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Is Methotrexate (MTX) an effective treatment in partially or totally reducing the symptoms of Myasthenia Gravis (MG) patients?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not Methotrexate (MTX) is an effective treatment in partially or totally reducing the symptoms of Myasthenia Gravis (MG) patients.

STUDY DESIGN: Review of three English language studies; one Case Series Study following 3 patients with concomitant MG and Rheumatoid Arthritis treated with MTX published in 2014, one Single-Blind Randomized Control Trial (RCT) comparing MTX and AZA (Azathioprine) published in 2011, and one Double-blind, placebo-controlled Randomized Control Trial published in 2016.

DATA SOURCES: Three primary research studies published in peer reviewed journals; found on the PubMed database. Each study's results included patient oriented outcomes that were relevant to this selective EBM review.

OUTCOMES MEASURED: Each study assessed the MG outcomes and quality of life measures after treatment with Methotrexate. The two RCTs used the following assessment tools to quantify their outcomes: Quantitative MG (QMG) Score, Manual Muscle Testing (MMT), MG Quality of Life (MGQOL), MG-Activities of Daily Living (MG-ADL), Minimum Manifestations Status (MMS), and MG Composite Change.

RESULTS: The Case Series Study showed an association between MTX and improved MG symptoms; however it did not show cause and effect. The Single-Blind RCT compared MTX and AZA (enrollment: AZA n = 15; MTX n = 16). Similarities between both groups were found in regards to MMS after 24 months (AZA n = 7; MTX n = 9; p = 0.83; ABI = .03; NNT = 34), and safety; giving promise to MTX's efficacy. The Double-blind, placebo-controlled RCT (enrollment: MTX n = 25; Placebo n = 25) found MTX did not improve QMG, MMT, MGQOL, MG-ADL, or MG Composite Change over 12 months. Withdrawals: Placebo n = 7; MTX n = 1; no serious MTX-related adverse events were encountered. Both RCT's data was determined to be not statistically significant due to small enrollment size. P-values were >0.05 and 95% CI were too wide to be precise.

CONCLUSION: Based on the Case Series Study and two RCTs, MTX is not an effective treatment in partially or totally reducing the symptoms of MG patients.

KEY WORDS: Myasthenia Gravis, Methotrexate

INTRODUCTION

Myasthenia gravis (MG) is a chronic autoimmune neuromuscular condition associated with weakness and fatigability of voluntary skeletal muscles of the body[3]. Muscles most commonly affected control eye movement, the eye lids, chewing, swallowing, coughing and facial expressions; less commonly affected are the muscles used to control breathing and the movement of extremities[6]. This review evaluates one Case Series Study and two Randomized Control Trials (RCTs) which study Methotrexate (MTX) to determine if it can reduce or eliminate the symptoms of MG patients.

It is estimated that 20 out of every 100,000 individuals in the United States have been diagnosed with MG; this equates to approximately 60,000 people. MG is believed, however, to be a significantly underdiagnosed disease and the prevalence is probably much higher.[6]

In a 2009 study, costs related to the treatment of MG were higher than those of other chronic neurological diseases. The average total annual health plan cost for MG patients was $20,190. $15,675 of which was attributed to the treatment of MG. Match-paired controls had an average total annual health plan cost of only $4,515. The MG annual costs were broken down as follows: 23% in Home Health (includes IVIg costs), 17% in MD office visits, 8% in Pharmacy costs (does not include IVIg costs), 27% in Inpatient services, and 23% in Outpatient services. Total annual MG-related pharmacological costs were $9.4 million. Pharmacological costs were as follows: 85% IVIg, 9.3% non-steroidal immunosuppressants, 5.7% cholinesterase inhibitors, and 0.2% corticosteroids.[7]

MG's muscle weakness is due to circulating antibodies which are produced by plasma cells, part of the body's own immune system, which block or destroy as much as 80% of

acetylcholine receptors at the postsynaptic junctions. This leads to the inhibition of skeletal muscle contractions.[3,6] Common symptoms include ptosis, blurred vision, diplopia, dysphonia, difficulty chewing, dysphagia, extremity weakness, muscle fatigue and dyspnea. Muscle weakness tends to increase with continued use and improves with periods of rest. Symptoms vary for each patient and can fluctuate throughout a patient's life. MG occurs in all races, both genders and at any age. No strong genetic components have not been found, however it does occasionally occur in more than one member of a family. MG is not an infectious disease, therefore it is not contagious. Currently the cause of MG is unknown, and there is no cure for this disease.[6]

There are various methods to treat MG; treatments are individualized to each patient based on the severity of their symptoms, their sex, age, and degree of impairment. First-line therapy for symptomatic treatment is an anti-acetylcholinesterase agent, which allows the neurotransmitter Acetylcholine to remain at the neuromuscular junction longer so that more receptors can be activated.[6,11]

Other first-line MG treatments are aimed at suppressing the immune system and the associated antibody response to induce remission, prevent disease progression and restore function at the neuromuscular junction[11]. Corticosteriods alone or in combination with other immunosuppressant drugs are disease modifying agents for MG. Corticosteriods, such as Prednisone, can be quite effective in reducing MG symptoms. However, they have serious dose-limiting side effects including generalized immunosuppression, hyperglycemia, hypertension, myopathy, weight gain, cataracts, and osteoporosis. Azathioprine (AZA) and Cyclosporine are the only immunosuppressants proven to be effective for treating MG in RCTs when compared to placebos.[9] They are often used as steroid-sparing therapies, either reducing the need for or lower

the corticosteroid doses, sparing the patient the steroid's adverse side effects. These immunosuppressants however, come with their own sets of side effects. Cyclosporine is associated with hypertension, renal insufficiency, and hirsutism. AZA is associated with systemic hypersensitivity, hepatotoxicity, and myelosuppression.[5]

Methotrexate has been used and proven to be effective in the treatment of other autoimmune disorders, such as Rheumatoid Arthritis (RA), Crohn's disease, and Multiple Sclerosis. It has many advantages include PO dosing once a week, a generic formulation, a moderate side effect profile, inexpensive cost compared to other immunosuppressants like AZA, easy accessibility, and the potential to be used for longer periods of time compared to corticosteroids.[2,5,11]

OBJECTIVE

The objective of this selective Evidence Based Medicine (EBM) review is to determine whether or not Methotrexate (MTX) is an effective treatment in partially or totally reducing the symptoms of Myasthenia Gravis (MG) patients.

METHODS

The criteria used to select the studies for this EBM review include: the population studied was over the age of 18 years old, who were diagnosed with Myasthenia Gravis class II, III, or IV, who were stable on prednisone, but were not on any steroid-sparing immunosuppressants. Table 1 provides additional demographics and characteristics for the three studies included in this review which include one Case Series Study and two Randomized Control Trials. The common intervention among the studies was MTX. Comparison groups in the two RCTs included experimental groups that received AZA in one study or a placebo in the second study. Outcomes

measured included MG outcomes and quality of life measures, all of which assess MG symptom improvement.

The studies were found by the author using key words "Myasthenia Gravis" and "Methotrexate" in the PubMed database. All three studies were published in English in peer reviewed journals. The sources were selected based on relevance to the clinical question and inclusion of patient oriented outcomes (POEMs). Inclusion criteria for the sources included that the studies must be a type of primary research study published within the last 15 years. Exclusion criteria for the sources included patients under the age of 18, patients who had recent thymectomies, or patients who were treated with an immunosuppressive therapy within the last 60 days with exception of Prednisone. A summary of the statistics reported or used in regard to the two RCTs include: p-values and 95% CI (Confidence Interval) which were provided in the studies, as well as CER (Control Event Rate), EER (Experimental Event Rate), ABI (Absolute Benefit Increase), RBI (Relative Benefit Increase) and NNT (Number Needed to Treat) which were calculated.

Table 1 – Demographics & Characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Karahmet[3] (2014)	Case Series Study	3	31,36, & 60	Patients with concomitant MG & RA	N/A	0	MTX 15 mg weekly
Heckman[2] (2011)	Single Blind RCT	31	AZA: 42.7 +/-16.8 MTX: 47.9 +/- 14.8	Diagnosed within previous 6 months with MGFA class II, III, or IV. Severity of functional disability of ADLs where immunosuppressive therapy is indicated due to Pyridostigmine failure as a monotherapy.	Those with MG confined to the EOM or concomitant illness such as uncontrolled thyroid disease or additional polymyositis, or subjects with HBV or HIV infections.	6	MTX (17.5 mg weekly + *Folate 25 mg weekly*) or AZA (2.5 mg/kg daily)

Barohn[1] (2015) Pasnoor[4] (2014) Pasnoor[5] (2012) Pasnoor[9] (2016)	Double Blind RCT	50	18+ years old; 26.6 to 87.2 (full range)	MGFA grade 2, 3, or 4; stable on 10 mg/day of Prednisone or equivalent with alternate day dosing x 30 days.	Thymoma, thymectomy (within last 3 months), tumor, infection, hepatic / renal insufficiency, or ILD. On immunosuppressive therapy w/in last 60 days. Prior use of MTX within prior 2 years. Daily NSAID use.	8	MTX or Placebo Dosing: 10 mg weekly x 2 weeks, then 15 mg x 2 weeks, then 20 mg weekly until the end of the study *(+ Folic acid daily)*.

OUTCOMES MEASURED

For the Case Series Study, outcomes addressed were improvement in muscle weakness and fatigue, however no specifics were provided in how the outcomes were measured over the one year period of follow-up.[3]

For the Single-blind, MTX vs. AXA RCT, the Quantitative MG (QMG) score and the MG Activities of Daily Living (MG-ADL) score were calculated to determine those with Minimum Manifestations Status (MMS) of MG. Visits were scheduled at baseline, 1, 2, 4, and 6 months after study entry, followed by visits every 3 months for 2 years. At each visit the patient's progress was assessed by blind assessors. Outcomes were analyzed in as per-protocol analysis in which data measurements of those who withdrew were censored after the date on which they were no longer on the study medication. Data of all subjects were included in the denominator for proportionate outcomes such as MMS, number of failures and "responders". Only those who reached sustained MMS up until the end of the 24-month study were considered relevant. Patients were questioned at each visit in regards to compliance; with non-compliance, the recorded dose reflected the dose that was taken.[2]

For the Double-blind, placebo-controlled RCT, MG outcomes and quality of life measures were analyzed using the QMG, MG-ADL, Manual Muscle Testing (MMT), MG Quality of Life (MGGOL), and MG Composite (MGC) change over 12 months; each were evaluated every four weeks for 12 months. Data was analyzed in an intent-to-treat fashion, using multiple imputation method for any missing data.[1,9] *See Table 2 for detailed descriptions of outcome measurements.*

Table 2 – Outcome Measurements & Descriptions

Outcome Measurements	**Description of Measurements**
QMG	13 item ordinal scale which measures ocular, bulbar, extremity fatigue and strength, along with respiratory function. Scale of 0-3 for each item, with 0 = normal, 3 = severe. Total score can range from 0-39. Time frame: Change from Baseline to completion of study.[1]
MG-ADL	8 item scale to assess MG symptoms. 0 = normal to 24 = severe. Time frame: Change from Baseline to completion of study.[1]
MMT	Measures the strength of muscle groups in face, neck, arms, and legs; grading amount of weakness. Normal = 0, mild = 1, moderate = 2, severe = 3, unable to perform = 4. Total score can range from 0-76. Time frame: Change from Baseline to Month 12.[1]
MGQOL	15 item patient-reported scale indicating how MG affects QOL per the past 7 days. 0 = not all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = very much. Total score can range from 0-76. Time frame: Change from Baseline to Month 12.[1]
MGC change over 12 months	Composite of the QMG, MG-ADL, and MMT; each item was weighted and then assigned a score. 0 = no effects of MG; 50 = being in the hospital on a ventilator. Time frame: Change from Baseline to Month 12.[1]

RESULTS

In the Case Series Study, three patients with concomitant MG and RA were treated with 15 mg of MTX weekly and were followed for one year. The MTX treatment was given to treat the RA, however all three patients experience beneficial effects in their MG symptoms of muscle weakness and fatigue. The study did not provide continuous or dichotomous data in regards to its results, nor was it a controlled trial. This study shows an association between MTX and

improved MG symptoms; however it does not show cause and effect. When considering the side effects of other immunosuppressive therapies, the researchers believed MTX could be an effective treatment for MG. They acknowledge that more detailed studies are needed to determine the exclusive role of MTX in regard to MG.[3]

Between 2005 and 2010, thirty-one subjects entered the Single-blind, MTX vs. AZA, RCT. Twenty-four subjects were randomized to either MTX (n=11) or AZA (n=13). The remaining seven subjects were not randomized. The majority were due to economic restraints which did not allow them the ability to afford the more expensive AZA if randomized to that group, therefore they were included in the MTX group (n=5). The two remaining participants demanded the Standard of Care treatment of AZA (n=2). Baseline values between the MTX and AZA group, including: duration of MG symptoms, proportion of Prednisone, baseline bodyweight, MGFA severity grade, and QMG scores were similar. Results showed that similar proportions of subjects in each group reached sustained MMS by the end of the 24 month trial (AZA n = 7; MTX n = 9; p = 0.83). The MTX-group's median time to sustained MMS was 10.5 months, where the AZA-group's median time to sustained MMS was 12-15 months. The MMS treatment outcomes were used to calculate ABI and NNT for this study; *refer to Table 3*.

Table 3

MMS Treatment Outcomes at 6-monthly intervals[2]

	6 months	*12 months*	*18 months*	*24 months*
AZA, n (%)	2/15 (13%)	4/15 (27%)	5/15 (33%)	7/15 (53%)
MTX, n (%)	3/16 (19%)	5/16 (31%)	5/16 (31%)	9/16 (56%)

Treatment Effect of MTX vs. AZA

CER	*EER*	*RBI*	*ABI*	*NNT*	*P-Value*
.53	.56	.06	.03	34	0.83

According to this study, for every 34 patients treated with MTX, one additional MG patient will sustain MMS, compared to patients treated with AZA. The p-value for the treatment effect of MTX vs. AZA is 0.83. Since the p-value is >0.05, this shows that the findings are not statistically significant due to the small subject group size of 31 participants. In regards to the safety of the study, intolerable diarrhea (AZA n = 1; MTX n = 1), hearing loss and acne (AZA n = 1), and loss of appetite (MTX n = 1) accounted for the study withdrawals, showing that AZA and MTX were equally well tolerated.[2]

In summary, MTX has an earlier onset of action, similar efficacy and tolerability to AZA, demonstrating prolonged remission from MG symptoms; also MTX may be the drug of choice in financially constrained patients.[2]

Between April 2009 and September 2014, 50 subjects entered a Double-blind, placebo-controlled RCT (MTX n = 25; Placebo n = 25) at 19 sites across the U.S. and Canada conducted by The Methotrexate in MG Investigators of the Muscle Study Group. Baseline values including age, gender, self-reported race/ethnicity, clinical MG parameters and Prednisone dosing were similar between both groups. The data included in this trial was continuous. The author reported Change in mean from Baseline to Month 12 and t-test values; *Table 4 summarizes these values*.[9]

Table 4 – Treatment Effect of MTX vs. Placebo[1,9]			
QMG Score (12 month change); *method: t-test, 2 sided; groups: All Groups*			
MTX (95% CI)	Placebo (95% CI)	P-Value	MTX – Placebo (95% CI)
-1.4 (-2.9 to 0.1)	0.3 (-1.8 to 2.4)	0.29	-1.7 (-4.9 to 1.5)
MMT (12 month change); *method: t-test, 2 sided; groups: All Groups*			
MTX (95% CI)	Placebo (95% CI)	P-Value	MTX – Placebo (95% CI)
-5.5 (-7.4 to 3.8)	-3.3 (-6.6 to 0.1)	0.28	-2.2 (-6.3 to 1.8)
MGQOL (12 month change); *method: Wilcoxon (Mann-Whitney); groups: All Groups*			
MTX (95% CI)	Placebo (95% CI)	P-Value	MTX – Placebo (95% CI)
-4.6 (-9.1 to 0.1)	-3.7 (-8.4 to 1.0)	0.82	-0.9 (-7.2 to 5.4)
MG-ADL (12 month change); *method: t-test, 2 sided; groups: All Groups*			
MTX (95% CI)	Placebo (95% CI)	P-Value	MTX – Placebo (95% CI)
-1.2 (-2.3 to 0.5)	0.26 (-0.9 to 1.5)	0.21	-1.5 (-3.7 to 0.8)

MG Composite Change over 12 months; *method: t-test, 2 sided; groups: All Groups*			
MTX (95% CI)	Placebo (95% CI)	P-Value	MTX – Placebo (95% CI)
-4.6 (-6.4 to 2.7)	-1.3 (-3.7 to 1.1)	0.09	-3.3 (-7.1 to 0.5)
**General Note – if a study participant terminated their participation, their last results were pulled forward.*			

The estimate of the treatment effect is not precise due to the fact that all of the p-values are >0.05, showing that they are not statistically significant due to the small sample size. The small sample size also attributes to the CI ranges being too wide to be precise. One participant from the MTX group withdrew from the study due to travel problems. Seven participants from the Placebo group withdrew from the study due to the following reasons: 3 due to worsening of symptoms, 1 due to myalgia, 1 due to comorbid illness, 1 due to elevated LFTs, and 1 due to death (stroke). Safety was assessed by adverse event reporting. No MTX subjects experienced any serious adverse events, therefore the study was deemed safe. 23 out of 25 (92%) participants from each group experienced some form of adverse event during the 12 month study, though 66% of these events were determined to be unrelated to the study. Most notably, the MTX group experience more GI issues, including upset stomach, diarrhea or constipation (MTX 60%; Placebo 44%). The MTX group also experienced more sinus infections or URIs (MTX 52%; Placebo 28%). Both group's participants experienced similar adverse events of general fatigue (MTX 40%; Placebo 32%), general pain (MTX 52%; Placebo 56%; *most common adverse event*), and worsening of MG symptoms (MTX 40%; Placebo 32%).[1,4,5,9]

If MTX was proven to be effective in treating MG symptoms and reducing the use of Prednisone, patients would have been able to benefit from MTX's oral weekly dosing, including a generic formulation, a moderate side effect profile, inexpensive cost, easy availability, and potential use for longer periods of time. Unfortunately, MTX did not perform as the study had hoped in reducing MG symptoms and improving the MG patient's quality of life.[1,4,5,9]

DISCUSSION

MTX was well tolerated in both RCTs, showing only its typical benign side effects such as GI upset. None of its more serious side effects surfaced during the studies, which include stomatitis, rash, abnormal blood counts and pulmonary toxicity. Folic acid concomitantly is required to help avoid these side effects. MTX is also teratogenic therefore women of child-bearing age need to weigh the risk versus benefit of the use of this agent and use several forms of birth control while using this agent.[11]

The major limitation of both RCTs was the smaller than anticipated size of the study due to recruiting issues which, resulted in the data being not statistically significant[2,9]. Also due to the limited funding of one study, several socioeconomically challenged participants were not about to be blinded due to AZA's more expensive cost; this could have led to biases against MTX when reporting symptom improvement[2]. The researchers of the most recent RCT also are considering that perhaps their study was not long enough with its 12 months duration, they referenced the prior RCT which compared AZA vs. MTX, which indicated that AZA required up to 15 months to reach its full therapeutic potential. Another weakness the researchers considered was that their study contained an older mean age in their population (mid-60s), which means the study population included more late-onset MG subjects. The significance in this being that patients with later onset of MG, tend to have a milder course of symptoms than younger patients with MG. Milder symptoms could make detecting MTX's benefits more difficult than in studies with younger MG subjects. In the RCT comparing AZA vs. MTX, the mean age was 20 years younger (mid-40s) and the MTX effects seemed more significant.[9,10]

CONCLUSION

The results of the Case Series Study and earlier Single-blind RCT showed promise that MTX could be an effective treatment in partially or totally reducing the symptoms of MG patients. However, the most recent Double-blind RCT suggests that MTX is no more effective in reducing symptoms in MG than a placebo, when both are paired with Prednisone.

Dr. Daniel Drachman, MD from the John Hopkins School of Medicine Neurology Department, responded to the disappointing negative results of this last MTX RCT. He feels that a meaningful RCT for a new Gold Standard therapy for MG is nearly impossible at this point. His belief stems from the fact that MG has been found to be the most treatable autoimmune disease and therefore virtually all diagnosed MG patients start treatment immediately. This makes recruitment for future studies extremely difficult, which both RCTs had experienced. Also the early and effective treatment of MG patients with Prednisone, makes gauging any new immunosuppressant's effectiveness controversial and unreliable.[8]

When looking ahead at future therapies for MG, various monoclonal antibodies such as Alemtuzumab, Belimumab, Eculizumab, Etanercept, and immunomodulatory drug Leflunomide may be the next generation of Gold Standard MG agents. These chemical and biological agents target different components of the immune system and may have a role in improving the treatment of MG.[11] Though MTX may not be the next Gold Standard agent for MG, researchers did learn some valuable lessons for future studies. The MG community needs to carefully consider which agents they study next. This is due to the need for larger numbers of participants, a very limited commodity in this population, that will need to be followed for long periods of time, to ensure the study captures the full treatment effect of the agent.[9]

REFERENCES

1. Barohn R. Efficacy of methotrexate in myasthenia gravis. ClinicalTrials.gov Website. https://clinicaltrials.gov/ct2/show/NCT00814138. Updated November 18, 2015. Accessed January 2, 2016.

2. Heckmann JM, Rawoot A, Bateman K, Renison R, Badri M. A single-blinded trial of methotrexate versus azathioprine as steroid-sparing agents in generalized myasthenia gravis. *BMC Neurol*. 2011;11:97-2377-11-97. doi: 10.1186/1471-2377-11-97 [doi].

3. Karaahmet OZ, Bal A, Dulgeroglu D, Bahceci HK, Cakci A. Methotrexate treatment in myasthenia gravis. *J Clin Neuromuscul Dis*. 2014;16(2):106-107. doi: 10.1097/CND.0000000000000057 [doi].

4. Pasnoor M, He J, Herbelin L, Dimachkie M, Barohn R, Muscle Study Group. Phase II trial of methotrexate in myasthenia gravis (S16.002). *Neurology*. 2014;82 no. 10 Supplement S16.002(April 8, 2014).

5. Pasnoor M, He J, Herbelin L, Dimachkie M, Barohn RJ, Muscle Study Group. Phase II trial of methotrexate in myasthenia gravis. *Ann N Y Acad Sci*. 2012;1275:23-28. doi: 10.1111/j.1749-6632.2012.06804.x [doi].

6. What is Myasthenia Gravis (MG)? MFGA. http://myasthenia.org/. Accessed November 17, 2016.

7. Guptill JT, Sharma BK, Marano A, Soucy A, Krueger A, Sanders DB. Estimated cost of treating myasthenia gravis in an insured U.S. population. *Muscle & Nerve*. 2012;45(3):363-366. doi:10.1002/mus.22327.

8. Drachman DB. Comment: Methotrexate for patients with generalized myasthenia gravis. *Neurology.* 2016;87(1):63-63. doi:10.1212/wnl.0000000000002818.

9. Pasnoor M, He J, Herbelin L, et al. A randomized controlled trial of methotrexate for patients with generalized myasthenia gravis. *Neurology*. 2016;87(1):57-64. doi:10.1212/wnl.0000000000002795.

10. Silvestri NJ, Wolfe GI, Lacomis D. What's in the Literature? *Journal of Clinical Neuromuscular Disease*. 2016;18(2):108-117. doi:10.1097/cnd.0000000000000159.

11. Gotterer L, Li Y. Maintenance immunosuppression in myasthenia gravis. *Journal of the Neurological Sciences*. 2016;369:294-302. doi:10.1016/j.jns.2016.08.057.