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Efficacy of azathioprine and mycophenolate mofetil in acetylcholine receptor antibody positive generalized myasthenia gravis patients

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Abstract

Background & Objective: Corticosteroids are the first-line immunosuppressive drug. Azathioprine and mycophenolate mofetil are commonly used as steroid-sparing agents or additional immunosuppressive drugs. However, the efficacies of azathioprine and mycophenolate mofetil are lacking, especially in acetylcholine receptor antibody-positive generalized myasthenia gravis patients (AChR Ab-positive generalized MG). The objectives are firstly to determine the efficacy of azathioprine in AChR Ab-positive generalized MG patients; and secondly to determine the efficacy of mycophenolate mofetil in patients who did not respond or were intolerant to azathioprine. *Methods:* A retrospective study of AChR Ab-positive generalized MG patients who were treated with prednisolone in combination with azathioprine and who had switched treatment from azathioprine to mycophenolate mofetil was conducted. Treatment response and adverse effects were evaluated. *Results:* Of 105 patients, 95 patients (90.5%) could tolerate and respond to prednisolone in combination with azathioprine, 6 patients (5.7%) had adverse effects, and 4 patients (3.8%) did not respond to azathioprine. Patients who had adverse effects or did not respond to azathioprine were switched to mycophenolate mofetil. Of the 105 patients, 7.6% had MGFA Post-intervention Status (MGFA-PIS) at the last follow-up or before switching from azathioprine to mycophenolate mofetil as Complete Stable Remission (CSR), 2.9% as Pharmacologic Remission (PR), 10.5% as Minimal Manifestations -1 (MM-1), 30.4% as MM-2, 48.6% as MM-3 and the median Medical Research Council (MRC) sum score was 60.0 points. Ten of the 105 patients were switched from azathioprine to mycophenolate mofetil. MGFA-PIS was better after switching treatments in these ten patients than that before the switching.
Conclusion: This study supports the efficacy and safety of azathioprine as an additional immunosuppressive drug in combination with prednisolone for treatment in AChR Ab-positive generalized MG patients. Mycophenolate mofetil can be considered as alternative immunosuppressive drug for patients who cannot tolerate adverse effects or have no response to azathioprine.

Keywords: Acetylcholine receptor antibody, generalized myasthenia gravis, azathioprine, mycophenolate mofetil.

INTRODUCTION

Myasthenia gravis (MG) is the most common autoimmune neuromuscular junction disorder caused by immunoglobulin G (IgG) autoantibodies against acetylcholine receptors. Approximately 85% of generalized MG patients had antibodies against acetylcholine receptors (AChR Ab), 5% against muscle-specific kinase (MuSK Ab), and 10% against low-density lipoprotein receptor-4 (LRP-4 Ab), agrin, or undetectable autoantibodies.[1-3]

Based on the international consensus guideline for managing MG, corticosteroids have been used as the first-line immunosuppressive drug. Additional immunosuppressive drugs, such as azathioprine, mycophenolate mofetil, methotrexate, cyclophosphamide, and rituximab, were considered when 1) high-dose or long-term corticosteroids are needed as steroid-sparing agents. 2) corticosteroids alone are ineffective. and 3) patients have adverse effects or contraindications for corticosteroids.[4-8]

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In previous studies, 30 to 80% of generalized MG patients using azathioprine combined with prednisolone had remission with few side effects.[9,10] Another randomized controlled trial showed the benefit of azathioprine combined with prednisolone in acetylcholine receptor antibody-positive generalized myasthenia gravis patients (AChR Ab-positive generalized MG). This combination reduced prednisolone dosage, increased remission, and had fewer side effects.[11] However, the efficacy of azathioprine and prednisolone compared with prednisolone was unclear in another study.[12] Even though azathioprine is well tolerated, many patients have not responded to azathioprine, and adverse effects have been reported.[9-11] In these conditions, other immunosuppressive drugs such as mycophenolate mofetil, methotrexate, cyclophosphamide, or rituximab have been recommended.[4-7] In the previous observational studies, using mycophenolate mofetil has shown clinical improvement, remission, prednisolone dosage reduction, and fewer side effects.[13-15] However, two randomized controlled trials in AChR Ab-positive generalized MG patients did not show a benefit of mycophenolate mofetil combined with prednisolone over prednisone alone.[16,17]

Many studies have demonstrated the benefit of azathioprine and mycophenolate mofetil in generalized MG patients.[9-11,13-15] However, only a few studies have been performed in AChR Ab-positive generalized MG patients[11,15] and some studies have not demonstrated the benefit of mycophenolate mofetil in AChR Ab-positive generalized MG patients.[16,17] The evidence for the efficacy of azathioprine and mycophenolate mofetil in AChR Ab-positive MG patients is still limited. The primary goal of this study was to determine the effectiveness of azathioprine in AChR Ab-positive generalized MG. The secondary goal was to assess the efficacy of mycophenolate mofetil in AChR Ab-positive generalized MG patients who did not respond or were intolerant to azathioprine.

METHODS

After Institutional Review Board (IRB) approval, a retrospective study was conducted at the Neurological Institute of Thailand. Medical records of myasthenia gravis (MG) patients from 1st January 2014 to 31st December 2023 were reviewed. Inclusion criteria were 1) generalized MG patients with positive Acetylcholine receptor antibody (AChR Ab), 2) patients who received treatment and follow-up at our institute, and 3) patients who never received any immunosuppressive drugs. Ocular MG patients, MuSK Ab-positive MG patients, or seronegative MG patients were excluded. Once AChR Ab-positive generalized MG patients were identified, the medical records were reviewed to assess demographic features, clinical manifestations, Myasthenia Gravis Foundation of America (MGFA) clinical classification, disease duration before treatment, disease severity, Medical Research Council (MRC) scale for muscle strength, follow-up duration, treatment response, and adverse effects. MGFA post-intervention status (MGFA-PIS) and MRC sum score were used to evaluate the clinical status of MG patients after treatment.[18] MGFA clinical classification divided MG patients into 5 main subgroups (classes I-V) based on clinical features and disease severity.

All patients in the present study started treatment with pyridostigmine and prednisolone in combination with azathioprine. The dose of medication was adjusted by the attending physicians depending on disease symptoms and disease severity. Treatment response was defined by the improvement of symptoms, medication dosage, and MGFA post-intervention status (MGFA-PIS).[18] MGFA-PIS was used to evaluate the clinical changes in MG patients after treatment based on 1) disease activity and medication as Complete Stable Remission (CSR), Pharmacologic Remission (PR), Minimal Manifestations (MM 0-3) and 2) changes in clinical status as improved, unchanged and worse. MGFA-PIS is shown in Supplement Figure 1. Patients who were clinically unchanged or worse after receiving azathioprine were classified as not responding and were switched to mycophenolate mofetil. Also, patients with adverse events from azathioprine were switched to mycophenolate mofetil. In patients who received azathioprine and prednisolone, treatment response was evaluated at the first evaluation and the last visit or before switching from azathioprine to mycophenolate mofetil. In patients who switched from azathioprine to mycophenolate mofetil, treatment response was evaluated at the time before stopping azathioprine and at the last visit after receiving mycophenolate mofetil.

Statistical analysis

Descriptive summaries were presented as frequencies and percentages for categorical variables, or median/mean, and ranges for continuous variables. Comparisons between study

groups were performed using Fisher's exact test or Wilcoxon rank sum test, as appropriate. All tests were two-sided, and p-values less than 0.05 were statistically significant. Statistical analyses were performed using SPSS for Windows version 16.0.

RESULTS

Demographic characteristics

One hundred and five AChR Ab-positive generalized MG patients were identified. The demographic and clinical characteristics are shown in Table 1. Of 105 patients, 71 (67.6%) were women, and 34 (32.4%) were men. The mean age at onset was 45.7 years (SD 15.9). Disease duration before evaluation and treatment was 94 days (IQR 29,365). A repetitive stimulation test was performed in 91 patients and showed a decremental pattern in 81 patients (89%). CT chest was done in 88 patients, 66 (75%) were normal, 4 (4.5%) were thymic hyperplasia, and 18 (20.5%) were thymoma. For clinical manifestation at the first evaluation, 92 patients (87.6%) had ptosis, 60 (57.1%) diplopia, 85 (81.0%) bulbar weakness, 12 (11.4%) respiratory failure, and 94 (89.5%) proximal muscle weakness. The median MRC sum

Table 1: The demographic and clinical characteristics of AChR Ab-positive generalized MG patients

	Total (N = 105)
Gender (n; %)	
Male	34 (32.4)
Female	71 (67.6)
Age at onset (years; mean, SD)	45.7 (15.9)
Disease duration (days; median, IQR 25,75)	94.0 (29.0, 365.0)
AChR Ab positivity (n; %)	105 (100.0)
RNS - decremental pattern (n; %)	81/91 (89.0)
CT chest (n; %)	
Normal	66/88 (75.0)
Thymic hyperplasia	4/88 (4.5)
Thymoma	18/88 (20.5)
Clinical manifestation at 1st visit (n; %)	
Ptosis	92 (87.6)
Ophthalmoparesis	60 (57.1)
Bulbar weakness	85 (81.0)
Respiratory failure	12 (11.4)
Proximal muscle weakness	94 (89.5)
MRC sum score (points; median, IQR 25,75)	56.0 (51.0,58.0)
MGFA Clinical classification (n; %)	
IIa	18 (17.1)
IIb	65 (61.9)
IIIa	3 (2.9)
IIIb	7 (6.7)
V	12 (11.4)
Medication at the early treatment (mg/day; median, IQR 25,75)	
Prednisolone	40.0 (27.5, 50.0)
Azathioprine	100.0 (100.0, 100.0)
Pyridostigmine	240.0 (180.0, 240.0)
Thymectomy (n; %)	55 (52.4)
Follow-up duration (years; median, IQR 25,75)	4.4 (2.4, 7.3)

AChR - Acetylcholine Receptor, RNS – repetitive nerve stimulation test, MRC sum score - Medical Research Council (MRC) sum score, MGFA - Myasthenia Gravis Foundation of America

score at the first evaluation was 56 points (IQR 51, 58). For MGFA Classification at the initial assessment, 18 patients (17.1%) were class IIa, 65 (61.9%) class IIb, 3 (2.9%) class IIIa, 7 (6.7%) class IIIb, and 12 (11.4%) class V. During the study, 31 patients (29.5%) had myasthenic crisis, and all patients received IVIg or plasmapheresis for the rescue therapy.

In the early treatment period, all patients received azathioprine in combination with prednisolone as immunosuppressive treatment. Ninety-five patients (90.5%) could tolerate and had a response to azathioprine. However, 10 patients (9.5%) had to switch from azathioprine to mycophenolate mofetil because of adverse effects in 6 patients (5.7%) and no response to azathioprine in 4 patients (3.8%). For the adverse effect, 4 patients (3.8%) had transaminitis, and 2 patients (1.9%) had leukopenia.

Treatment response in patients receiving azathioprine and prednisolone

The treatment response of 105 patients who received azathioprine and prednisolone is shown in Table 2. The follow-up duration was 4.2 years (IQR 2.5, 7.3). Of patients with the symptoms, ptosis improved in 64.5%, diplopia in 77.4%, bulbar weakness in 77.0%, and motor weakness in 88.2%. The median MRC sum scores before and after treatment were 54.0 and 60.0 points. At the last follow-up, 55 patients (52.4%) had no proximal muscle weakness, ptosis, diplopia, or bulbar weakness. Twenty-nine patients (27.6%) had no proximal muscle weakness but still had ptosis, diplopia, bulbar weakness, or in combination. However, 21 patients (20.0%) still had proximal muscle weakness (MRC sum score range 48-58 points). MGFA-PIS at the last follow-up was 7.6% CSR, 2.9% PR, 10.5% MM-1, 30.4% MM-2, and 48.6% MM-3.

The medication dosage was adjusted based on clinical response. If symptoms were improved, the medication dosage was reduced. Regarding the medication dosage, at the last follow-up or before switching from azathioprine to mycophenolate mofetil, 85.7% of 105 patients could reduce prednisolone dosage, 42.9% could reduce azathioprine dosage, and 64.8% could reduce pyridostigmine dosage.

Treatment response in patients switching from azathioprine to mycophenolate mofetil

The treatment response in 10 patients who switched from azathioprine and mycophenolate mofetil is shown in Table 3. The median total follow-up duration in this group was 5.4 years (IQR 1.3, 7.3). The median treatment duration before switching was 1.1 years (IQR 0.4, 4.3). When comparing clinical data before and after the switch from azathioprine to mycophenolate mofetil, 8 patients had proximal muscle weakness during receiving azathioprine and 7 patients (87.5%) were improved after receiving Mycophenolate Mofetil. Of these 7 patients, 4 had no proximal muscle weakness and 3 patients had some degree of proximal muscle weakness (MRC sum score range 52-58 points). Three of 9 patients (33.3%) had improvement in ptosis. Three of 8 patients (37.5%) had improvement in diplopia. Six of 10 patients (60%) had improvement in bulbar weakness. The MRC sum score before and after switching were 58.0 and 60.0 points.

Based on MGFA-PIS, 10% of patients were MM-2 and 90% were MM-3 before switching. After switching, 40% of patients were MM-2 and 60% were MM-3. Regarding the dose of medications, after switching from azathioprine to mycophenolate mofetil, 70.0% of patients could reduce prednisolone dosage and 40% could minimize pyridostigmine dosage. There was no profound adverse effect in patients receiving mycophenolate mofetil.

DISCUSSION

The goal of treatment for generalized myasthenia gravis (MG) patients is to control disease activity, decrease the severity of symptoms, and achieve remission. The recommended treatments are anticholinesterase inhibitors, corticosteroids, immunosuppressive drugs, and thymectomy in AChR Ab-positive generalized MG patients.[4-6]

Immunosuppressive drugs are one of the important treatments for reaching this goal. Their mechanism is suppressing the autoantibodies against acetylcholine receptors or clustering proteins in synaptic clefts. The international consensus guideline for managing MG recommended corticosteroids as the first-line immunosuppressive drug. Conventional immunosuppressive drugs such as azathioprine, mycophenolate mofetil, methotrexate, and cyclophosphamide were considered additional immunosuppressive drugs or steroid-sparing agents.[4-8]

The efficacy of corticosteroids alone or in combination with other immunosuppressive drugs has been shown in previous studies.[9,10,13-15] However, in clinical practice, it is difficult

Table 2: Treatment response of AChR Ab-positive generalized MG patients

Symptoms	Improve	Worse	Unchanged	At start treatment (N = 105)	Last follow-up/ Before switch to MMF (N = 105)
Ptosis (n; %)	60/93 (64.5)	1/93 (1.1)	32/93 (34.4)	-	-
Ophthalmoparesis (n; %)	48/62 (77.4)	2/62 (3.2)	12/62 (19.4)	-	-
Bulbar weakness (n; %)	67/87 (77.0)	2/87 (2.3)	18/87 (20.7)	-	-
Motor weakness (n; %)	82/93 (88.2)	7/93 (7.5)	4/93 (4.3)		
MRC sum score (points.; median, IQR 25,75)	-	-	-	54.0 (50.0, 58.0)	60.0 (60.0, 60.0)
MGFA-PIS (n; %)					
CSR	-	-	-	-	8 (7.6)
PR	-	-	-	-	3 (2.9)
MM-0	-	-	-	-	0 (0)
MM-1	-	-	-	-	11 (10.5)
MM-2	-	-	-	-	32 (30.4)
MM-3	-	-	-	-	51 (48.6)
Medication	**Decreased dosage**	**Increased dosage**	**Unchanged dosage**	**At start treatment (N = 105)**	**Last follow-up/ Before switch to MMF (N = 105)**
Prednisolone (n; %)	90/105 (85.7)	0/105 (0)	15/105 (14.3)	-	-
Prednisolone (mg/day; median, IQR 25,75)	-	-	-	40 (27.5, 50)	5 (0, 20)
Azathioprine (n; %)	45/105 (42.9)	1/105 (1.0)	59/105 (56.1)	-	-
Azathioprine (mg/day; median, IQR 25,75)	-	-	-	100 (100, 100)	100 (25, 100)
Pyridostigmine (n; %)	68/105 (64.8)	2/105 (1.9)	35/105 (33.3)	-	-
Pyridostigmine (mg/day; median, IQR 25,75)	-	-	-	240 (180, 240)	180 (60, 180)

MRC sum score - Medical Research Council (MRC) sum score, MGFA - Myasthenia Gravis Foundation of America, CSR - Complete Stable Remission, PR - Pharmacologic Remission, MM - Minimal Manifestations, MMF - Mycophenolate Mofetil

to achieve remission. Most patients achieved minimal manifestations (MM), and some were refractory to treatment.[19,20] The previous studies used corticosteroids alone or combined with other immunosuppressive drugs in MG patients, 1 to 2.4% achieved CSR, 74.8 to 88 % achieved MM, and 2.4 to 5% did not respond to treatments.[19,20] However, long-term use of these immunosuppressive drugs had side effects, and approximately 2.4 -15% of the patients did not respond to the treatments.[19-22]

Table 3: Treatment response after switching from Azathioprine to Mycophenolate Mofetil in AChR Ab-positive generalized MG patients

Symptoms	Improve	Worse	Unchanged	Before switch to MMF (N = 10)	After switch to MMF (N = 10)
Ptosis (n; %)	3/9 (33.3)	0/9 (0)	6/9 (66.7)	-	-
Ophthalmoparesis (n; %)	3/8 (37.5)	2/8 (25.0)	3/8 (37.5)	-	-
Bulbar weakness (n; %)	6/10 (60.0)	0/10 (0)	4/10 (40.0)	-	-
Motor weakness (n; %)	7/8 (87.5)	0/8 (0)	1/8 (12.5)		
MRC sum score (points.; median, IQR 25,75)	-	-	-	58.0 (48.0, 58.5)	60.0 (56.5, 60.0)
MGFA-PIS (n; %)					
CSR	-	-	-	0 (0)	0 (0)
PR	-	-	-	0 (0)	0 (0)
MM-0	-	-	-	0 (0)	0 (0)
MM-1	-	-	-	0 (0)	0 (0)
MM-2	-	-	-	1 (10.0)	4 (40.0)
MM-3	-	-	-	9 (90.0)	6 (60.0)
Medication	**Decreased dosage**	**Increased dosage**	**Unchanged dosage**	**Before switch to MMF (N = 10)**	**After switch to MMF (N = 10)**
Prednisolone (n; %)	7 (70.0)	1 (10.0)	2 (20.0)	-	-
Prednisolone (mg/day; median, IQR 25,75)	-	-	-	50 (37.5, 60)	22.5 (0, 32.5)
Mycophenolate Mofetil (n; %)	3/10 (30.0)	1/10 (10.0)	6/10 (60.0)	-	-
Mycophenolate Mofetil (mg/day; median, IQR 25,75)	-	-	-	1,000 (1,000, 1,125)	1,000 (375, 1,125)
Pyridostigmine (n; %)	4 (40.0)	3 (30.0)	3 (30.0)	-	-
Pyridostigmine (mg/day; median, IQR 25,75)	-	-	-	210 (180, 240)	180 (60, 255)

MRC sum score - Medical Research Council (MRC) sum score, MGFA - Myasthenia Gravis Foundation of America, CSR - Complete Stable Remission, PR - Pharmacologic Remission, MM - Minimal Manifestations, MMF - Mycophenolate Mofetil

The present study supports the efficacy and safety of azathioprine in combination with prednisolone in AChR Ab-positive generalized MG patients. Most patients can tolerate and respond to azathioprine; 90.5% of the 105 patients in this study received azathioprine in combination with prednisolone from the early treatment period until the last follow-up. In the patients receiving azathioprine combined with prednisolone, most of the patients had a good response to treatment; 7.6% achieved CSR, 2.9% PR, 10.5% MM – 1, 30.4% MM - 2, and 48.6% MM – 3. Complete remission (CSR) in the present study was slightly higher than in the previous study.[19,20] However, the manifestations (MM) were not significantly different. Adverse effects were found in 5.7 % of the 105 patients and severe opportunistic infection was not found in the present study.

The previous study showed the efficacy of azathioprine and mycophenolate mofetil in MG patients by improving their quality of life. No difference in clinical outcomes was observed between azathioprine and mycophenolate mofetil groups. However, adverse events were more severe in azathioprine than mycophenolate mofetil.[23] The present study also showed the efficacy and

safety of mycophenolate mofetil combined with prednisolone in AChR Ab-positive generalized MG patients. Many patients had clinical improvement after switching the medication based on the improvement of proximal muscle weakness, ptosis, diplopia, bulbar weakness, MRC sum score, and MGFA-PIS. Serious adverse effects of Mycophenolate Mofetil were not found in the present study. However, the number of patents in the switching group was too small, and it was insufficient to demonstrate the efficacy of mycophenolate mofetil over azathioprine, but it supports the role of mycophenolate mofetil as an alternative immunosuppressive drug in AChR Ab-positive generalized MG patients who cannot tolerate the adverse effect or did not respond to azathioprine.

Limitations of the present study; muscle weakness in MG usually fluctuates so the Myasthenia Gravis Composite (MGC) score is more suitable than the MRC sum score for evaluating Muscle weakness in MG patients. Because this study was a retrospective observational study, the information for the Myasthenia Gravis Composite (MGC) score was lacking. The second limitation was the variation in treatment dosage which depends on the decisions of attending neurologists. The third limitation was a small sample size in the switching group, resulting in statistical power inadequacy to demonstrate the efficacy of mycophenolate mofetil.

In conclusion, the present study supports the efficacy and safety of azathioprine as an additional immunosuppressive drug in combination with prednisolone for treatment in AChR Ab-positive generalized MG patients. Most patients can tolerate and achieve minimal manifestations (MM). For patients who cannot tolerate adverse effects or have no response to azathioprine, mycophenolate mofetil could be considered as an alternative immunosuppressive drug.

DISCLOSURE

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Supplement Figure 1 : MGFA Post-intervention Status (MGFA-PIS)

Complete Stable Remission (CSR) - The patient has had no symptoms or signs of MG for at least 1 year and has received no therapy for MG during that time. There is no weakness of any muscle on careful examination by someone skilled in the evaluation of neuromuscular disease. Isolated weakness of eyelid closure is accepted.
Pharmacologic Remission (PR) - The same criteria as for CSR except that the patient continues to take some form of therapy for MG. Patients taking cholinesterase inhibitors are excluded from this category because their use suggests the presence of weakness.
Minimal Manifestations (MM) - The patient has no symptoms of functional limitations from MG, but has some weakness on examination of some muscles. This class recognizes that some patients who otherwise meet the definition of CSR or PR do have weakness that is only detectable by careful examination.
MM-0 - The patient has received no MG treatment for at least 1 year.
MM-1 - The patient continues to receive some form of immunosuppression, but no cholinesterase inhibitors or other symptomatic therapy.
MM-2 - The patient has received only low-dose cholinesterase inhibitors (<120 mg pyridostigmine/day) for at least 1 year.
MM-3 - The patient has received cholinesterase inhibitors or other symptomatic therapy and some form of immunosuppression during the past year.

Change in Status
Improved (I) - A substantial decrease in pretreatment clinical manifestations or a sustained substantial reduction in MG medications as defined in the protocol. In prospective studies, this should be defined as a specific decrease in QMG score.
Unchanged (U) - No substantial change in pretreatment clinical manifestations or reduction in MG medications as defined in the protocol. In prospective studies, this should be defined in terms of a maximum change in QMG score.
Worse (W) - A substantial increase in pretreatment clinical manifestations or a substantial increase in MG medications as defined in the protocol. In prospective studies, this should be defined as a specific increase in QMG score
Exacerbation (E) - Patients who have fulfilled criteria of CSR, PR, or MM, but subsequently developed clinical findings greater than permitted by these criteria.
Died of MG (D of MG) - Patients who died of MG, of complications of MG therapy, or within 30 days after thymectomy.