Comparative effectiveness of azathioprine and mycophenolate mofetil for myasthenia gravis (PROMISE-MG): a prospective cohort study

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Summary

Background Myasthenia gravis is an autoimmune disorder of the neuromuscular junction. Treatment typically includes symptomatic oral cholinesterase inhibitors, immunosuppression, and immunomodulation. In addition to corticosteroids, azathioprine and mycophenolate mofetil are the most frequently used immunosuppressants in North America. We aimed to evaluate the comparative effectiveness of these two drugs, and to assess the effect of the dose and duration of treatment.

Methods We did a prospective cohort study at 19 academic centres in Canada and the USA. We included patients (aged ≥18 years) with autoimmune myasthenia gravis, who were never treated with immunosuppressants. Treating clinicians determined the choice of medication, dose, follow-up intervals, and drug monitoring. Outcome measures and adverse events were recorded at each visit. We assessed two co-primary outcomes. The first was the patient-reported Myasthenia Gravis-Quality of Life 15-revised (MGQOL-15r) score, measured as the mean change from treatment initiation to the follow-up visit with the lowest score. A clinically meaningful reduction (CMR) in MGQOL-15r was defined as a 5-point decrease. The second was a composite clinical outcome of disease improvement (Myasthenia Gravis Foundation of America Post-Intervention Status Minimal Manifestations or better) and low adverse event burden (defined as grade ≤1 Common Terminology Criteria for Adverse Events). We also compared these outcomes in patients receiving an adequate dose and duration of azathioprine (≥2 mg/kg per day for at least 12 months) or mycophenolate mofetil (≥2 g per day for at least 8 months) and a lower dose or shorter duration of these agents. We used propensity score weighting with generalised linear regression models. This study is registered with ClinicalTrials.gov (NCT03490539).

Findings Between May 1, 2018, and Aug 31, 2020, 167 patients were enrolled; 85 did not receive azathioprine or mycophenolate mofetil and were excluded. Four were excluded from outcome analyses because they had scores of 0 on an outcome measure at treatment initiation. Of the 78 patients included in analyses, 47 received mycophenolate mofetil (median follow-up 25 months [IQR 13·5–31·5]) and 31 received azathioprine (median follow-up 20 months [IQR 13–30]). The mean change in MG-QOL15r was –10·4 (95% CI –18·9 to –1·3) with mycophenolate mofetil and –6·8 (–17·2 to 3·6) with azathioprine (mean difference –3·3, 95% CI –7·7 to 1·2; p=0·15). 38 (81%) of 47 patients receiving mycophenolate mofetil and 18 (57%) of 31 receiving azathioprine had a CMR in MG-QOL15r (risk difference 24·0%; 95% CI –0·2 to 48·0; p=0·052). The clinical composite outcome was achieved in 22 (47·7%) of 47 patients who received mycophenolate mofetil and nine (28·1%) of 31 who received azathioprine (risk difference 19·6%, 95% CI –4·9 to 44·2; p=0·12). Descriptive analysis did not find a difference in the proportion of patients reaching a CMR in MG-QOL15r between the adequate dose and duration group and the lower dose or shorter duration group. Adverse events occurred in 11 (32%) of 34 patients who received azathioprine and nine (19%) of 48 who received mycophenolate mofetil. The most frequent adverse events were hepatotoxicity with azathioprine (five [15%] of 34) and gastrointestinal disturbances (seven [15%] of 48) with mycophenolate mofetil. There were no study-related deaths.

Interpretation More than half of patients treated with azathioprine and mycophenolate mofetil felt their quality of life improved; no difference in clinical outcomes was noted between the two drugs. Adverse events associated with azathioprine were potentially more serious than those with mycophenolate mofetil, although mycophenolate mofetil is teratogenic. Lower than recommended doses of azathioprine might be effective, with reduced dose-dependent adverse events. More comparative effectiveness studies are required to inform treatment choices in myasthenia gravis.

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Research in context

Evidence before this study

We conducted three searches MEDLINE, using PubMed, from database inception up to Sept 17, 2023, for relevant clinical studies evaluating azathioprine and mycophenolate mofetil for the treatment of myasthenia gravis, with no date or language restrictions applied, using the "Clinical Trials" filter. Advanced searches of EMBASE were also done with quick limits: "case control study" OR "clinical study" OR "controlled clinical trial" OR "randomised controlled trial", "Cochrane review" AND "article" AND "human". The first search was for relevant clinical studies of azathioprine, using the search terms "azathioprine" AND "myasthenia gravis"; 25 studies were identified through PubMed and the EMBASE search provided 42 records. Six studies were relevant to the study question. Full-text review identified four case series and unblinded studies showing varying efficacy of azathioprine. A multicentre, double-blind, placebo-controlled randomised controlled trial comparing prednisolone with prednisolone plus azathioprine in 34 patients showed a steroid-sparing effect of azathioprine at 15 months of treatment. A small, randomised, single-blind trial showed a similar steroid-sparing effect of methotrexate and azathioprine after 10 months of treatment. The second search was for relevant clinical studies of mycophenolate mofetil, using the search terms "mycophenolate" AND "myasthenia gravis"; 14 studies were identified through PubMed and 25 records with the EMBASE search. A case report was excluded. Eight relevant studies were identified. Full-text review identified four case series and open-label studies that showed mycophenolate mofetil to be efficacious in improving outcomes and reducing corticosteroid dosage. Three randomised controlled trials of 12–36 weeks' duration did not show efficacy of mycophenolate mofetil. The interpretation of one study, a case series of mycophenolate mofetil in various diseases, was limited by the design. The final search was for studies comparing the two drugs, using the search string "(azathioprine or mycophenolate) AND myasthenia gravis AND comparative effectiveness". This search retrieved ten articles, none of which were comparative effectiveness studies. The EMBASE search provided 15 records. Five were abstracts of the present study, PROMISE-MG, presented at various meetings. One was a report of the process of identifying a patient-centered outcome measure for PROMISE-MG. One was a protocol for a planned systematic review and network meta-analysis to compare the efficacy and acceptability of oral immunosuppressive drugs in myasthenia gravis. Eight were not relevant to the study question. Azathioprine and mycophenolate mofetil are frequently used as the initial non-steroidal immunosuppressive agents in myasthenia gravis, but evidence for their efficacy is limited by the high risk of bias of most available studies.

Added value of this study

PROMISE-MG is, to our knowledge, the only comparative effectiveness study evaluating azathioprine and mycophenolate mofetil in a prospective cohort of patients with myasthenia gravis in routine clinical practice. With a rigorous study design and statistical analysis, the study was conducted at 19 academic centres in Canada and the USA. A patient-centered outcome, the Myasthenia Gravis-Quality of Life 15, revised, was selected as the co-primary outcome after obtaining input from patients about the validated outcome measures available for myasthenia gravis. Avoiding hospital admission was identified as an additional important outcome. The main novel aspects of this study were the prospective study design, measurement of outcomes in routine clinical practice, combining effectiveness and adverse effects as a primary outcome, inclusion of patient and stakeholder input, long duration of follow-up, and rigorous statistical analyses of observational data. This sets standards for future comparative effectiveness research in myasthenia gravis, as new treatments are rapidly being studied and approved.

Implications of all the available evidence

Azathioprine and mycophenolate mofetil were both shown to be effective at improving quality of life, function, and muscle strength. However, considerations beyond effectiveness—such as sex, childbearing potential, and comorbidities—are essential when choosing treatments. The adverse events associated with azathioprine (ie, transaminitis, influenza-like hypersensitivity reaction, haematological adverse events, and pancreatitis) are potentially more serious than those associated with mycophenolate mofetil (mostly gastrointestinal side-effects); however, mycophenolate mofetil is teratogenic. Our findings suggested that azathioprine doses of less than 2 mg/kg per day (ie, lower than the target daily dose of ≥2 mg/kg) might be effective, and use of lower doses could reduce dose-related side-effects. In some patients, mycophenolate mofetil can take up to 18 months to have a clinically meaningful effect, which is important because the drug was previously thought to act within 6 months, so a longer duration of treatment might be needed before it can be deemed ineffective. The findings of PROMISE-MG emphasise the importance of evaluating the comparative effectiveness of treatments for myasthenia gravis, because drug development is rapidly progressing. For example, two new classes of drugs—complement C5 inhibitors and neonatal Fc receptor antagonists—are effective and rapidly acting therapies, but neither drug class treats the upstream pathogenesis of myasthenia gravis. These new therapies are also limited by availability and cost. Azathioprine and mycophenolate mofetil are effective, relatively safe, and inexpensive treatment options for myasthenia gravis, and are complementary to the new therapies.

Introduction

The treatment of myasthenia gravis includes symptomatic oral cholinesterase inhibitors, immunosuppression with corticosteroids and other agents, and immunomodulation.[1,2] The choice of the immunosuppressant is determined by disease characteristics (eg, antibody type,

symptom severity and evolution), comorbidities, patient or clinician preferences, availability, and costs or payer coverage. Systematic reviews have emphasised the scarcity of evidence for the efficacy of many agents despite their use in clinical practice.[3,4] Most evidence comes from cohort studies, case series, and small randomised controlled trials. Recent consensus guidance emphasises the absence of comparative effectiveness research for myasthenia gravis treatments.[1,2] Comparative effectiveness research compares the benefits and harms of different methods to prevent, diagnose, treat, or monitor a condition. A related concept is patient-centered outcomes research, which helps patients and caregivers make informed health-care decisions.

Although azathioprine is frequently used to treat myasthenia gravis, there is little high-quality evidence for its use in clinical practice. Case series and unblinded studies have shown varying efficacy.[5–8] A multicentre randomised trial showed a steroid-sparing effect after 15 months of treatment.[9] Another randomised controlled trial showed a steroid-sparing effect of methotrexate and azathioprine after 10 months of treatment.[10] Case series and open-label studies have suggested that mycophenolate mofetil might be efficacious for improving outcomes,[11–14] but this possibility has not been confirmed in randomised controlled trials.[15–17] Mycophenolate is believed to have a shorter latency to effect (approximately 6 months) than azathioprine (approximately 15 months).[9,14] The recommended dose of azathioprine for myasthenia gravis is 2·5–3 mg/kg orally per day and that of mycophenolate mofetil is 2–3 g orally per day.[2] These drugs are often used in clinical practice at lower doses or for shorter durations than those recommended for immunosuppressive effect. While azathioprine and mycophenolate mofetil are frequently used as initial non-steroidal immunosuppressants, to the best of our knowledge no studies have been done to directly compare the two treatments. We aimed to evaluate the comparative effectiveness of azathioprine and mycophenolate mofetil for the treatment of myasthenia gravis, by use of patient-reported outcomes and clinician-reported outcomes, and to analyse the effect of adequate doses of azathioprine and mycophenolate mofetil for adequate durations versus lower doses or shorter durations.

Methods

Study design and participants

PROMISE-MG was a prospective cohort study at 19 academic centres in Canada and the USA. Adults (aged ≥18 years) with autoimmune myasthenia gravis were eligible for inclusion. Myasthenia gravis was confirmed by the clinical picture (ie, history and physical findings of fluctuating, fatiguable weakness of oculo-bulbar or extremity muscles, or both) and either serum acetylcholine receptor (AChR) or muscle specific kinase (MuSK) antibodies, abnormal electrodiagnostic testing (repetitive nerve stimulation or single-fibre electromyography), unequivocal response to cholinesterase inhibitors, or a combination of these. Treatment with pyridostigmine was allowed if started up to 3 months before initial evaluation. Patients who had received corticosteroids for a non-myasthenia gravis indication at least 90 days before initial evaluation, and patients admitted to hospital whose baseline outcome measures were obtained within 24 h after initiation of intravenous immunoglobulin or plasma exchange, were eligible for inclusion.

Patients were excluded if they were receiving or had ever received corticosteroids for myasthenia gravis or had received corticosteroids for a non-myasthenia gravis indication up to 30 days before initial evaluation; were receiving or had ever received non-steroidal immunosuppressants, intravenous immunoglobulin, or plasma exchange for myasthenia gravis; or had undergone thymectomy. The primary investigators ascertained the eligibility of patients who received corticosteroids for a non-myasthenia gravis indication 31–89 days before initial evaluation.

A central independent review board, Copernicus (Cary, NC, USA), approved the study protocol, with additional approvals as required by local institutional review boards. Changes to the protocol are documented in the appendix (pp 12–21).

See Online for appendix

We used a new-user design with active comparators, by identifying patients who started azathioprine or mycophenolate mofetil and had follow-up evaluations after treatment initiation, similar to a randomised controlled trial. Potentially eligible patients were identified at their first visit after Jan 1, 2017. After institutional review board approval, eligible patients provided written informed consent for use of their data retrospectively from Jan 1, 2017, and prospectively up to 40 months after treatment initiation. The database was locked on Sept 3, 2021 (appendix p 6).

Procedures

This study was designed and conducted with input from a patient (KB was the patient representative), the Myasthenia Gravis Foundation of America (MGFA; Westborough, MA, USA), and a care management company (Accordant Health Services, CVS Health, High Point, NC, USA). No requirements were made for study interventions or testing; standard-of-care treatments were used as per the treating clinicians' judgement and patient preferences. The outcome measures selected are used routinely in clinical practice; site investigators were instructed to perform all the outcome assessments (described below) at each visit. Treating clinicians decided the frequency of follow-up and laboratory monitoring, and the outcome measures and adverse events were recorded at each clinical visit. Thus, the interval between outcome measurements varied between and within patients, as in routine clinical practice. The follow-up period was 20–40 months (appendix p 6).

We used a centralised REDCap database designed for the study, which contained items concordant with the myasthenia gravis-specific common data elements developed under the US National Institute of Neurological Disorders and Stroke (NINDS) Common Data Elements Project.[18] We recorded baseline demographics, myasthenia gravis diagnostic criteria, past history, and medications, as well as the following covariates that could affect treatment choices: age at myasthenia gravis onset, patient-reported sex, race, body-mass index (BMI), disease duration, comorbidities (hypertension, diabetes, history of cancer or psychiatric illness, chronic liver or kidney disease), pregnancy, lactation, presence of AChR or MuSK antibodies, cumulative prednisone dose, disease distribution (ocular vs generalised), MGFA clinical class, use of rescue therapies, and thymus imaging. Changes in medications for myasthenia gravis, adverse events, and myasthenia gravis-related hospital admissions were recorded at each follow-up. Disease severity and effectiveness of treatment were assessed by MGFA clinical class,[19] MGFA post-intervention status (MGFA-PIS),[19] Myasthenia Gravis Quality of Life-15, revised (MG-QOL15r),[20] Myasthenia Gravis-Activities of Daily Living (MG-ADL),[21] Myasthenia Gravis-Composite (MGC),[22] and Myasthenia Gravis-Manual Muscle Test (MG-MMT).[23] During the COVID-19 lockdown, MGFA clinical class, MG-QOL15r, MGFA-PIS, and MG-ADL were recorded via telephone visits, as frequently as deemed necessary for clinical care by the site investigator. Data were entered into the database by study site personnel and were reviewed for accuracy by the primary investigators.

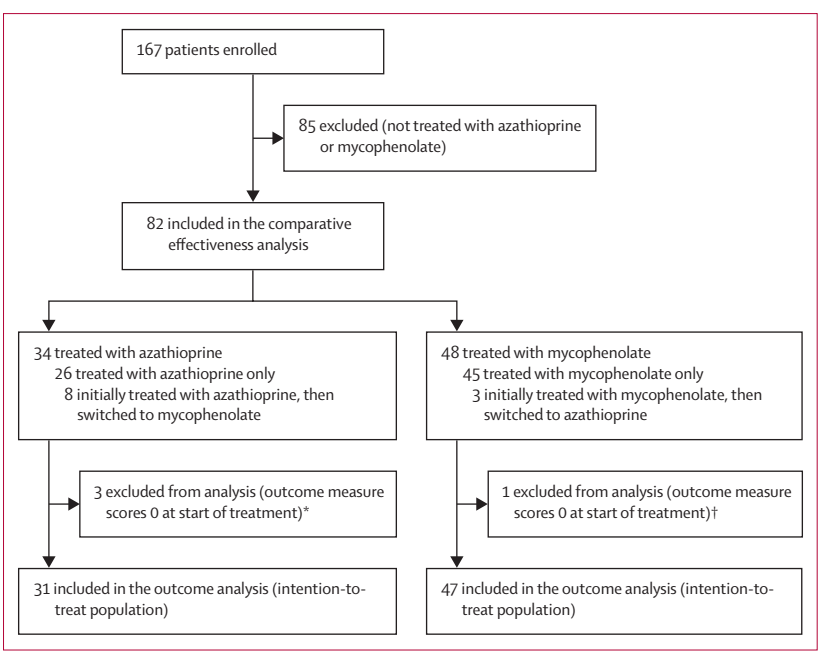

Figure: **Participant flow**
No patients were lost to follow-up in either group. MGC=Myasthenia Gravis Composite. MG-MMT=Myasthenia Gravis Manual Muscle Test. MG-ADL=Myasthenia Gravis Activities of Daily Living. *Two patients with MGC, MG-MMT scores of 0; and one patient with MG-ADL, MGC, and MG-MMT scores of 0. †One patient with MG-MMT, MGC, and MG-ADL scores of 0.

Outcomes

The study incorporated two co-primary outcomes. The first outcome was MG-QOL15r, which is a patient-centered outcome that was selected as per the mandate of the funding agency, with input from patients (appendix pp 7–8).[24] MG-QOL15r is a 15-item quality of life measure specific to myasthenia gravis, with each item graded from 0 to 2. The score ranges from 0 to 30, and lower scores indicate better quality of life.[20] The outcome measure was the mean difference between azathioprine and mycophenolate mofetil in the reduction (improvement) of MG-QOL15r scores from the start of treatment to the follow-up visit with the lowest score.[20,24] A 5-point reduction in MG-QOL15r was considered a clinically meaningful reduction (CMR).

The second outcome was a composite clinician-reported outcome that evaluated clinical improvement from treatment initiation to the post-treatment visit with the lowest MGQOL-15r score, and adverse events associated with treatment.[2] Clinical improvement was defined as Minimal Manifestations or better on MGFA-PIS (ie, "the patient has no symptoms or functional limitations from myasthenia gravis but has some weakness on examination"). Adverse events were categorised as no more than grade 1 on the Common Terminology Criteria for Adverse Events (CTCAE; version 4.03).[25] Adverse events were reported in the study database by the site investigators, and all CTCAE grades were adjudicated by an independent evaluator for accuracy during data analysis.

Secondary outcomes measures comprised the mean difference between treatment groups in the change from treatment initiation to the follow-up visit with the lowest score in MG-ADL, MGC, and MG-MMT scores, and the number of hospital admissions for myasthenia gravis. The MG-ADL is an eight-item measure with each item scored from 0 to 3, with a score range of 0 to 24. Lower scores indicate less severe impairment.[21] The MGC is a weighted composite clinician-reported outcome and patient-reported outcome with ten items. The total score ranges from 0 to 50, and lower scores indicate better function and strength.[22] The MG-MMT assesses muscle strength of 30 muscle groups, where 0 indicates normal strength and four indicates paralysis. The score ranges from 0 to 120, and lower scores indicate better muscle strength.[23] A 2-point reduction in MG-ADL,[26] and 3-point reductions in MGC[22] and MG-MMT, were considered CMRs.

Statistical analysis

For sample size estimations, we performed a power analysis of the inverse probability weighting propensity score method (appendix pp 9–10). The planned sample size was 220 to allow for 10% dropouts. SAS (version 9.4)

	Unweighted			Weighted* (overlap weighting)†		
	Mycophenolate mofetil (n=47)	Azathioprine (n=31)	SD‡	Mycophenolate (n=47)	Azathioprine (n=31)	SD
Sex						
Male	28 (60%; 45 to 73)	19 (61%; 44 to 76)	−0·04	64% (38 to 84)	64% (38 to 84)	0·00
Female	19 (40%; 28 to 55)	12 (39%; 24 to 56)	0·04	36% (16 to 62)	36% (16 to 62)	0·00
White race	45 (96%; 85 to 100)§	30 (97%; 82 to 100)§	−0·05	95% (68 to 100)§	95% (68 to 100)§	0·00
BMI, kg/m²	31 (19 to 42)	31 (20 to 41)	−0·02	31 (25 to 37)	31 (23 to 38)	0·04
Age at onset, years	66 (42 to 90)	64 (44 to 85)	0·16	64 (53 to 76)	65 (53 to 78)	−0·07
Myasthenia gravis early onset (<50 years)	2 (4%; 0 to 15)	2 (7%; 1 to 22)	−0·10	4% (0 to 30)	4% (0 to 30)	0·00
Disease severity, ocular (MGFA Class I)	7 (15%; 7 to 28)	7 (23%; 11 to 40)	−0·12	16% (3 to 43)	15% (3 to 43)	0·00
Presence of AChR or MuSK antibody	39 (83%; 70 to 91)	22 (71%; 54 to 84)	0·23	85% (57 to 97)	84% (57 to 97)	0·00
Thymoma	2 (4%; 0 to 15)	2 (7%; 1 to 22)	−0·10	8% (0 to 34)	8% (0 to 34)	0·00
Hypertension	27 (57%; 43 to 71)	17 (55%; 38 to 71)	0·05	53% (29 to 76)	53% (29 to 76)	0·00
Diabetes	12 (26%; 15 to 40)	4 (13%; 5 to 30)	0·33	17% (4 to 44)	17% (4 to 44)	0·00
History of psychiatric illness	3 (6%; 2 to 18)	1 (3%; 0 to 18)	0·15	5% (0 to 31)	5% (0 to 31)	0·00
History of cancer	8 (17%; 9 to 30)	2 (7%; 1 to 22)	0·33	11% (1 to 39)	11% (1 to 39)	0·00
MG-QOL15r score	13 (1 to 26)	14 (−2 to 30)	−0·07	14 (6 to 21)	14 (3 to 24)	0·00
MG-ADL score	6 (1 to 11)	7 (1 to 14)	−0·50	7 (4 to 10)	7 (2 to 11)	0·00
MGC score	10 (−1 to 21)	12 (−2 to 27)	−0·33	11 (5 to 18)	11 (2 to 21)	0·00
MG-MMT score	9 (−5 to 23)	11 (−3 to 25)	−0·23	11 (2 to 19)	11 (1 to 20)	0·00
Total prednisone cumulative dose, mg	1465 (−3591 to 6521)	1719 (−3759 to 7197)	−0·10	1298 (−1037 to 3633)	1313 (−1551 to 4177)	−0·01

Data are n (%, 95% CI) or mean (95% CI). SD=standardised difference. BMI=body-mass index. MGFA=Myasthenia Gravis Foundation of America. AChR=acetylcholine receptor. MuSK=muscle-specific thyrosine kinase. MG-QOL15r=Myasthenia Gravis Quality of Life 15 (revised). MG-ADL=Myasthenia Gravis Activities of Daily Living. MGC=Myasthenia Gravis Composite. MG-MMT=Myasthenia Gravis Manual Muscle Test. *Weighted n is derived from the propensity score model. †Difference between groups after propensity score weighting using the overlap weighting method. ‡Standardised difference is the difference in means or proportions divided by the SE and measures the effect size difference between groups. §Mycophenolate: White, n=44; Black, n=1; Asian, n=1; unknown; n=1. Azathioprine: White, n=30; Asian, n=1.

Table 1: **Baseline covariates included in the generalised linear regression analysis, before and after propensity score weighting**

and R (version 4.2.3) were used for statistical analyses (appendix p11). We assumed that missingness was completely at random and imputed continuous variables by using the mean and categorical variables with the category that had the greatest number of observations.

Overlap propensity score weighting was used to evaluate the comparative effectiveness of oral azathioprine and oral mycophenolate mofetil. We modelled the propensity to have received mycophenolate mofetil. Propensity scores were calculated from logistic regression models with treatment as the dependent variable and the baseline covariates as independent variables. After calculating overlap weight propensity scores (appendix p 3), we assessed covariate balance by reporting the standardised difference in each baseline covariate. The threshold for balance assessment was 0·1 (10%). We compared treatments by weighted outcome regression using generalised linear regression models with appropriate link functions: the identity link for mean and risk differences and Cox proportional hazards models for time to event. As a sensitivity analysis for propensity score model specification, we repeated the propensity score model with the addition of restricted cubic splines for variables that had statistically significant non-linearity (baseline MG-QOL15r p=0·03 and MG-ADL p=0·045 for non-linearity). We then repeated the analysis of all outcomes (appendix p 22). This approach was not prespecified to be the primary analysis to avoid overfitting in the very limited sample size (31 people receiving azathioprine as an outcome of the propensity score model).

Outcomes were also compared between patients receiving adequate doses and durations of azathioprine and mycophenolate mofetil and those receiving lower doses or shorter durations of these drugs separately. An adequate dose and duration for azathioprine was defined as at least 2 mg/kg per day for at least 12 months, and for mycophenolate mofetil as at least 2 g per day for at least 8 months.[2] For patients who did not receive this dose or duration of treatment (ie, the lower dose or shorter duration group), their index date was defined as the first point at which an adequate dose and duration could have been met (ie, 12 months after treatment start for azathioprine and 8 months after treatment start for mycophenolate mofetil). The comparison of outcomes was descriptive and not statistically adjusted because of small numbers.

We report mean differences for continuous outcomes, risk differences and proportions for binary outcomes, and hazard ratios for time-to-event analyses. Robust variance estimators were used to derive 95% CIs. Two-sided p values less than or equal to 0·05 were considered statistically significant.

Two exploratory post-hoc analyses were performed. First, time-to-event analyses were done, with the event being the first point at which a CMR was achieved in all outcome measures (except for the composite clinical outcome); the origin time was the date of treatment initiation, which is also the start time. Follow-up for the survival outcome was started immediately at the origin of treatment. The end date was either the first time a CMR was achieved or censored at the last follow-up date. The second post-hoc analysis was of doses of azathioprine and mycophenolate mofetil in patients who had CMRs in all outcome measures versus those who did not (except for the composite clinical outcome).

This study is registered with ClinicalTrials.gov (NCT03490539).

Role of the funding source

The funder of the study had no role in data collection, data analysis, data interpretation, writing of the report, or the decision to publish the manuscript.

Results

Between May 1, 2018, and Aug 31, 2020, 167 patients were enrolled within the timeframe available to allow for adequate follow-up. Follow-up ended on Jan 31, 2021 (appendix p 6). Baseline characteristics of the full study cohort are shown in the appendix (pp 3–4). 96 (93%) patients were White males; the median age at myasthenia gravis onset was 67 years (IQR 57–73). Median disease duration at the initial visit was 5 months (IQR 3–13).

82 (49%) patients received mycophenolate mofetil (n=48) or azathioprine (n=34; figure). 11 patients received both drugs and were included in the treatment group according to their first treatment (intention-to-treat population). Four patients were excluded from outcome analyses because their scores on MG-ADL, MGC, or MG-MMT were 0 at treatment initiation. The final outcome analysis comprised 78 patients, of whom 47 (60%) were in the mycophenolate mofetil group (median follow-up 25 months [IQR 13·5–31·5]) and 31 (40%) were in the azathioprine group (median follow-up 20 months [IQR 13–30]). 14 (18%) of 78 participants had ocular myasthenia gravis and 64 (82%) had generalised myasthenia gravis. Missing data that were imputed included baseline MG-MMT (n=2), AChR antibodies (n=2), and race (n=1). Table 1 shows the final covariates included in the generalised linear regression analyses. The unadjusted standardised difference in baseline characteristics was most pronounced for patients with a history of cancer and diabetes. After propensity score weighting, the treatment groups were well matched. In the mycophenolate mofetil group, AChR antibodies were present in 36 (77%) of 47 patients; three (6%) had MuSK antibodies. In the azathioprine group, 21 (68%) of 31 patients had AChR antibodies; one (3%) had MuSK antibodies. 55 (70%) of 78 patients received prednisone before azathioprine or mycophenolate mofetil (34 [72%] of 47 in the mycophenolate mofetil group and 21 [68%] of 31 in the azathioprine group). The unweighted cumulative prednisone dose did not differ significantly between azathioprine-treated and mycophenolate mofetil-treated patients.

The mean change in MG-QOL15r was –10·4 (95% CI –18·9 to –1·3) in the mycophenolate mofetil group and –6·8 (–17·2 to 3·6) in the azathioprine group (mean difference –3·3 [95% CI –7·7 to 1·2]; p=0·15; table 2). A CMR in MG-QOL15r was reached in 38 (81%) patients receiving mycophenolate mofetil and 18 (57%) receiving azathioprine (risk difference 24·0% [95% CI, –0·2 to 48·0]; p=0·052; table 3). The clinical composite outcome was reached in 22 (47·7%) of 47 patients receiving mycophenolate mofetil versus nine (28·1%) of 31 receiving azathioprine (risk difference 19·6% [95% CI –4·9 to 44·2]; p=0·12; table 2). At least 70% of patients had a CMR in MGC, MG-ADL, and MG-MMT, and proportions did not differ between treatments (table 3). Ten (13%) of 78 patients required hospital admission for myasthenia gravis, five (16%) in the azathioprine group and five (11%) in the mycophenolate mofetil group (propensity score weighted proportions: azathioprine 17·6% [95% CI 4·5 to 44·8]; mycophenolate mofetil 8·7% [0 to 35·6]; risk difference –8·9% [95% CI –27·1 to 9·5]; p=0·34; table 2).

	Mycophenolate (n=47)	Azathioprine (n=31)	Group difference*†	p value
Primary outcomes				
Difference in MG-QOL15r	–10·4 (–18·9 to –1·3)	–6·8 (–17·2 to 3·6)	–3·3 (–7·7 to 1·2)	0·15
Clinical composite outcome‡ at MG-QOL15r minimum date	22§, 47·7% (24·8 to 71·6)	9§, 28·1% (10·9 to 54·8)	19·6% (–4·9 to 44·2)	0·12
Secondary outcomes				
Difference in MGC	–9 (–16·3 to –1·7)	–7·7 (–17·2 to 1·8)	–1·3 (–4·8 to 2·1)	0·44
Difference in MG-ADL	–5·2 (–9 to –1·4)	–4·1 (–8·7 to 0·5)	–1·1 (–2·9 to 0·7)	0·24
Difference in MG-MMT	–8·4 (–16·3 to –0·5)	–8 (–17·8 to 1·8)	–0·4 (–4·3 to 3·5)	0·84
Hospital admissions for myasthenia gravis	5, 8·7% (0·0 to 35·6)	5, 17·6% (4·5 to 44·8)	–8·9% (–27·1 to 9·5)	0·34

Data are mean (95% CI), unless otherwise specified. MG-QOL15r=Myasthenia Gravis Quality of Life 15 (revised). MGC=Myasthenia Gravis Composite. MG-ADL=Myasthenia Gravis Activities of Daily Living. MG-MMT=Myasthenia Gravis Manual Muscle Test. *Negative numbers favour mycophenolate except for the co-primary composite outcome, where positive numbers favour mycophenolate. †Data shown as means for continuous outcomes and percentages for proportions. ‡Composite outcome is achieving MGFA post-intervention status minimal manifestations or better, with Common Terminology Criteria for Adverse Events grade 1 or better. §Weighted n is derived as the sample size multiplied by the weighted proportion, rounded to the nearest whole number.

Table 2: **Weighted differences in outcomes between azathioprine-treated and mycophenolate-treated patients**

	Unweighted		Weighted		Percentage difference (95% CI)*	p value†
	Mycophenolate	Azathioprine	Mycophenolate‡	Azathioprine‡		
MG-QOL15r ≥5-point reduction	37 (80%; 67–90)	17 (55%; 38–71)	38 (81%; 54–95)	18 (57%; 32–79)	24·0% (–0·2 to 48·0)	0·052
MGC ≥3-point reduction	37 (80%; 67–90)	24 (83%; 65–93)	39 (83%; 56–96)	26 (84%; 56–97)	–0·7% (–19·0 to 18·0)	0·94
MG-ADL ≥3-point reduction	39 (85%; 72–93)	24 (77%; 60–89)	42 (89%; 62–99)	26 (81%; 54–95)	8·0% (–10·0 to 26·0)	0·38
MG-MMT ≥3-point reduction	36 (78%; 64–88)	21 (72%; 54–86)	39 (82%; 55–95)	22 (70%; 43–88)	12·0 % (–11·0 to 35·0)	0·32

Data are n (%, 95% CI) unless otherwise specified. MG-QOL15r=Myasthenia Gravis Quality of Life 15 (revised). MGC=Myasthenia Gravis Composite. MG-ADL=Myasthenia Gravis Activities of Daily Living. MG-MMT=Myasthenia Gravis Manual Muscle Test. *Wald confidence limits. †Positive values favour mycophenolate. ‡Weighted n is derived as the sample size multiplied by the weighted proportion, rounded to the nearest whole number.

Table 3: **Proportion of patients with a clinically meaningful reduction in outcomes**

In a post-hoc analysis, the median time to achieve a CMR in MG-QOL15r was 3·4 months (IQR 2·3–9·7) for mycophenolate mofetil and 6·4 months (1·3–12·7) for azathioprine (appendix p 2). The maximum time to achieve a CMR in MG-QOL15r was 31 months for mycophenolate mofetil and 21·6 months for azathioprine (appendix p 2). In the mycophenolate mofetil group, the time to reach a CMR in secondary outcomes in at least 75% of patients ranged from 13 months for MG-MMT and MG-ADL to 18 months for MGC (post-hoc analysis). In the azathioprine group, the time to reach a CMR in at least 75% of patients ranged from 14 months for MGC to 23 months for MG-MMT. A CMR was not reached by 75% of azathioprine-treated patients for MG-QOL15r within the follow-up period of the study (post-hoc analysis; appendix p 2). The median dose to achieve a CMR in MGC, a composite clinician-reported outcome and patient-reported outcome, was 2 g per day (IQR 1·5–2·0) for mycophenolate mofetil and 1·2 mg/kg per day (0·9–1·6) for azathioprine (appendix pp 2–3).

32 (68%) of 47 mycophenolate mofetil-treated patients and seven (23%) of 31 azathioprine-treated patients received an adequate dose and duration; thus, 15 (32%) of 47 mycophenolate mofetil-treated patients and 24 (77%) of 31 azathioprine-treated patients received a lower dose and shorter duration (table 4). For patients who received an adequate dose of azathioprine, the median time beyond 12 months to achieve the adequate dose was 4 months (IQR 3–6). For patients who received an adequate dose of mycophenolate mofetil, the median time beyond 8 months to achieve an adequate dose was 0 days (IQR 0–7). Thus, most patients who attained an adequate dose did so within the first 8 months after starting mycophenolate mofetil, whereas azathioprine-treated patients required a median of 16 months to reach an adequate dose.

The median decrease in MG-QOL15r score was 5 points in patients treated with mycophenolate mofetil, regardless of whether they had an adequate dose and duration (IQR –13 to 1) or lower dose or shorter duration (IQR –10 to –2; table 4). For azathioprine-treated patients, the median decrease in MG-QOL15r score was 9·5 points (IQR –13·0 to –6·0) for those who received an adequate dose and duration, and 1·0 (–7·0 to 1·0) for those who received a lower dose or shorter duration. With an adequate dose and duration of mycophenolate mofetil, 12 (38%) of 32 patients reached the composite co-primary outcome, compared with four (36%) of 11 who received a lower dose. Two (29%) of seven patients receiving an adequate dose and duration of azathioprine, and four (21%) of 19 receiving a lower dose or shorter duration, reached the composite outcome (table 4). No specific dose

	Adequate dose and duration of mycophenolate	Lower dose or shorter duration of mycophenolate	Adequate dose and duration of azathioprine	Lower dose or shorter duration of azathioprine
Co-primary outcomes				
MGQOL-15r				
Number of patients	31	11	6	18
Median difference (IQR); range	–5 (–13 to 1); –23 to 5	–5 (–10 to –2); –25 to 6	–10 (–13 to –6); –18 to 0	–1 (–7 to 1); –27 to 13
Primary composite outcome: MGFA-PIS MM and CTCAE grade ≤1*†				
Number of patients*	32	11	7	19
Yes	12 (38%)	4 (36%)	2 (29%)	4 (21%)
No	20 (63%)	7 (64%)	5 (71%)	15 (79%)
Secondary outcomes				
MGC				
Number of patients†	30	10	3	14
Median difference (IQR); range	–5 (–9 to –1); –18 to 6	–6 (–11 to –2); –25 to 3	–3 (–26 to 6); –26 to 6	–5 (–10 to –1); –36 to 4
MG-ADL				
Number of patients*	31	11	6	19
Median difference (IQR); range	–3 (–6 to –1); –12 to 1	–3 (–6 to –1); –11 to 2	–2 (–6 to 0); –13 to 0	–2 (–6 to 0); –14 to 4
MG-MMT				
Number of patients*	31	10	3	15
Median difference (IQR); range	–4 (–8 to –1); –20 to 2	–4 (–9 to –1); –32 to 2	–10 (–21 to –4); –21 to –4	–3 (–12 to 0); –23 to 12

MG-QOL15r=Myasthenia Gravis Quality of Life 15 (revised). MGFA-PIS MM=Myasthenia Gravis Foundation of America-post intervention status minimal manifestations. CTCAE=Common Terminology Criteria for Adverse Events. MGC=Myasthenia Gravis Composite. MG-ADL=Myasthenia Gravis Activities of Daily Living Scale. MG-MMT=Myasthenia Gravis Manual Muscle Test. *Primary composite outcome: MGFA-PIS MM with CTCAE for adverse events ≤1. †Number of patients differs slightly between outcomes because all patients did not have all outcomes at the analysis timepoint.

Table 4: **Outcomes in the adequate dose and duration and lower dose groups treated with mycophenolate or azathioprine (descriptive statistics only)**

	Azathioprine (n=34)	Mycophenolate (n=48)
Total adverse events	11 (32%)	9 (19%)
Serious adverse events (CTCAE ≥2)	6/11 (55%)	3/9 (34%)
Drug discontinuations	10/11 (91%)	4/9 (44%)
Deaths	0	0
Details of adverse events		
Hepatotoxicity	5 (15%)	0
Influenza-like delayed hypersensitivity reaction	3 (9%)	0
Anaemia	1 (3%)	1 (2%)
Lymphopenia	1 (3%)	0
Pancreatitis	1 (3%)	0
Gastrointestinal disturbances	0	7 (15%)
Renal dysfunction	0	1 (2%)

Data are n (%) or n/N (%). CTCAE=Common Terminology Criteria for Adverse Events. We defined acceptable adverse events as grade 0 or 1 CTCAE.

Table 5: **Summary of adverse events**

of either drug was more favourable for secondary outcomes.

The results of the three sensitivity analyses were not substantially different from those of the main analysis (appendix pp 23–24). The sensitivity analysis based on restricted cubic splines in the propensity score model resulted in the same conclusions as the primary analysis. A few endpoints were numerically different but with substantially overlapping CIs (appendix p 22).

All 82 patients who received either mycophenolate mofetil or azathioprine were included in the analysis of adverse events (table 5; appendix pp 4–5). Adverse events associated with azathioprine were observed in 11 (32%) of 34 patients and the most frequent was hepatotoxicity, followed by influenza-like delayed hypersensitivity reaction, haematological adverse events, and pancreatitis. Five (46%) adverse events were CTCAE grade 1, four were grade 2, and two were grade 3. Adverse events associated with mycophenolate mofetil were reported in nine (19%) of 48 patients, and the most common were gastrointestinal disturbances. Six (67%) of nine adverse events were CTCAE grade 1, two were grade 2, and one was grade 3. No differences were noted in the frequency of adverse events between azathioprine and mycophenolate mofetil (risk difference 13% [95% CI −5 to 32]) or the severity of adverse events between grade 1 and higher grades (risk difference 22% [–20 to 53]). Excluding three patients with delayed hypersensitivity, five (63%) of eight adverse events associated with azathioprine occurred at doses of 2 mg/kg per day or higher. With mycophenolate mofetil, six (67%) of nine adverse events occurred at doses of 2 g per day or higher.

Discussion

In this prospective comparative effectiveness cohort study, more than half of patients treated with azathioprine and mycophenolate mofetil felt their quality of life was improved with treatment, but no difference was noted between azathioprine and mycophenolate mofetil. Numerically fewer azathioprine-treated patients reached the composite measure of improved disease status with acceptable side-effects, but the difference compared with mycophenolate mofetil was not significant. A CMR was reached by at least 70% of patients in secondary patient-reported and clinical outcome measures, with no differences between the two drugs. Both drugs are, therefore, useful as early immunosuppressive agents for myasthenia gravis.

This comparative effectiveness study in myasthenia gravis provides many important insights. Although both mycophenolate mofetil and azathioprine were effective treatments for myasthenia gravis, the proportion of patients who had CMRs, and the magnitude of reduction in the outcome measure scores, was generally higher in the mycophenolate mofetil group. Statistical imprecision related to the small sample size is likely to have precluded detection of differences between mycophenolate mofetil and azathioprine. Although the frequency of adverse events and CTCAE severity grades did not differ between drugs, wide CIs indicate imprecision. Adverse events due to azathioprine were potentially more serious. The aggregate data might favour the use of mycophenolate mofetil in clinical practice. However, mycophenolate mofetil is a teratogen.[27] Therefore, considerations beyond effectiveness, such as sex, childbearing potential, and comorbidities, are essential when choosing treatments for myasthenia gravis, and the choice is influenced by physician and patient preferences.

The proportion of patients reaching a CMR and the time to CMR differed to some degree between outcomes. The absence of a placebo might have affected this result. This finding underscores the challenges of selecting outcome measures in clinical practice and trials.

We found no consistent differences in outcomes between patients who received an adequate dose and duration of mycophenolate mofetil and azathioprine and those who received a lower dose or shorter duration. Two-thirds of patients treated with mycophenolate mofetil received a dose that was similar to the usually recommended dose of 2–3 g per day; conversely, three quarters of patients treated with azathioprine received a dose that was lower than or in the lower range of the recommended dose of 2–3 mg/kg per day, or for less than 12 months. The effectiveness of azathioprine might, therefore, have been reduced in our study because a lower dose was more frequently given. Despite this, more than half of patients treated with azathioprine had CMRs in all outcomes. The effects of dose and duration are difficult to interpret given the small sample size. Due to the observational design of our study, the lower dose or shorter duration group might have shown better or equal outcomes compared with the adequate dose group if the lower dose or shorter duration was driven by

clinical improvement more rapidly or at a lower dose (ie, reverse causation). More patients received mycophenolate mofetil at an adequate dose or duration than azathioprine. This difference might have been driven by concerns about the side-effects of azathioprine. The time taken to reach the target mycophenolate mofetil dose was more rapid compared with azathioprine, which was much slower, perhaps due to clinicians' experience with adverse effects or knowledge of the long latency to clinical effect. This approach could have affected the response to azathioprine. However, these results suggest that azathioprine doses of less than 2 mg/kg per day could be effective and could reduce dose-dependent side-effects. The time for at least 75% of patients on mycophenolate mofetil to improve was 13–18 months, which might be a reason why previous randomised controlled trials of mycophenolate mofetil versus placebo have not shown a benefit at earlier timepoints.

There are many limitations to PROMISE-MG. Despite mimicking clinical practice, the generalisability of this study could be limited by the setting of academic medical centres. Most patients were White, had late-onset myasthenia gravis, and patients with severe myasthenia gravis or myasthenic crisis were excluded, also limiting the generalisability of the findings. Our results do not provide guidance about the choice of these agents in relation to comorbidities, which were infrequent. The number of hospital admissions was too small to draw conclusions. No pregnant women were enrolled. Personal preferences and the experience of site investigators could have influenced drug and dose selection; this is typical of clinical practice. Non-standardised administration of outcome measures could have contributed to variability; we avoided training of investigators in order to simulate clinical practice. Recruitment was lower than the planned 220 patients. A higher than anticipated proportion of patients had ocular myasthenia gravis, which is not initially treated with immunosuppressants. Most patients who received azathioprine or mycophenolate mofetil had generalised myasthenia gravis, but ocular disease in the remaining patients might have masked differences. More than two-thirds of patients received prednisone. Despite propensity score weighting, a confounding effect of prednisone in individual patients cannot be excluded. We used a 5-point change in MG-QOL15r as the CMR, but this change needs to be verified. Although we adjusted for clinically relevant confounders, the observational design remains vulnerable to residual confounding due to measurement error in the confounders and unmeasured confounding.

The PROMISE-MG findings provide important information for the clinical management of patients, as the algorithm of myasthenia gravis treatment evolves. Two newly approved classes of drugs—complement C5 inhibitors and neonatal Fc receptor antagonists—are effective, rapidly acting therapies, but neither class treats the upstream pathogenesis of myasthenia gravis.[28–32] In clinical practice, they are often used along with traditional immunosuppressants for quick disease control, while waiting for the immunosuppressant to become effective. These new therapies are also limited by availability and cost. Azathioprine and mycophenolate mofetil are effective at improving quality of life, function, and muscle strength in patients with myasthenia gravis, are relatively safe, and are inexpensive options that are complementary to the new therapies for myasthenia gravis. It is possible that mycophenolate mofetil might be more effective than azathioprine, but the small sample size of PROMISE-MG has affected the ability to detect a difference. The adverse events associated with azathioprine were potentially more serious than those associated with mycophenolate mofetil. However, azathioprine doses lower than typically used (ie, 1–2 mg/kg per day) might be effective and reduce side-effects. Further comparative effectiveness studies should be done to inform treatment choices in myasthenia gravis.

PROMISE-MG Study Group

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Contributors

PN contributed to conceptualisation of the study; literature review, writing, and revising the grant; study design and methodology; funding acquisition; study oversight and project administration; investigation and data collection; data analysis, verification and interpretation; and writing the initial draft and revision of the manuscript. DBS participated equally with the first and corresponding author in study conceptualisation, data curation, formal analysis, funding acquisition, investigation, project administration, resources, supervision, validation, writing (review and editing of the manuscript), figures, data collection, and data analysis; and accessed and verified the data. LT contributed to study design and methodology, data analysis, and interpretation of results. DT generated all results, tables, and figures; and contributed to analysis and interpretation of the data, and writing and editing of the methods and results sections of the manuscript. JB contributed to study oversight and project administration; investigation and data collection; data verification and interpretation; and writing the Patient-Centered Outcomes Research Institute (PCORI) report. RD contributed to conceptualisation of the study, literature review, writing and revising the grant, study design and methodology, data verification and interpretation, and reviewing the initial and final drafts of the manuscript. AK contributed to conceptualisation of the study, oversight of trial, review of outcomes and interpretation, and review of the initial and revised draft of the manuscript. KB contributed to conceptualisation of the study, study oversight, and reviewing the initial and final drafts of the manuscript. BL contributed to statistical analysis. JTG contributed to conceptualisation of the study, literature review, writing and revising the grant, study design and methodology, funding acquisition, study oversight and project administration, investigation and data review, data verification and interpretation, and critical review of the manuscript. All authors had full access to all the data in the study, provided final

approval of the manuscript content, and had responsibility for the decision to submit the manuscript for publication.

Declaration of interests

PN has received payments to her institution from the Patient-Centered Outcomes Research Institute (PCORI); travel support from the Myasthenia Gravis Foundation of America; research support from Alexion, Momenta/Janssen, and UCB/Ra; honoraria from the American Academy of Neurology and the American Association of Neuromuscular and Electrodiagnostic Medicine; payment for continuing medical education presentations from WebMD, AcademicCME, Neurodiem, Partners for Advancing Clinical Education, PeerVoice, and Haymarket CME; has participated in advisory boards for Alexion, Argenx, Janssen, and Dianthus; has served on a data safety monitoring board for Sanofi; and received consulting fees from GlaxoSmithKline and CVS Pharmacy. DBS has received payments to his institution from PCORI, consulting fees from Partnership for Health Analytic Research (PHAR), Becker, Modus Outcomes, Wise, Windrose Consulting Group, Avora Capital Advisors, and Sentient; publishing royalties for the book Single Fiber EMG; has participated in a data safety monitoring board for Horizon, Roche, Janssen, and Sanofi-Aventis; holds stocks in Regeneron and has participated in medical advisory boards for Accordant Health Services. JTG has received payments to their institution from PCORI and is currently employed by Argenx. LT, DT, JB, RD, AK, KB, and BL declare no competing interests.

Data sharing

De-identified participant data and a data dictionary will be shared at the request of investigators, with a signed data agreement, upon contacting pnarayan@bidmc.harvard.edu or donald.sanders@duke.edu.

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References

1 Narayanaswami P, Sanders DB, Wolfe G, et al. International consensus guidance for management of myasthenia gravis: 2020 update. *Neurology* 2021; **96:** 114–22.
2 Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: Executive summary. *Neurology* 2016; **87:** 419–25.
3 Hart IK, Sathasivam S, Sharshar T. Immunosuppressive agents for myasthenia gravis. *Cochrane Database Syst Rev* 2007; **2007:** CD005224.
4 Schneider-Gold C, Gajdos P, Toyka KV, Hohlfeld RR. Corticosteroids for myasthenia gravis. *Cochrane Database Syst Rev* 2005; **2005:** CD002828.
5 Bromberg MB, Wald JJ, Forshew DA, Feldman EL, Albers JW. Randomized trial of azathioprine or prednisone for initial immunosuppressive treatment of myasthenia gravis. *J Neurol Sci* 1997; **150:** 59–62.
6 Mantegazza R, Antozzi C, Peluchetti D, Sghirlanzoni A, Cornelio F. Azathioprine as a single drug or in combination with steroids in the treatment of myasthenia gravis. *J Neurol* 1988; **235:** 449–53.
7 Heckmann JM, LeePan EB, Eastman RW. High-dose immunosuppressive therapy in generalised myasthenia gravis—a 2-year follow-up study. *S Afr Med J* 2001; **91:** 765–70.
8 Gajdos P, Elkharrat D, Chevret S, et al. A randomised clinical trial comparing prednisone and azathioprine in myasthenia gravis. Results of the second interim analysis. *J Neurol Neurosurg Psychiatry* 1993; **56:** 1157–63.
9 Palace J, Newsom-Davis J, Lecky B. A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis. *Neurology* 1998; **50:** 1778–83.
10 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.
11 Ciafaloni E, Massey JM, Tucker-Lipscomb B, Sanders DB. Mycophenolate mofetil for myasthenia gravis: an open-label pilot study. *Neurology* 2001; **56:** 97–99.
12 Hanisch F, Wendt M, Zierz S. Mycophenolate mofetil as second line immunosuppressant in myasthenia gravis—a long-term prospective open-label study. *Eur J Med Res* 2009; **14:** 364–66.
13 Chan JW. Mycophenolate mofetil for ocular myasthenia. *J Neurol* 2008; **255:** 510–13.
14 Hehir MK, Burns TM, Alpers J, Conaway MR, Sawa M, Sanders DB. Mycophenolate mofetil in AChR-antibody-positive myasthenia gravis: outcomes in 102 patients. *Muscle Nerve* 2010; **41:** 593–98.
15 Sanders DB, Hart IK, Mantegazza R, et al. An international, phase III, randomized trial of mycophenolate mofetil in myasthenia gravis. *Neurology* 2008; **71:** 400–06.
16 Muscle Study Group. A trial of mycophenolate mofetil with prednisone as initial immunotherapy in myasthenia gravis. *Neurology* 2008; **71:** 394–99.
17 Meriggioli MN, Rowin J, Richman JG, Leurgans S. Mycophenolate mofetil for myasthenia gravis: a double-blind, placebo-controlled pilot study. *Ann NY Acad Sci* 2003; **998:** 494–99.
18 National Institute of Neurological Disorders and Stroke Common Data Elements. Myasthenia gravis. https://www.commondataelements.ninds.nih.gov/Myasthenia%20Gravis (accessed November 4, 2020).
19 Jaretzki A 3rd, Barohn RJ, Ernstoff RM, et al. Myasthenia gravis: recommendations for clinical research standards. *Neurology* 2000; **55:** 16–23.
20 Burns TM, Sadjadi R, Utsugisawa K, et al. International clinimetric evaluation of the MG-QOL15, resulting in slight revision and subsequent validation of the MG-QOL15r. *Muscle Nerve* 2016; **54:** 1015–22.
21 Wolfe GI, Herbelin L, Nations SP, Foster B, Bryan WW, Barohn RJ. Myasthenia gravis activities of daily living profile. *Neurology* 1999; **52:** 1487–89.
22 Burns TM, Conaway M, Sanders DB. The MG Composite: a valid and reliable outcome measure for myasthenia gravis. *Neurology* 2010; **74:** 1434–40.
23 Sanders DB, Tucker-Lipscomb B, Massey JM. A simple manual muscle test for myasthenia gravis: validation and comparison with the QMG score. *Ann NY Acad Sci* 2003; **998:** 440–44.
24 Narayanaswami P, Sanders DB, Bibeau K, Krueger A, Venitz J, Guptill JT. Identifying a patient-centered outcome measure for a comparative effectiveness treatment trial in myasthenia gravis. *Muscle Nerve* 2022; **65:** 75–81.
25 US National Institutes of Health, US Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0. May 28, 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf (accessed April 12, 2020).
26 Muppidi S, Wolfe GI, Conaway M, Burns TM. MG-ADL: still a relevant outcome measure. *Muscle Nerve* 2011; **44:** 727–31.
27 Hoeltzenbein M, Elefant E, Vial T, et al. Teratogenicity of mycophenolate confirmed in a prospective study of the European Network of Teratology Information Services. *Am J Med Genet A* 2012; **158A:** 588–96.
28 Howard JF Jr, Bril V, Vu T, et al. Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol* 2021; **20:** 526–36.
29 Howard JF Jr, Utsugisawa K, Benatar M, et al. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. *Lancet Neurol* 2017; **16:** 976–86.
30 Vu T, Meisel A, Mantegazza R, et al. Terminal Complement Inhibitor Ravulizumab inGeneralized Myasthenia Gravis. *NEJM Evid* 2022; **1:** 1–12.
31 Bril V, Drużdż A, Grosskreutz J, et al. Safety and efficacy of rozanolixizumab in patients with generalised myasthenia gravis (MycarinG): a randomised, double-blind, placebo-controlled, adaptive phase 3 study. *Lancet Neurol* 2023; **22:** 383–94.
32 Howard JF Jr, Bresch S, Genge A, et al. Safety and efficacy of zilucoplan in patients with generalised myasthenia gravis (RAISE): a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Neurol* 2023; **22:** 395–406.