Methotrexate Use in Generalized Autoimmune Myasthenia Gravis: A Case Series

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ABSTRACT

Methotrexate (MTX) is an inexpensive and well-tolerated immunosuppressive medication that is used anecdotally in autoimmune myasthenia gravis (MG). However, the efficacy in MG is unclear at this time. This retrospective analysis describes six patients with acetylcholine receptor antibody-positive MG who were treated with MTX and corticosteroids. The efficacy of MTX was measured by steroid-sparing effect and the Myasthenia Gravis Foundation of America (MGFA) classification. MTX initiation was associated with a reduction in prednisone dosage in all patients. Minimal manifestation status was reached at an average duration of 10 months in 5 patients. No patients were hospitalized for myasthenia gravis exacerbations. There were no major side effects experienced with MTX use. This retrospective analysis suggests that MTX is safe and probably efficacious as a corticosteroid-sparing agent in the management of MG.

Keywords: *Myasthenia gravis, Methotrexate, Immunosuppression, Corticosteroid, Acetylcholine receptor antibody*

Introduction

Autoimmune myasthenia gravis (MG) is a disorder of neuromuscular junction transmission characterized by T-cell mediated destruction of the post-synaptic membrane acetylcholine receptor. Treatment often necessitates the use of immunosuppressant medications including corticosteroids and corticosteroid-sparing agents.[1] Azathioprine (AZA) and mycophenolate are the two most common medications used in the United States for this purpose and are considered first-line corticosteroid-sparing agents.[2-3] Choices after these two medications are unclear and may include eculizumab, cyclosporine, tacrolimus, or methotrexate (MTX). MTX has been used for over 50 years in various clinical indications with anecdotal evidence of positive efficacy in MG. However, studies on its efficacy in MG have generated conflicting results.[4-6] The objective of this study is to describe our experience of using MTX in a small group of patients with generalized MG.

Methods

This retrospective analysis includes six patients with acetylcholine receptor (AChR) antibody-positive MG who were treated with oral MTX and prednisone at the Cleveland Clinic Neuromuscular Center between May 2006 and July 2020. Patients were selected from the myasthenia gravis database curated at the Cleveland Clinic Neuromuscular Center. Outcomes assessed included daily prednisone dosage, MTX dosage, Myasthenia Gravis Foundation of America (MGFA) classification[7] at 6-month intervals, intravenous immune globulin (IVIG) or plasmapheresis usage, hospitalizations for MG exacerbation or crisis, earliest time to reach minimal manifestation status, and earliest time to cessation of prednisone. MTX dosing and any side effects documented are recorded. The study was approved by our institutional review board.

Results

Six MG patients, four females and two males, were included (Table 1). All patients were positive for AChR antibodies. The average age of onset of MG was 57 years (range: 32 to 87 years). In three patients, MTX was started following an average disease duration of 7 years (range: 2 to 16 years). In two patients, MTX was started at the time of MG diagnosis. In the remaining patient, MTX was started for rheumatoid arthritis and was continued after MG diagnosis was made 7 years later. Two patients underwent thymectomy. Four patients received prior immunosuppression (prednisone, tacrolimus, azathioprine, mycophenolate, and cyclosporine). Coexisting autoimmune conditions were present prior to MG diagnosis in four patients (systemic lupus erythematosus, rheumatoid arthritis, psoriasis). The average duration of follow-up was 65 months from MTX initiation. Four patients were on MTX for coexisting autoimmune conditions (Table 1).

Minimal manifestation status (MMS) was achieved in five patients. The time from MTX initiation to reach minimal manifestation status was 9.6 months (range: 1-26 months). The remaining patient was classified as MGFA 2b throughout the study. One patient was given monthly IVIG concurrently with the first three months of MTX use. Following MTX initiation, no hospitalizations for MG exacerbation occurred in any patient. A mild exacerbation occurred in one patient that required a brief reintroduction of prednisone from months 19-24 at 10mg with successful taper to 2.5 mg daily over the subsequent 2 years. In four patients, prednisone was discontinued with the average

Table 1. Demographics and immunosuppressant usage

Patient	Sex	MG Onset age (years)	MGFA Classification at initiation of MTX	Prednisone dose (mg/d) at initiation of MTX	Maximal MTX dose (mg)	Final MTX dose (mg)	Thymectomy	Immunosuppressant usage prior to MTX	Coexisting autoimmune conditions
1	F	32	IIb	7	22.5	20	Yes	P, C	SLE
2	F	44	IIb	0	25	25	No	T, A, MM, P	None
3	M	67	I	20	20	20	Yes	MM, A, C	RA
4	M	87	IIa	40	15	15	No	None	Psoriasis
5	F	51	IIa	20	12.5	12.5	No	None	RA, Celiac
6	F	72	I	30	19	10	No	A, MM	None

Abbreviations: A, azathioprine; C, cyclosporine; F, female; M, male; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; MM, mycophenolate mofetil; MTX, methotrexate; P, prednisone; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; T, tacrolimus

time to cessation being 10.8 months (range 9-12 months). In one patient, prednisone daily dosage was less than 7.5 mg throughout the study and the remaining patient was placed on MTX monotherapy. The prednisone daily dosage was <7.5mg by month 7 following MTX initiation in all patients (Figure 1). The average MTX dose at the final visit was 17mg weekly (range 10-25mg). All patients tolerated MTX well and the only side effects noted in two patients included mild transaminitis and diarrhea, without the need of adjusting MTX dosage.

Discussion

In this small retrospective study, the efficacy and corticosteroid sparing effects of MTX were noted without significant side effects. The prednisone daily dosage was <7.5mg by month 7 following MTX initiation in all patients, representing an efficient dosage reduction. In a similar fashion, minimal manifestation status was achieved in 9.6 months in 5 of 6 patients which is a major clinical milestone to attain. Four patients were on MTX for other autoimmune conditions prior to their MG diagnosis, representing a clinical situation that is not uncommon. Furthermore, patients did not require hospitalization or rescue IVIG/plasmapheresis despite having a typical MG severity prior to treatment. Our experience indicates that MTX can likely be continued together with low dose prednisone or as monotherapy with good control of MG symptoms.

The use of MTX in the treatment of MG was initially reported in 1969,[8] but is now regaining interest with positive anecdotal evidence. Our findings are consistent with several

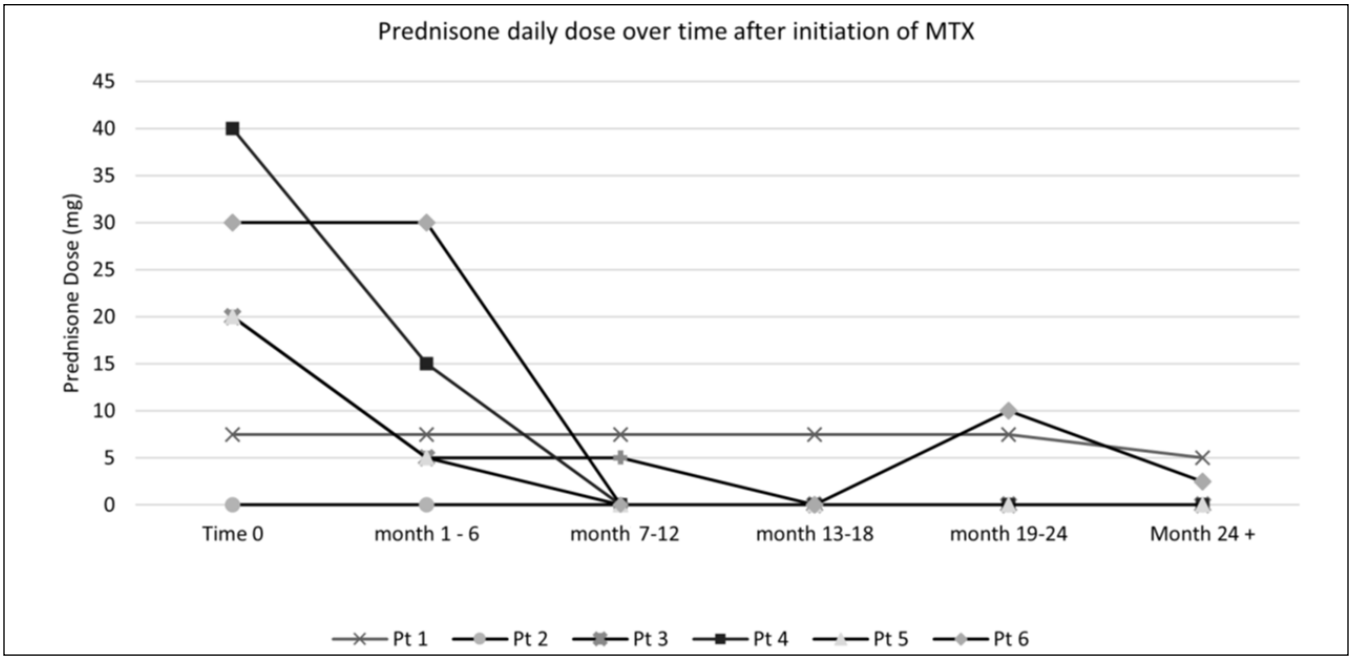

Figure 1. Change of prednisone daily dose over time following MTX initiation

small studies. For example, Karaahmet *et al.* described improvement in 3 patients with MG and rheumatoid arthritis after MTX treatment.[4] In a larger single-blinded trial, Heckmann *et al.* randomized 24 generalized MG patients to receive azathioprine or MTX in addition to prednisone for 24 months.[5] This included predominantly newly-diagnosed patients with MGFA class II-V (86% MGFA III-V) disease. The average prednisone dosage was reduced by more than 50% in both groups with no significant difference in the frequency of relapse and remission. This study suggested MTX and AZA are similarly effective in the treatment of generalized MG.

Pasnoor *et al.* completed a randomized, placebo-controlled trial of 50 generalized MG patients who were on stable doses of prednisone with a median dose of 20mg per day.[6] In contrast to the study by Heckmann *et al.*,[5] they found that the addition of MTX for 12 months versus placebo resulted in no difference in the average daily prednisone dose between the two groups from months 4 to 12. However, the study may have been limited by the inclusion of patients with mild severity (MGFA II and III) and a short study duration.

The major limitations of this single center case series primarily relates to the small sample size and retrospective design. The lack of any prospective data collection or control group limits the generalizability of our conclusions. Nevertheless, our data seem to support that MTX can be used in special situations as a corticosteroid sparing agent in the management of MG, especially for those who have coexisting rheumatological conditions. Future controlled prospective studies would help clarify whether MTX can serve as an effective steroid-sparing agent by employing a larger study group over longer study period.

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