean; CI = 95% confidence interval.
* All subjects received IS therapy within 2 years of symptom onset. Age at symptom onset was comparable between high-dose patients and controls (P = 0.34).
† P-value of t-test (1-tailed). Chi-test ($P\chi^2$) was performed with df = 1.
‡ Controls were evaluated after a mean of 2.66 (SD 0.52, range 2 - 3.5) years of low-dose IS therapy.
§ At 1.5 years one patient died with severely decompensated GMG.

The MG patients evaluated after 1 year of 'high-dose' IS therapy started with a mean MGS at study entry of 15.27 and ended with 1.79 (Table II). This is significantly different from the controls who scored 12.17 after 1 year of 'low-dose' therapy (Table II). Fifty-three per cent of the 'high-dose' IS group were in remission and not taking anticholinesterases, compared with 16% of the controls. During the second 6 months the 'high-dose' group was receiving a mean dose of 2.43 mg/kg azathioprine (SD 0.33), and only 3 of the controls were receiving azathioprine at a mean dose of 1.27 mg/kg (SD 0.65, N = 3) ($P \leq 1 \times 10^{-7}$). In the 'high-dose' group the mean prednisone requirements were 0.23 mg/kg (SD 0.21) in the second 6-month treatment period compared with the controls receiving 0.48 mg/kg (SD 0.28, $P_{t\text{-test}} = 0.02$); 3 of the 'high-dose' subjects had been successfully tapered off their prednisone.

The 10 patients on 'high-dose' IS therapy followed up for 2 years started with a mean MGS of 16.30 and ended with 1.22. The 8 controls on low-dose IS therapy scored 7.13 after an average of 2.7 years (Table III). Again, half of the 'high-dose' IS group were in remission (off anticholinesterases) compared with 13% of the controls. During the final 6-month treatment period the 'high-dose' group received a mean azathioprine dose of 2.33 mg/kg (SD 0.39); 3 patients were maintained on azathioprine alone. Only 2 controls were receiving azathioprine (mean 1.15 mg/kg, $P \leq 1 \times 10^{-7}$). The mean prednisone requirement for this period was 0.13 mg/kg (SD 0.14) for the 'high-dose' group and 0.34 mg/kg (SD 0.30, P = 0.03) for the control group. One-third of the 'high-dose' group had been successfully weaned off prednisone.

Scrutinising the records of a larger number of historical controls (N = 56) who received IS treatment between 1986 and 1996, and within 2 years of symptoms, showed that the control

Table IV. Morbidity in the 'high-dose' IS group compared with 'low-dose' controls

	Hospital admissions (% subjects* (*N*)†)	Plasma exchange (% subjects* (*N*))	ICU admissions (% subjects* (*N*))
'Low-dose' controls			
≤ 1 year of IS therapy (*N* = 56)	48‡ (40)§	20¶ (11)§	30‡ (24)§
1 - 2 yrs of IS therapy (*N* = 32)	25¶ (15)‖	19¶ (6)	9¶ (4)‖
'High-dose' IS therapy			
≤ 1 year of IS therapy (*N* = 17)	6‡ (1)	6¶ (1)	0‡
1 - 2 yrs of IS therapy (*N* = 10)	0¶	0¶	0¶

* % subjects refers to the number of patients affected by the events.
† Events related to the time of diagnosis have been excluded. *N* refers to the actual number of events.
‡ $P\chi^2 < 0.01$ (df = 1).
§ Nine patients had ≥ 2 hospital admissions, 3 had ≥ 3 courses of P/E and 5 had ≥ ICU admissions.
¶ Not significant.
‖ One patient died with decompensated GMG. Of the 56 original controls, data were only available on 32 for the evaluation period 1 - 2 years.

remission rate was similar to that of the smaller group of controls (Tables II and III); at 1 and 2 years the numbers in remission were 3% and 11% respectively. Two controls who defaulted from therapy were assumed to be in remission. Furthermore, compared with the 'low-dose' controls, hospital and ICU admissions were significantly reduced in the 'high-dose' IS group in the first year of therapy (Table IV). One control patient died after 1.5 years of therapy with severely decompensated active GMG and overwhelming infection.

The 'high-dose' IS drugs were well tolerated; 1 patient became Cushingoid and 2 developed hypertension on prednisone. Three patients developed transient lymphopenia on azathioprine doses of 2.3, 2.5 and 2.8 mg/kg respectively, but blood counts stabilised on lower doses. Two patients were excluded from the 'high-dose' group analysis — 1 defaulted for 2 months for socio-economic reasons and another was excluded as the doctors in a secondary hospital stopped medication for 2 months. Both these patients deteriorated transiently.

Discussion

There are two aspects to the treatment of MG. Therapy is firstly directed at symptomatic management by enhancing neuromuscular transmission at the residual AChR (i.e. those receptors not yet destroyed by the autoimmune attack). Availability of acetylcholine at the neuromuscular junction is increased by anticholinesterases such as pyridostigmine (Mestinon) which is given orally, and neostigmine (Prostigmin) which can be given by subcutaneous or intramuscular injection for a quicker onset of action. However, symptomatic therapy, whatever the dose, does not alter this immune-mediated disease.[12] Anticholinesterases are therefore important while the patient is symptomatic, but our data suggest that by aiming to render the patient asymptomatic with IS therapy, the medium-term outcome is considerably improved.

Secondly, the autoimmune attack against the AChRs must be immunosuppressed. As mentioned, IS therapy has already made a dramatic impact on the therapy of GMG; it should no longer have 'grave' implications in the majority of cases, and the mortality rate has approached zero in the last three decades.[1,15] Before our current study the morbidity was still considerable, with patients unable to maintain employment or even to perform housework. Furthermore, after many years of either only symptomatic or 'low-dose' IS therapy, very few patients went into remission.

We have demonstrated that 'high-dose' IS therapy, early in the evolution of GMG, results in a significant increase in the number of patients in remission. This is already evident within 1 year of initiation of therapy. Paradoxically, despite significant immunosuppression, these patients are more resistant to myasthenic decompensation from infectious disease and require less hospitalisation, ICU admissions and additional P/E. The treatment regimen is also much cheaper as the anticholinesterases (the most expensive item) is either stopped in most cases, or required less frequently. Also, prednisone is not the mainstay of immunosuppression and can often be successfully withdrawn. A double-blind placebo-controlled trial recently published,[18] albeit of a different design, found similar results. Patients receiving prednisolone alone or in combination with azathioprine (≤ 2.5 mg/kg), showed the azathioprine group to be associated with longer remissions and fewer side-effects when followed up for 3 years.[18]

Most GMG patients will need IS therapy, although in occasional patients the disease is mild with easily controlled symptoms. However, it must be stressed that patients often underplay or don't mention symptoms (especially difficulty

with chewing, swallowing or voice changes). These individuals with inadequately controlled bulbar symptoms are at particular risk of developing frequent upper and lower respiratory tract infection, as well as respiratory failure.

Most texts suggest high-dose azathioprine (2 - 3 mg/kg) as an alternative immunosuppressant to steroids in the treatment of GMG.[1,15,19] The main drawback is its long latent period before drug activity (3 - 6 months). Generally it is well tolerated, as found in our study. In rare instances an idiosyncratic reaction of diarrhoea and vomiting may develop, but this was not encountered among the patients in this study. Nausea was not a problem if the medication was taken after meals, and if necessary the dose was split into a twice-daily dose. Transient lymphopenia may occur but after cessation of azathioprine for a few days, it may be successfully re-introduced at a lower dose.

Concern was raised in 1984 regarding an increased risk of cancer in patients receiving azathioprine.[20] The experience of many has been that there is no clinically significant carcinogenic effect of azathioprine[21-23] although the risk may be increased after 10 years on high doses.[23]

This study may be criticised for not being more rigorous in its design. We decided against a case-control trial for two reasons — firstly, we felt that to withhold treatment that was generally advised from a control group would be unethical. Secondly, we anticipated small numbers of new patients to follow up and decided to enter them all and use the patients previously attending the clinic on the old regimen as controls. Although the controls were not followed in parallel to our study patients, they had also received IS therapy within 2 years of symptom onset. Further, we were able to assess some of the controls using the same scale (MGS) at comparable treatment duration endpoints as the 'high-dose' study group. The type of GMG, age of onset in the controls and timing of thymectomies in the EOMG subgroup were also comparable to those of our study patients. Also, it is noteworthy that the control remission rates found in this study are similar to those of previous studies.[11,24]

In conclusion, we have shown that 'high-dose' azathioprine and prednisone IS therapy early in GMG result in a higher clinical remission rate and significantly less morbidity in those not in remission. Prednisone can be withdrawn slowly and often successfully, relatively early. There are currently no guidelines as to how long the high-maintenance dose of azathioprine should be continued for those in remission on azathioprine alone. Mertens and colleagues[13] report that approximately 10% of their patients stay in remission following azathioprine withdrawal but do not specify after how many years the treatment is weaned.

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