Azathioprine in the Treatment of Myasthenia Gravis

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Twenty-four patients with myasthenia gravis were treated with azathioprine. Eighteen of the patients tolerated the drug. Six discontinued azathioprine therapy because of toxicity. Of the 18 patients, 15 (83%) improved while receiving azathioprine; in 8 (44%) improvement was felt to result solely from azathioprine. Initial response was seen after 4 to 10 months of treatment, with a mean of 6.4 months. Patients continued to improve for up to 24 months, with the mean time of peak improvement being 14 months. Relapse occurred within one year in all 6 patients in whom azathioprine administration was discontinued. Azathioprine is a reasonable alternative to corticosteroids in selected myasthenic patients requiring immunosuppression.

Witte AS, Cornblath DR, Parry GJ, Lisak RP, Schatz NJ: Azathioprine in the treatment of myasthenia gravis. Ann Neurol 15:602–605, 1984

Treatment for myasthenia gravis (MG) in the United States includes administration of anticholinesterases and corticosteroids, thymectomy, and plasmapheresis [3]. The use of cytotoxic immunosuppressive agents, unless combined with plasmapheresis, is not widely reported. There have been reports from other countries, however, of therapeutic success with either cyclophosphamide [7] or azathioprine [1, 4–6]. We report our experience with azathioprine in MG.

Patients and Methods

We reviewed the records of patients with MG who had been treated with azathioprine at the Hospital of the University of Pennsylvania, and analyzed the 24 patients with clinically generalized MG who tolerated azathioprine for at least 6 months or who discontinued azathioprine therapy because of toxicity.

Treatment with azathioprine was begun at a dose of 50 mg/day, with weekly increments of 50 mg until a total dose of 2 to 3 mg per kg of body weight was reached or toxicity necessitated cessation of therapy. A complete blood count and liver function tests were performed prior to therapy and were repeated at three days and then at weekly intervals until the maintenance dose was established. These tests were then repeated every 4 to 6 weeks. No attempt was made to change the white blood count or total lymphocyte count to any predetermined level.

Results

Azathioprine therapy was initiated for a variety of reasons. Eight patients were regarded as treatment failures with prednisone, thymectomy, or both. Ten patients had complications resulting from prednisone treatment (diabetes, cataracts, gastritis, marked weight gain, and myopathy). Preexistent marked obesity, diabetes, and hip osteoarthritis were relative contraindications to the use of prednisone in 3 patients. Two patients refused other forms of therapy, and 1 was thought to be at less risk from azathioprine than prednisone because of his age (74 years).

Eighteen patients were able to tolerate azathioprine for longer than 6 months. Fifteen (83%) definitely improved while receiving azathioprine (Tables 1 and 2), with improvement defined as either a greater than 50% reduction in daily prednisone dosage with or without clinical improvement, or clinical improvement of at least one grade in the Osserman classification [3]. Eight patients (44%) achieved complete pharmacological clinical remissions and became symptom free while receiving azathioprine alone.

The initial clinical response was seen after 4 to 10 months of treatment (mean, 6.4 months). Continued improvement was seen for up to 24 months following the initiation of therapy, with the peak of improvement occurring at a mean of 14 months. In patients requiring prednisone prior to azathioprine therapy, the mean dosage was reduced from 48 to 4.4 mg a day. Responses to azathioprine occurred at dosages ranging from 1.1 to 3.8 mg/kg/day (mean, 2.3 mg/kg/day). Three patients had no definite improvement.

Six patients developed toxicity necessitating cessation of azathioprine treatment (Table 3). In 5 of these toxicity occurred early in therapy. Dose-related toxicity occurred in 4 patients (see Table 3). Two developed transient anemia and leukopenia, and 2 developed mild elevations on liver function tests. These abnormalities resolved at lower doses of azathioprine.

In all 6 patients thus far tapered off azathioprine, relapse has occurred within 3 to 12 months. Five remain on regimens of azathioprine alone in complete pharmacological remission.

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Received July 14, 1983, and in revised form Jan 3, 1984. Accepted for publication Jan 6, 1984.

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Table 1. Response to Azathioprine and Relationship to Other Therapy

Patient No.	Date of Thx	Date of Institution of Therapy		Pred[a]		Mest[a]		Class[b]	
		Pred	Aza	Pre	Post	Pre	Post	Pre	Post
1	10/78	10/78	10/78 (0,0)[c]	25	0	780	0	IIB	0
2	...	3/78	1/80 (...,14)	40	0	750	0	IIB	0
3	9/79	8/79	12/79 (3,4)	40	0	630	0	IIB	0
4	10/77	10/77	8/79 (26,26)	60	0	450	0	IIB	0
5	3/81	9/81	6/82 (15,9)	40	10	830	830	IIA	IIA
6	9/71	1975	10/79 (96,48)	25	10	prn	0	IIA	0
7	5/78	3/78–8/78	1/80 (17,48)	0	0	540	540	IIB	0
8	7/80	7/80	7/80 (0,0)	60	0	600	180	IIA	0
9	6/79	8/79	8/79 (0,2)	40	0	480	0	IIA	I
10	6/77	1973	4/81 (46,94)	25	10	900	900	IIA	0–IIA
11	10/79	11/79	11/79 (1,0)	30	30	1100	0	IIA	0
12	3/78	3/78	5/78 (2,2)	55	0	720	0	IIB	0
13	1/76	7/77	6/78 (30,13)	55	10	900	900	0	0
14	...	...	6/79 (...)	...	...	450	0	IIA	0
15	11/81	4/80	10/82 (11,18)	25	25	600	600	IIA	0

[a]Average daily dose.
[b]Using the Osserman scale [3].
[c]Months from thymectomy to beginning azathioprine therapy, and from prednisone treatment to beginning azathioprine therapy.

Aza = azathioprine; Pred = prednisone; Mest = mestinon; Thx = thymectomy; Pre = before institution of azathioprine therapy; Post = after institution of azathioprine therapy.

Table 2. Thymic Histological Findings and Time Course of Response to Azathioprine

Patient No.	Age (yr)	Sex	Thymic Histology	Peak Dose Tolerated (mg/kg/day)	Time to Response (mo)	
					Initial	Best
1	54	M	Thymoma	2.0	7	14
2	84	M	...[a]	1.9	8	10
3	43	F	Thymoma	3.2	4	14
4	51	F	Thymoma	2.6	10	21
5	69	F	Thymoma	1.5	6	Ongoing
6	36	F	Hyperplasia	2.5	6	9
7	27	F	Involuted	3.8	4	19
8	40	F	Hyperplasia	2.4	6	13
9	32	M	Hyperplasia	2.0	4	4
10	53	F	Normal	2.2	6	Ongoing
11	24	M	Thymoma	2.5	6	8
12	42	F	Thymoma	1.9	7	24
13	55	F	Thymoma	2.3	9	Ongoing
14	58	M	...[a]	1.8	6	9
15	64	M	Thymoma	1.1	2	Ongoing

[a]No thymectomy performed; no evidence of thymoma by radiological criteria [2].

M = male; F = female.

Table 3. Azathioprine Toxicity

Patient No.	Side Effect	Result
5	Decreased WBC at 2.3 mg/kg/day	Resolved at 1.5 mg/kg/day
6	Increased LFT values at 3.1 mg/kg/day	Resolved at 2.5 mg/kg/day
15	Increased LFT values at 1.7 mg/kg/day	Drug temporarily stopped, then restarted at 1.1 mg/kg/day
16	Mild pancytopenia at 3.4 mg/kg/day	Resolved at 2.9 mg/kg/day
19	High fever 1st wk	Drug stopped
20	Increased LFT values at 0.7 mg/kg/day	Drug stopped
21	High fever 1st wk	Drug stopped
22	Cholestatic jaundice at 2.1 mg/kg/day after 4 mo	Drug stopped, with return to normal LFT values
23	Severe pancytopenia at 2.6 mg/kg/day	Drug stopped
24	Increased LFT values at 2.0 mg/kg/day	Drug stopped

WBC = white blood count; LFT = liver function tests.

Discussion

The first large experience with cytotoxic immunosuppressives in the treatment of MG was that of Mertens and colleagues [5], who reported 38 patients treated with a variety of agents (6-mercaptopurine, azathioprine, methotrexate, and actinomycin D). Multimodality therapy was employed, including low-dose azathioprine (100 mg/day). From the data presented it is impossible to separate patients who benefited from azathioprine from those in whom benefit might have resulted at least in part from other therapies. Eighty-four percent, however, were stated to have improved. Matell and associates [4] treated 26 myasthenic patients with azathioprine (2 mg/kg/day) who had not responded to either corticosteroids or ACTH, and noted improvement in 78%. Important factors such as relationship to thymectomy, thymic histological findings, and concurrent use of steroids were not discussed. Mertens and co-workers [6] recently reported 78 patients treated with azathioprine and other agents, of whom 91% showed definite improvement.

Our data are uncontrolled, but they have been carefully analyzed. Failure to improve three years following thymectomy or after 6 months of prednisone treatment, with (1) subsequent improvement on a regimen of azathioprine or (2) relapse following tapering of azathioprine after prior complete pharmacological remission, appears to be reasonable evidence of azathioprine response. Using these criteria, of the 15 patients who improved with azathioprine, 8 patients are definite responders. The responses in others (Nos. 1, 5, 7, 8, 9, 11, and 15) are less certain.

We have used azathioprine predominantly in older patients, avoiding women of childbearing age if at all possible, although there is little evidence to implicate the drug as teratogenic. We also attempted to withdraw therapy periodically in patients in complete pharmacological remission, particularly if thymectomy had been performed: all 6 patients thus managed have relapsed. Mertens and colleagues [6] reported similar results. In patients with a long duration of illness or a surgically proved thymoma, it is likely that long-term immunosuppression will be needed [3, 8], and we do not now advocate withdrawal of therapy.

We noted three types of hepatic toxicity. The first occurred early in therapy and was felt to be idiosyncratic. A second type occurred late, appearing immediately after dosage increments. Liver function test values returned to normal following either a return to the previous dosage or temporary discontinuation and reinstitution at a lower dose. Third, 1 patient developed cholestatic hepatic toxicity after 3 months at a stable dose, illustrating the need for continual monitoring by blood studies in all patients.

Azathioprine is an appropriate therapy for some patients with MG. Rather than as a last resort, azathioprine should be considered early in the course in selected patients when anticholinesterases do not suffice. We have no fixed ages at which we will or will not use azathioprine. Multiple factors, such as age, sex, complicating medical problems, and patient lifestyle, all play a role in the decision to use azathioprine. We recommend azathioprine either as sole immunosuppressive therapy or for its steroid-sparing effects in MG.

Supported by grants from the Muscular Dystrophy Association.

The authors thank Drs Donald Schotland, William Bank, and John Bevilacqua for permitting inclusion of their patients in this study.

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Computed Tomography in Alexander's Disease

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Computed tomography demonstrated contrast-enhancing lesions in the periventricular frontal regions, caudate nuclei, and thalami in an infant with Alexander's disease. The distribution of the enhancing lesions corresponded to the areas in which Rosenthal fibers were most prominent. These radiological findings have not been described in other white matter diseases; thus, they may help to distinguish Alexander's disease from Canavan's disease and decrease the necessity for diagnostic brain biopsy.

Farrell K, Chuang S, Becker LE: Computed tomography in Alexander's disease. Ann Neurol 15:605–607, 1984

Alexander's disease is a progressive, neurodegenerative disorder that can be diagnosed during life only by brain biopsy. We describe a distinctive pattern of contrast enhancement on computed tomographic (CT) scan of an infant with Alexander's disease.

Case Report

The first child, a female, born to a healthy father and an epileptic mother taking phenytoin and phenobarbital was delivered by cesarean section at 43 weeks and weighed 3.2 kg. There was no perinatal asphyxia, and the neonatal period was uneventful. At 4 weeks of age the infant became sleepy and irritable and began to lose weight. At 9 weeks she was admitted to the hospital with vomiting and inability to suck. Her weight was 3.65 kg (below the 3rd percentile), length 58 cm (75th percentile), and head circumference was 38.5 cm (50th percentile). She was bright and alert but did not suck and had poor head control and generalized increase in tone. An unenhanced CT scan at 11 weeks showed mild to moderate enlargement of both lateral ventricles, with normal white and gray matter densities (Fig 1A). Following contrast en-

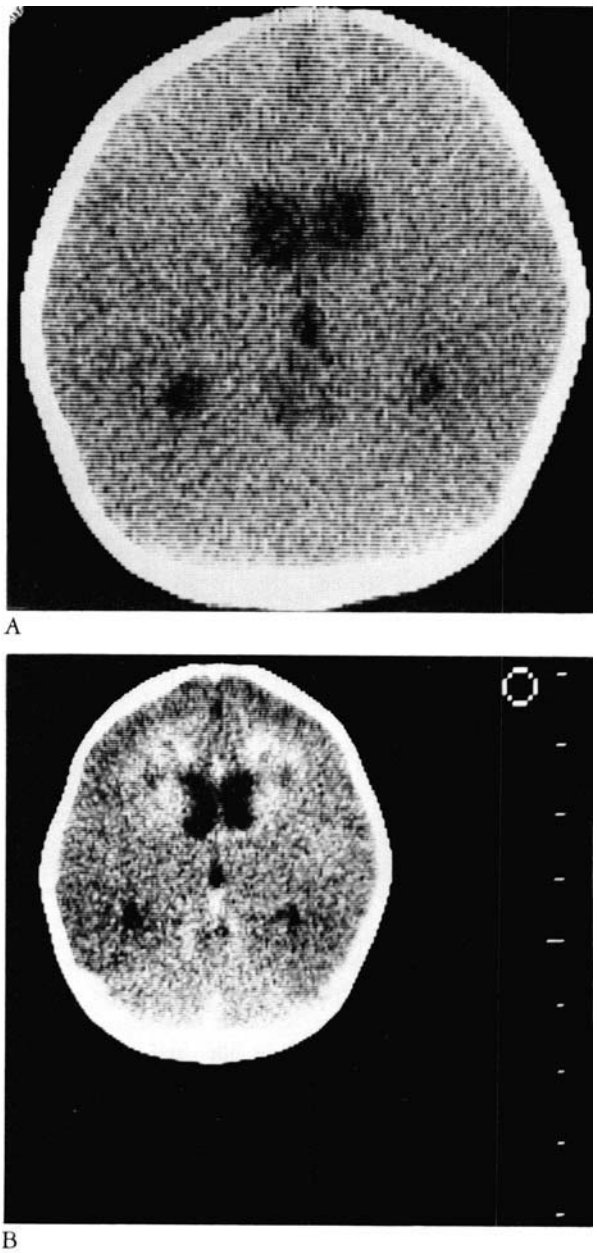

Fig 1. (A) Unenhanced axial computed tomographic (CT) scan with Ohio Nuclear Delta 50, showing slight dilatation of the frontal horns with normal gray and white matter densities. (B) Enhanced axial CT scan demonstrating enhancement in the white matter of the frontal horns as well as the head of the caudate nuclei. The enhancement of the thalami is not shown on this particular level.

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Received June 13, 1983, and in revised form Oct 7. Accepted for publication Nov 13, 1983.

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