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Efficacy of Prednisone for the Treatment of Ocular Myasthenia (EPITOME): A Randomized Controlled Trial

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Abstract

Objective—We evaluated the safety, tolerability, and effectiveness of prednisone in patients with ocular myasthenia gravis (OMG) concurrently treated with pyridostigmine.

Methods—Randomized, double-blind, placebo-controlled trial. Participants whose symptoms failed to remit on pyridostigmine were randomized to receive placebo or prednisone, initiated at 10mg every other day and titrated to a maximum of 40mg/day over 16-weeks. Primary outcome measure was treatment failure.

Results—Fewer subjects were randomized than the 88 planned. Of the 11 randomized, 9 completed 16-weeks of double-blind therapy. Treatment failure incidence was 100% (95% CI 48–100%) in the placebo group (n=5) vs. 17% (95% CI 0–64%) in the prednisone group, $P = 0.02$ (n=6). Median time to sustained minimal manifestation status (MMS) was 14-weeks, requiring an average prednisone dosage of 15mg/day. Adverse events were infrequent and generally mild in both groups.

Conclusions—A strategy of low-dose prednisone with gradual escalation appears to be safe, well tolerated, and effective in treating OMG.

Keywords

ocular myasthenia; prednisone; steroids; clinical trial; neuromuscular

Introduction

Myasthenia gravis (MG) is a generalized disorder that often manifests initially as focal weakness. The most common focal presentation involves weakness of the extraocular muscles, eyelid levators and orbicularis oculi, with symptoms of ptosis and diplopia. The estimated prevalence of MG is approximately 10 per 100,000, and approximately 60% of patients initially present with isolated ocular symptoms[1–3]. Estimates of the frequency with

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Conflicts of Interest

None

which these patients progress to develop generalized myasthenia gravis vary widely from 50% to 80%[2, 4–11,12].

The goals of treatment for ocular myasthenia gravis (OMG) are to return the individual to a state of clear vision and to prevent the development or limit the severity of generalized myasthenia gravis (GMG). Treatments proposed for OMG include drugs with a purely symptomatic effect such as cholinesterase inhibitors, as well as drugs that suppress the immune system, such as corticosteroids. Proponents of steroids point to the limited efficacy of pyridostigmine, the possibility that chronic cholinesterase-inhibitor therapy may exacerbate the cholinergic deficit in myasthenia[13], the potentially greater beneficial effects of prednisone, and the potential for steroids to reduce the risk of progression from ocular to generalized disease. Opponents of steroids emphasize the potential risk of serious side effects and question whether these risks are justified in the setting of purely ocular symptoms.

There has been 1 prior randomized controlled trial (RCT) relevant to the use of steroids in OMG[5, 9, 14]. This trial, however, did not permit any conclusion regarding the efficacy of steroid therapy, as patients were only treated for 8 days and outcomes were reported solely in terms of the degree of ophthalmoplegia. There have also been 7 non-randomized observational studies[15–21], 5 of which suggested a possible benefit of steroids in reducing the risk of progression to GMG[15–17, 19, 21] and 2 of which suggested a favorable symptomatic effect[20, 21]. However, in view of the paucity and limited methodological quality of the available data, controversy persists regarding the optimal approach to the treatment of patients with OMG[22–24]. The importance of the clinical question and the absence of convincing evidence of efficacy and safety, combined with the equipoise among neuromuscular specialists, provide justification for an RCT to evaluate the safety and efficacy of prednisone in the treatment of OMG[14].

Materials and Methods

Study design[25]

The Efficacy of Prednisone in the Treatment of Ocular Myasthenia (EPITOME) trial was a randomized, double blind, parallel group, placebo-controlled trial of prednisone for treatment of OMG. Following enrollment, all subjects were treated with pyridostigmine for a period of 4–6 weeks, with dosage escalated until efficacy [i.e., minimal manifestation status (MMS)[26]] or toxicity that could not be mitigated with a selective muscarinic antagonist; the maximum pyridostigmine dosage permitted was 480mg/day. Subjects whose symptoms failed to remit continued to take pyridostigmine and were randomized to either prednisone or placebo for 16 weeks (Stage 1). Following this 16-week period of double-blind therapy, subjects whose symptoms failed to remit were crossed over to treatment with high dosagee prednisone (60mg/day) for a period of 16 weeks (Stage 2). For subjects whose symptoms did remit during Stage 1, study drug was tapered in a double-blind manner during Stage 2 (Figure 1). The institutional review board (IRB) of each participating center approved the study protocol, and all subjects provided written informed consent. The study was registered with clinicaltrials.gov (NCT NCT00995722).

Study participants

Trial eligibility criteria (Supplementary table S1, available online) aimed to enroll a sample of patients with new or recent onset of purely ocular myasthenia who had not previously received immunosuppressive or modulating therapy and who had not already received prednisone. Patients were enrolled at 6 academic centers across the United States and Canada including the University of Miami (Miami, FL), Duke University (Durham, NC), Kansas University Medical Center (Kansas City, MS), Yale University (New Haven, CT), University of Vermont (Vermont, NH), and University of Toronto (Toronto, Ontario).

Investigational Product

Prednisone and placebo tablets were over-encapsulated by the University of Iowa Research Pharmacy to produce matching capsules. The Clinical Materials Services Unit (CMSU) at the University of Rochester was responsible for investigational product packaging, labeling, and distribution to study sites.

Randomization and Blinding

Participants were randomized 1:1 to receive either prednisone or matching placebo. The randomization schedule was developed by the Muscle Study Group (MSG) Biostatistics Center at the University of Rochester. Randomization was stratified by center and included blocking to ensure approximate balance of treatment group assignments within each center at any point during the trial. Randomization was implemented using a secure web-based module that was accessible by each site; the module returned the appropriate drug pack number following confirmation of subject eligibility. All study staff, other than the programmer in the MSG Biostatistics Center who generated the randomization plan and the CMSU research pharmacist, remained blinded to treatment assignments throughout the study. To promote maintenance of blinding, an evaluator blinded to drug assignment and the occurrence of adverse events performed all efficacy outcome assessments. The treating neurologist was responsible for reviewing safety data.

Interventions

During Stage 1, the trial evaluated a prednisone dosing strategy of starting low and titrating upward as needed based on efficacy and safety/tolerability, rather than a fixed dose of prednisone. Prednisone was started at a dosage of 10mg every other day; it was then initially increased to 10mg/day, then 20mg alternating with 10mg, and so forth, with adjustments in dose made no more frequently than every 2 weeks. The maximum dosage allowed during Stage 1 was 40mg/day. The dose was titrated according to whether MMS had been attained and the presence and nature of adverse events. Dosage escalation was constrained by toxicity that did not respond to appropriate medical intervention. The strategy of starting low (and utilizing an alternate day approach) was motivated by the empiric belief that higher doses of prednisone are more likely to be associated with steroid-induced side effects, especially in patients with relevant comorbidities (e.g. diabetes). During Stage 2, participants who had not achieved MMS during Stage 1 were assigned to receive high dosage prednisone (60mg/day), and the dose was tapered thereafter based on efficacy and safety/tolerability. The dose was initially reduced to 50mg/day, then 40mg/day, and so forth down to 10mg/day,

with adjustments made every 2 weeks. After 2 weeks at 10mg/day, the dose could be reduced to 10mg every other day, the lowest dosage permitted during open-label treatment.

Outcomes

The schedule of in-person visits and telephone contacts is outlined in Figure 1. The primary outcome measure was treatment failure, defined as failure to achieve sustained MMS[26], progression to GMG, or toxicity leading to discontinuation of study drug by Week 16. Sustained MMS was defined as the appearance of MMS that was maintained across 2 consecutive in-person evaluations 4 weeks apart. Progression to GMG was based on a clinical assessment by the treating neurologist that included MG-specific manual muscle testing[27] and careful inquiry about the presence of swallowing or breathing symptoms that could be attributed to MG. Secondary outcome measures included the time to sustained MMS, change in ocular Quantitative Myasthenia Gravis (QMG) score[25], changes in quality of life as measured by the National Eye Institute Visual Function Questionnaire (NEI-VFQ-25)[28], the 10-item neuro-ophthalmological supplement to the NEI-VFQ-25[29], and the MG-Qol-15[30], each administered at baseline and Week 16, as well as the occurrence of individual adverse events. To enhance detection of steroid-related side effects (even if not reported subjectively), all study participants underwent glucose tolerance tests (or hemoglobin A1c measurement for known diabetics) as well as bone dual energy x-ray absorptiometry (DEXA) scans and ophthalmological examinations (for cataracts and glaucoma) prior to randomization and again at the time of study completion. All outcome assessments were performed at least 12 hours after the last dose of pyridostigmine.

Sample size

Preliminary studies indicated that 75% of OMG patients would achieve remission on prednisone plus pyridostigmine (after failing to remit on pyridostigmine alone), compared to 31% on pyridostigmine alone[20]. Sample size estimates were based on the assumptions that (a) fewer than 75% of the prednisone treated participants would achieve MMS, i.e. that at least 25% would experience treatment failure; (b) that < 31% of the placebo treated group would remit, i.e. ≥ 69% would experience treatment failure; and (c) the rate of adverse events requiring drug discontinuation would be ~10% and, as a result, ≥ 35% (≥ 25% + 10%) of subjects in the prednisone group would experience treatment failure. A total sample size of 80 subjects (40 per group) was determined to provide at least 80% power to detect a group difference of 30%–35% in the incidence of treatment failure using a chi-square test and a 5% significance level, as long as the proportion of treatment failures in the placebo group was at least 75%. We planned to enroll 88 subjects to account for a projected loss-to-follow-up rate of ≤ 10%.

Statistical methods

The Fisher exact test was used to compare the incidence of treatment failure in the treatment groups. All randomized subjects were included in the analysis in accordance with the intention-to-treat principle. Analysis of covariance was used to compare mean values of secondary outcome variables (changes in ocular QMG score and quality of life scores) between treatment groups at Week 16, adjusting for the baseline value of the outcome variable. A significance level of 5% (two-tailed) was used for hypothesis testing.

Safety monitoring

An independent data and safety monitoring board (DSMB), comprising 2 neurologists and a statistician, approved the study protocol and periodically reviewed study data for participant safety, study conduct, and progress. An independent and blinded medical monitor reviewed all serious adverse events (SAEs).

Results

Participants

The trial was open for enrollment for 34 months between January 2011 and October 2013 at 9 clinical centers in the United States and Canada. The trial was closed early due to slow participant accrual. This decision was made by the Trial Steering Committee (with approval of the DSMB) while blinded to treatment group and study results. One hundred forty-five patients were approached for participation; 23 declined to participate, and 107 failed pre-screening. Among the remaining 15 patients assessed for eligibility, 11 were randomized, 6 (55%) to prednisone and 5 (45%) to placebo. One of the participants randomized to placebo withdrew consent prior to receipt of study drug, but was included in the analysis in accordance with the intention-to-treat principle. One participant stopped treatment at Week 12 due to early trial closure. The remaining 9 participants completed 16 weeks of double-blind treatment (Figure 2). There were no substantial differences between treatment groups with respect to baseline characteristics (Table 1).

Efficacy

No subjects progressed to GMG or discontinued study drug due to toxicity. All 5 placebo-treated subjects (100%) experienced treatment failure by failing to achieve sustained MMS (95% CI 48–100%), compared to 1 of 6 subjects (17%) in the prednisone-treated group (95% CI 0–64%) ($P = 0.02$, Fisher exact test). The 1 prednisone-treated patient who did not achieve MMS was withdrawn at week 16 due to early trial closure. The prednisone-treated subjects achieved MMS at Weeks 4 (n=1), 8 (n=2), 12 (n=1), and 16 (n=1). The median time to sustained MMS was 14 weeks. The median (range) prednisone dosage at the time of sustained MMS was 15mg/day (15–25mg/day). Per protocol, study subjects who achieved sustained MMS successfully tapered their prednisone dosage to a median (range) dose of 10mg/day (10–15mg/day) without relapse of symptoms. Observed mean responses on the secondary outcome measures were better in the prednisone group than in the placebo group, but the group differences were not statistically significant (Table 2). Individual subject responses are displayed in Figure 3.

Open-label high-dosage prednisone

Three of 5 placebo-treated participants switched to high-dosage prednisone (60mg/day) with rapid taper. Sustained MMS was attained in 2 subjects within 4 and 8 weeks, respectively. Of the other 2 participants randomized to receive placebo, 1 never received study drug and the other was withdrawn early due to study closure.

Safety

Thirty adverse events (AEs) were reported during the double-blind phase of the study, 8 of which led to a reduction in dose of study medication (Table 3). Twenty-two of these AEs occurred in the prednisone group, and 8 occurred in the placebo group. Four serious adverse events were reported during the course of the trial, 3 in the placebo group and 1 in the prednisone group, but none were judged to be related to study medication. Based on two-hour glucose tolerance tests and DEXA bone scans, there were no new diagnoses of impaired glucose tolerance, diabetes, or osteopenia/osteoporosis during the course of the trial. Weight gain in 2 prednisone-treated participants during the double-blind phase of the trial prompted a reduction in the dose of study drug, but both participants still achieved sustained MMS, 1 by Week 12 and 1 by Week 20.

Discussion

The major limitation of this study is the small sample size, which was a function of slow patient enrollment (approximately 1 eligible patient identified every 2 months, with approximately 1 patient enrolled every 3 months across the 9 study centers). Although initially planned as a 5 center clinical trial, a decision was made soon after enrollment opened to expand the number of enrolling centers. The reasons for slow patient accrual include strong patient preferences (either to be on steroids or not to take steroids), the availability of prednisone outside of the trial, prednisone initiation prior to referral to study centers, and logistics [patient travel, number of visits, and the complexity of coordinating availability of 2 physicians (treating neurologist and blinded evaluator) for each study visit]. Slow recruitment appears to be a common problem in MG RCTs, as many studies have terminated prematurely for this reason[31].

Notwithstanding the small number of participants enrolled in this trial, the primary efficacy analysis demonstrated a clinically and statistically significant benefit of prednisone compared to placebo. Five of 6 participants (83%) in the prednisone group achieved the primary end-point of sustained MMS at a median of 14 weeks on a median prednisone dosage of 15mg/day, compared to none of the 5 participants in the placebo group. The observation that none of the patients in the placebo group achieved MMS may, at least in part, be a function of an important element of study design – that all patients were initially treated with pyridostigmine and that those who responded were not randomized to receive study drug (i.e. those ”patients who responded to pyridostigmine alone were not randomized). Secondary outcome measures also favored the prednisone group (although not reaching statistical significance). The estimated effect of prednisone of 3.8 points in mean MG-QoL score would be considered clinically meaningful, but the effect is imprecisely estimated in this small trial

It is of interest that the 2 of the 3 placebo-treated patients who switched over to high-dose prednisone achieved MMS within 4 and 8 weeks, respectively. While EPITOME was designed to shed light on the utility of high-dose prednisone, the small number of subjects enrolled, the even smaller number switched over to high dose prednisone, and the unblinded nature of the data make it difficult to draw conclusions about the relative utility of this treatment approach.

Adverse events were typically mild and did not generally require drug discontinuation. However, it should be noted that the duration of steroid treatment was relatively short (maximum of 36 weeks), and so the long-term safety of low-dose steroids in this population remains unclear. Nevertheless, at the dosage needed to achieve clinical improvement, prednisone appears to be safe and well tolerated. These data support the strategy of treating patients with OMG whose symptoms have failed to remit on pyridostigmine therapy alone with an initial low-dosage of prednisone followed by a gradual titration until efficacy is achieved.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

AE	Adverse Event
CI	Confidence Interval
CMSU	Clinical Material Services Unit
DEXA	Dual Energy X-ray Absorptiometry
DSMB	Data Safety Monitoring Board
EPITOME	Efficacy of Prednisone for Treatment of Ocular Myasthenia
GMG	Generalized Myasthenia Gravis
IRB	Institutional Review Board
MG-QoL-15	Myasthenia Gravis Quality of Life – 15 item Scale
MMS	Minimal Manifestation Status
MSG	Muscle Study Group
QMG	Quantitative Myasthenia Gravis Score
NEI-VFQ-25	National Eye Institute Visual Function Questionnaire 25
NCT	Clinicaltrials.gov Identifier
OMG	Ocular Myasthenia Gravis
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event

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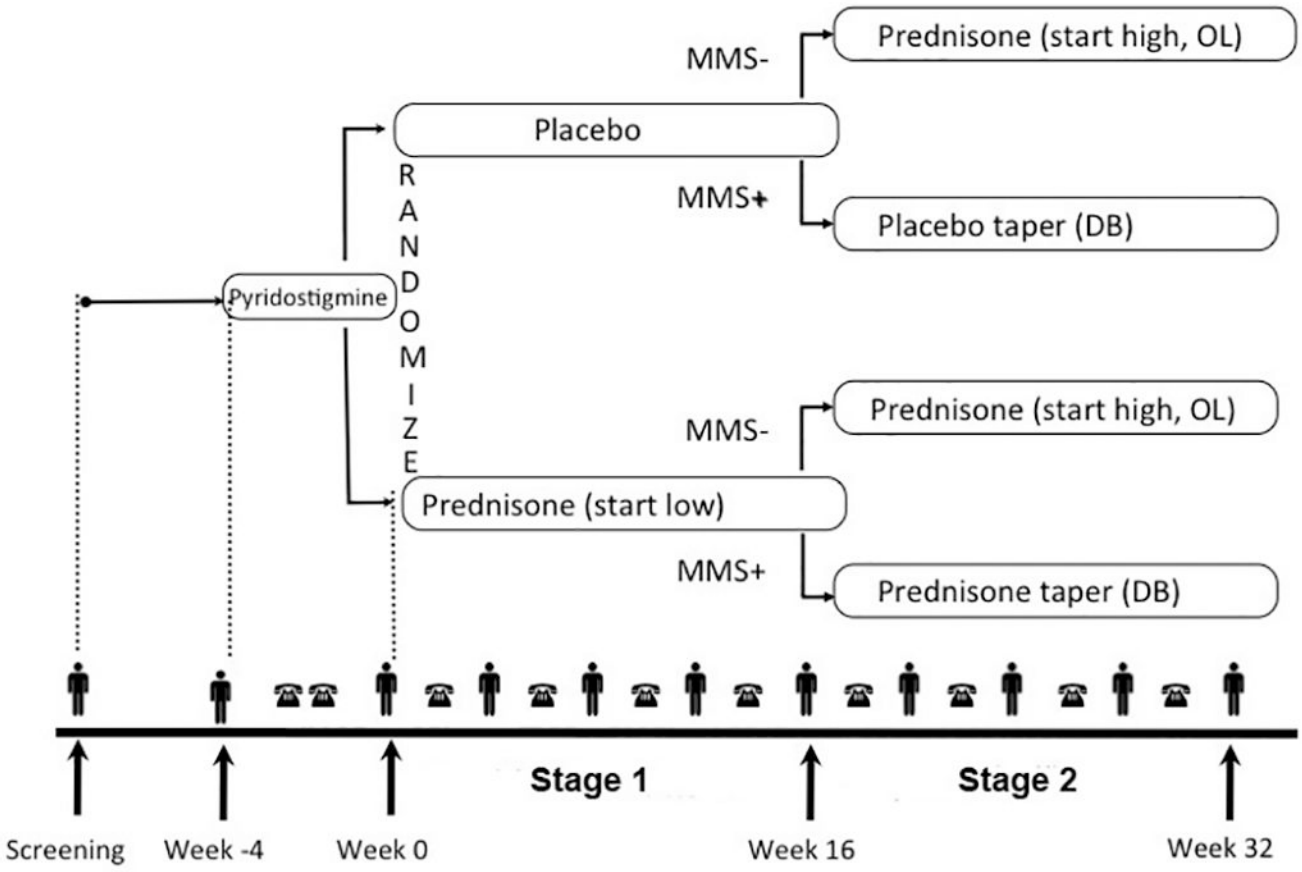

Figure 1. Study Schema

Following enrollment (Week -4), study participants were treated with escalating doses of pyridostigmine for a period of 4 weeks. Those who did not achieve MMS were randomized to receive prednisone or placebo in a double-blind manner (Stage 1). Outcomes were assessed at Week 16, following which those participants who had not yet achieved MMS were crossed over to receive open-label high-dose prednisone (Stage 2). MMS – minimal manifestation status; OL – open label; DB – double-blind. 🧍 indicates in-person visit; ☎ indicates telephone visit.

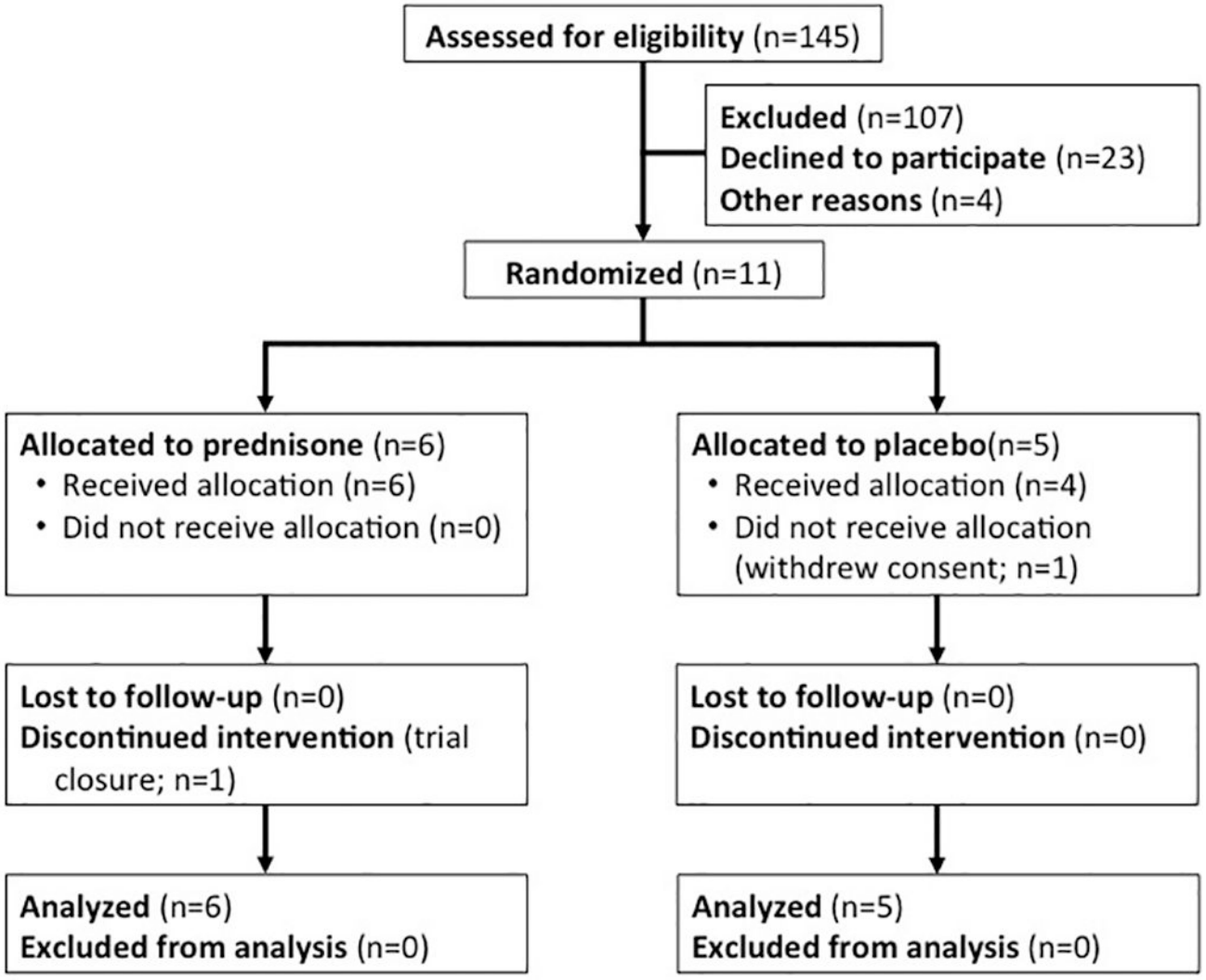

Figure 2. Participant Flow for Double-Blind Phase

Of the 145 patients assessed for eligibility, 11 were randomized, and 10 received study drug. No participants were lost to follow-up, and all 11 participants were included in the primary analysis.

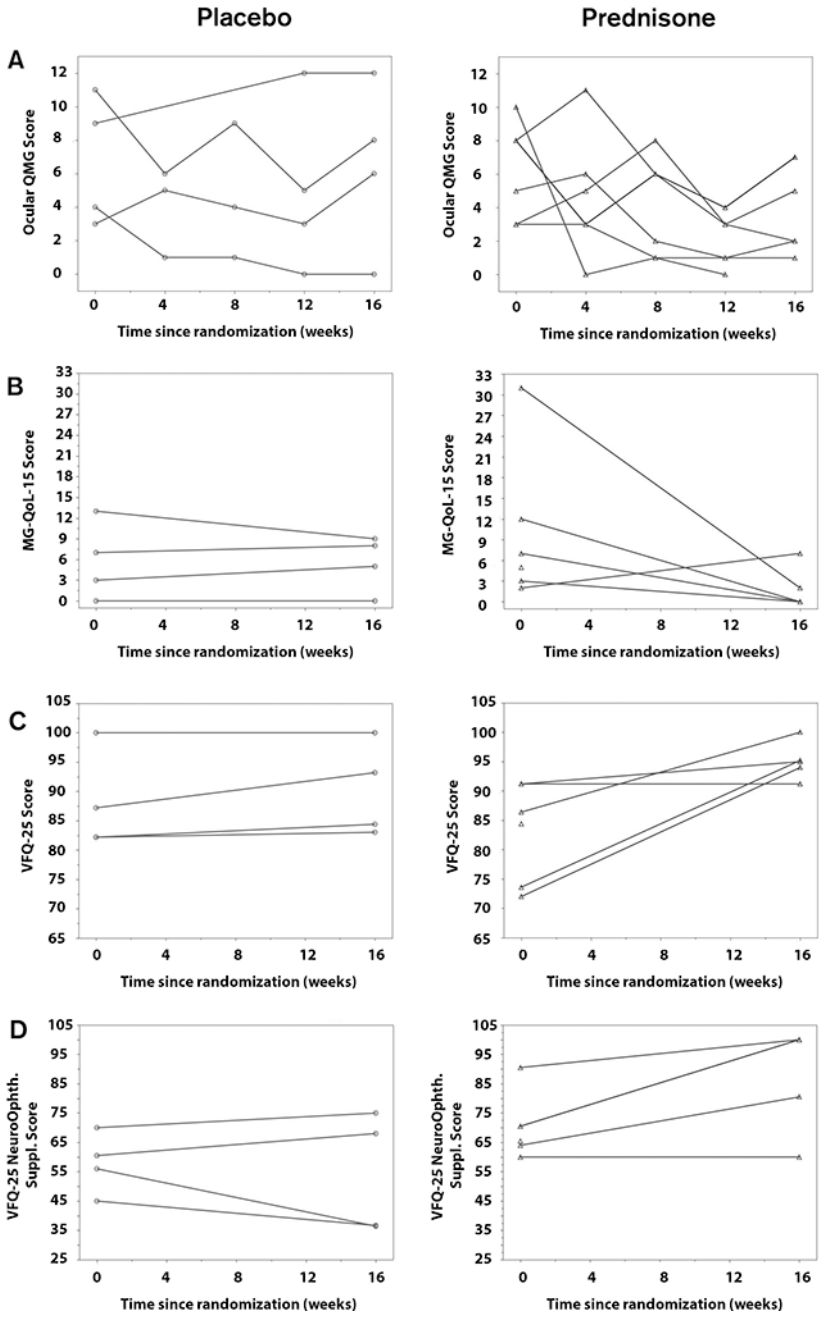

Figure 3. Secondary Outcome Measures

A. Ocular QMG scores at each time point between randomization (Week 0) and the end of the double-blind phase of the trial (Week 16); scores range from 0 (normal) to a maximum of 15. **B.** MG-QoL-15 scores at randomization and Week 16; scores range from 0 (normal) to a maximum of 60. **C.** NEI-VFQ-25 scores at randomization and Week 16; scores range from 0 to 100 (normal). **D.** NEI-VFQ-25 10-item neuro-ophthalmological supplement scores at randomization and Week 16; scores range from 0 to 100 (normal).

Table 1

Pre-Randomization Characteristics

	Placebo (n = 5)	Prednisone (n = 6)
Men, n (%)	2 (40%)	4 (67%)
Age (years), mean (SD)	62 (9)	64 (18)
White, n (%)	4 (80%)	4 (67%)
Disease duration (months), median (range)	5 (4–17)	7.5 (1–18)
Diagnostic tests, n (%)		
AChR Antibodies	3 (60%)	2 (33%)
Single fiber EMG	2 (40%)	2 (33%)
Ice test	1 (20%)	3 (50%)
Pyridostigmine dosage (mg/day), median (range)	360 (240–480)	330 (0–480)
Medical history, n (%)		
Impaired glucose tolerance	2 (40%)	2 (40%)
Diabetes	0	0
Glaucoma	0	0
Cataracts	3 (60%)	2 (33%)
Osteopenia or osteoporosis	3 (60%)	2 (33%)
MG-QoL-15 score, median (range)	3 (0–13)	6 (2–31)
NEI-VFQ-25 score, median (range)	87 (82–100)	85 (72–91)
NEI-VFQ-25 10-item neuro-ophthalmological supplement score, median (range)	61 (45–80)	68 (60–91)
Ocular QMG score, median (range)	6 (3–11)	6.5 (3–10)

Table 2

Secondary Outcome Measures at End of Double-Blind Treatment

Outcome Measure	Prednisone	Placebo	Rx Effect	95% CI	p-value
MG-QoL-15 score [1]	−6.30	−2.50	−3.81	−9.37 to 1.75	0.15
NEI-VFQ-25 score [2]	10.70	4.14	+6.56	−2.59 to 15.71	0.13
10-item supplement [2]	15.28	−1.70	+ 16.98	−9.22 to 43.17	0.16
Ocular QMG score [3]	−2.25	−0.05	−2.20	−7.20 to 2.80	0.37

Values presented are mean changes from baseline to Week 20, treatment effects (prednisone – placebo), 95% confidence intervals (CI), and *P*-values, all obtained from an analysis of covariance model that adjusts for the baseline value of the outcome variable.

[1]MG-Qol-15 score ranges from 0–60, where 0 is normal, and a reduction in score represents an improvement

[2]NEI-VFQ-25 and the 10-item neuro-ophthalmological supplement scores range from 0–100, where 100 is normal, and an increase in score represents an improvement.

[3]Ocular QMG score ranges from 0–15, where 0 is normal, and a reduction in score represents an improvement.

Table 3

Adverse Events Following Randomization

	Placebo	Prednisone
Gastrointestinal		
Constipation	0	1
Diarrhea	1	2 *
Flatulence	0	1
Nausea	0	2
Dysphagia	0	1
Neurological		
Agitation	0	1 *
Anxiety	1	0
Blepharospasm	0	1
Blurred vision	0	1
Headaches	0	1
Insomnia	1 *	0
Eye fasciculations	0	1
Face fasciculations	0	1
Cardiovascular		
Arrhythmia	0	1
Conduction disorder	1	0
Palpitations	1 *	0
Sinus tachycardia	1 *	0
Respiratory		
Bronchitis	0	1
Endocrine/Metabolic		
Impaired glucose tolerance	0	1 *
Weight gain	0	2 *
Miscellaneous		
Dizziness	1	0
Edema	0	2
Hematoma	0	1
Myalgia/Cramping	0	1
Eye pain (poked in eye)	1	0
TOTAL	8	22

* Indicates that AE led to a reduction in dose of study medication.

Dose was reduced because of diarrhea in only 1 of the 2 patients in the prednisone group.