THE TOP TEN: THERAPY IN MYASTHENIA GRAVIS

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Case 1: Initiation of Immunosuppressive Therapy

A 63 y/o white male presents with a 2-month history of fatigable ptosis, diplopia, slurred speech and proximal muscle weakness. Prior work-up included a positive acetylcholine receptor antibody and a repetitive stimulation study showing a 24% decrement with stimulation of the left facial nerve recording over the orbicularis oculi. The patient was started on pyridostigmine (Mestinon) 60 mg QID, however, after 2 weeks of therapy, he is still unable to arise from a chair without assistance and is unable to drive or read the newspaper due to persistent diplopia. What options should you consider for the initiation of immunosuppressant therapy?


Except in mild cases, patients with myasthenia gravis (mg) require immunosuppressant therapy to suppress the destructive activity of acetylcholine receptor antibodies at the neuromuscular junction. The lack of standardized outcome measures and direct comparison studies make it difficult to determine the “best” immunosuppressive regimen for mg.

Prednisone remains the most common therapy prescribed in mg, however there has recently been considerable debate in the literature as to whether steroids are “over-utilized” as initial therapy. The initial dose of prednisone is usually 60-100mg daily which can lead to transient worsening of symptoms within the first several weeks of therapy in up to 30% of patients. In addition, high dose steroid therapy can result in significant side effects including glucose intolerance, weight gain, mood swings, depression, facial puffiness, hypertension, hypokalemia, and gastritis. Long-term side effects are also common including osteoporosis, skin atrophy, cushingoid features, easy bruising, impaired wound healing, and avascular necrosis of the hip. In an attempt to avoid long-term, high dose prednisone therapy, several recent studies have evaluated alternative initial treatment regimens.

Palace et al (1) performed a randomized, double-blind controlled trial involving 34 anti-acetylcholine receptor antibody (achr-ab) positive mg patients treated with either prednisone given on alternate days plus daily azathioprine or prednisone plus daily placebo. All patients received initial high-dose prednisone (100 mg on alternate days or 1.5mg/kg) and patients randomized to receive azathioprine were treated with 2.5 mg/kg daily. The initial prednisone dose was maintained until remission developed and then the dose was tapered and adjusted to the minimal dose required to maintain remission. Patients were followed up for 3 years. The median prednisone dose did not differ between the two treatment groups at 12 months but was significantly reduced at 36 months (pred+plac, 40mg range 0 to 100mg; pred+aza, 0 mg, range 0 to 35 mg; p=0.02). At the end of the study, 63% of patients in the pred+aza group no longer required prednisone to maintain remission compared to 20% in the pred+plac group. Treatment failures were significantly lower in the pred+aza group (p=0.024). Median weight gains in years 2 and 3 were greater in the pred+plac group (6.3 kg and 5.3kg, respectively) when compared with the pred+aza group (2.0 kg in years 2 and 3). Abnormal liver function tests occurred in 0% of patients in years 2 and 3. The authors concluded that initial treatment with azathioprine as an adjunct to alternate day prednisone is associated with fewer treatment failures, longer remissions, and fewer side effects.
Koski (2) performed a study of 11 AchR-Ab positive MG patients to determine whether intravenous immunoglobulin (IVIG) could be used to facilitate the induction of immunosuppressive therapy. All patients had debilitating bulbar weakness with prominent dysarthria and dysphagia and/or a significant reduction up to 80% of their forced vital capacity. Patients were placed on either azathioprine (150-200 mg/d) or mycophenolate mofetil (2-3 grams/d). Since the effect of these agents is known to be delayed by up to six months, patients were also treated with IVIG 2 grams/kg the first month and 1 gram/kg over the following 3-4 months. Patients were evaluated monthly with the Drachman Scale (D5 being the most severely compromised and D0 = normal) and with the MG Foundation of American Clinical Classification (MGFA). Patients were initially rated on the Drachman scales as D3.82 ± 0.98. On the MGFA, 9 patients were either moderately, III a/b (N=5) or severely weak, IVb (N=4) and one was V, respirator dependent. All improved to D1.8 ± 1.1 after 3 months and D0.9+/-0.7 within a year. Vital capacity improved to >80% in all patients and 10 of 11 patients had normal bulbar function. On the MGFA classification, patients were 0 (N=2), I (N=4), or II (N=5). This study suggests that IVIG can be used successfully in the initial period of treatment with either azathioprine or mycophenolate mofetil, thereby eliminating the need to treat with high dose prednisone. The results of this study will be verified with a prospective, randomized trial which is currently being planned.

Meriggioli et al (3) reported a retrospective analysis of the use of mycophenolate mofetil (MyM) in 85 MG patients. The MGFA postintervention status (PIS) was used to characterize the treatment response for each patient in addition to manual muscle testing and quantitative MG scores (QMG) in selected patients. MyM doses ranged from 1-3 grams/day. Sixty-two patients (73%) achieved a PIS classification of pharmacologic remission, minimal manifestations, or improved, indicating clinical improvement. MMT and QMG scores were all significantly improved after treatment. Subgroup analysis revealed no significant differences in response based on AChR-Ab or thymectomy status, duration of MyM therapy, or disease severity, except that 38% of 13 patients with severe weakness (MGFA class IV) did not improve after taking MyM. The corticosteroid dose was decreased by at least 50% in 23 patients (37%) and by less than 50% in 13 (21%). The corticosteroid dose remained unchanged in 14 patients and was increased in one. In patients who improved, the mean time to onset of subjective improvement was 8.8 weeks; the mean time to first objective improvement was 10.8 weeks (range 4 to 40 weeks). The mean time to maximal objective improvement was 26.7 weeks (range 8 to 104 weeks). MyM was well tolerated in most patients and was discontinued because of side effects in only 6% of patients. The most common reason for discontinuing treatment was gastrointestinal intolerance, particularly diarrhea. This data suggests that MyM is effective as an adjunctive and steroid-sparing agent, and as the initial or sole form of immunotherapy in MG. The main advantage of MyM appears to be its tolerability and safety profile. Some evidence indicates that long-term use of both azathioprine and cyclosporine may increase the risk of developing certain malignancies. The long-term safety of MyM is not known, but rates of malignancy do not appear to be increased in transplant recipients receiving MyM chronically. A randomized, controlled trial of MyM in MG is currently in progress.

**Case 2: Treatment of the “Refractory” Patient**

A 45 y/o black female with a history of generalized, acetylcholine receptor positive myasthenia gravis is referred to your office for a second opinion for management of her immunosuppressant therapy. She has previously been treated with prednisone, azathioprine, cyclosporine, and mycophenolate mofetil and all of these agents have either been poorly tolerated or ineffective. What are your therapeutic options in this “refractory” patient?


Conventional treatment of MG with immunosuppressive agents that are currently available, such as prednisone, azathioprine, cyclosporine, and mycophenolate mofetil, is often effective. Occasionally, however, MG patients do not respond to substantial doses of these agents or cannot tolerate their adverse side effects. Treatment of these “refractory” patients has traditionally included repeated plasma exchange which provides only temporary benefit and is both expensive and inconvenient.
Achiron et al (4) evaluated the efficacy and safety of high-dose IVIG therapy in an open-label study of 10 patients with severe generalized MG who presented with an acute deterioration not attributable to concomitant infection and unresponsive to conventional therapy including pyridostigmine (240-360 mg/d, 8 patients), high-dose prednisone (30-60 mg/d, 9 patients), or azathioprine (100-300 mg/d, 5 patients). Patients were admitted and treated with 400mg/kg/d of IVIG for 5 consecutive days every 6 weeks. Clinical evaluations were performed at the onset of IVIG therapy and daily during the first week, once a week for the first month, and then once every 6 weeks for a period of 1 year. All 10 patients benefited from IVIG treatment. Initial improvement was observed at 6.4 ± 2.2 days after the start of IVIG treatment and became maximal at 10.5 ± 1.6 days. Severity of disease decreased from a mean Osserman score of 3.7 ± 0.5 (severe generalized disease) to 2.2 ± 0.7 (mild to moderate disease) (p<0.001). Forced expiratory volume (FEV) improved from a mean of 1148 ± 568 to 1810 ± 722 mL. The timed forward arms abduction increased from 15 ± 6.7 s to 64 ± 39.1 s (p<0.05). Ptosis evaluated by palpebral fissure width after 30 s of upward gaze improved from 6.7 ± 3.9 mm to 9.5 ± 2.4 (p<0.01). Acetylcholine receptor antibody titers decreased during IVIG induction period by a mean of 63%. The duration of IVIG single-course beneficial effects lasted for 32 ± 5 days. Subsequent IVIG treatments were highly efficacious in maintaining improvement and no exacerbations occurred. The severity of disease decreased by 2.5 ± 0.8 grades of the Osserman scale over the one year period (p<0.001), in parallel with a reduction of immunosuppressive therapy (p<0.005). Attempts to discontinue IVIG maintenance treatment following completion of the study were successful in seven of the 10 patients within 1.5 to 3 years. The authors concluded that IVIG seems to be highly potent for inducing rapid improvement in refractory MG during acute deterioration as well as for maintaining remission.

Drachman et al (5) reported the results of "rebooting" the immune system with high dose cyclophosphamide in 3 MG patients who had been refractory to treatment with thymectomy, plasmapheresis, and conventional immunotherapeutic agents. Patients were hospitalized and after hydration, were administered cyclophosphamide daily (50mg/kg ideal body weight) over 1 hour through a Hickman catheter for 4 days. Nausea was treated prophylactically with IV ondansetron. Intravenous mesna (10mg/kg) was administered 30 minutes before and 3, 6, and 8 hours after the infusion to prevent hemorrhagic cystitis. Prophylactic antibiotics were given beginning 1 day after the last dose of cyclophosphamide and continued until the neutrophil count exceeded 0 cell/mm³. Prophylaxis against Pneumocystis carinii pneumonia with sulfamethoxazole (800mg) and trimethoprim (160mg) was given 2 days a week for 6 months. Packed red blood cells (RBCs) were given to maintain a hematocrit level greater than 25% (2 units were given to each patient). Beginning on day 6 after the last dose of cyclophosphamide, granulocyte colony stimulating factor (GCSF) 5 ug/kg was given daily until the neutrophil count exceeded 0 cell/mm³. The duration of IVIG single-course beneficial effects lasted for 32 ± 5 days. Subsequent IVIG treatments were highly efficacious in maintaining improvement and no exacerbations occurred. The severity of disease decreased by 2.5 ± 0.8 grades of the Osserman scale over the one year period (p<0.001), in parallel with a reduction of immunosuppressive therapy (p<0.005). Attempts to discontinue IVIG maintenance treatment following completion of the study were successful in seven of the 10 patients within 1.5 to 3 years. The authors concluded that IVIG seems to be highly potent for inducing rapid improvement in refractory MG during acute deterioration as well as for maintaining remission.

Konishi et al (6) investigated the efficacy of low-dose FK506 (tacrolimus, 3-5 mg/day) for the treatment of MG in a 16-week open clinical trial in 19 patients. FK506 is a new macrolide immunosuppressant which specifically inhibits the activation of T-cells. At enrollment, 18 of the 19 patients were receiving steroid therapy and all patients had previously undergone thymectomy. Patients had an MG ADL score of 2 or more, suggesting the need for additional immunosuppression to heighten clinical improvement. FK506 was initially administered at a dose of 3 mg/day orally after dinner. Five patients were later given doses of up to 5 mg/day. The blood level of FK506 was less than 10 ng/ml in all but one, in whom it was 12 ng/ml. At the end of the trial, total MG scores measuring muscle strength (range: 0-27) improved by 3 points or more in 7 of 19 patients (37%), and the MG ADL score (range: 0-6) also improved by 1 point or more in 8 of 19 patients (42%). Nine of 19 patients (47%) showed improvement in either MG or ADL scores. Clinical improvement was achieved rapidly with improvement in lower-limb strength documented by 2 weeks in most patients. Anti-AChR antibody titers were significantly decreased and there was a marked suppression of IL-2 production, to less than 10% of the pre-treatment basal level. An increase in neutrophil count and decrease in lymphocyte count were commonly seen during the treatment, but they were not serious and exhibited no relationship to FK506 concentration. No increase in serum creatinine levels was observed and Hemoglobin A1c levels did not differ between values obtained at enrollment. Twelve of the patients who completed the 16-week treatment elected to continue the therapy for up to 2 years. The efficacy demonstrated in the short-term study was maintained without serious side effects. The authors conclude that FK506 could safely serve as an adjunct to steroid therapy for MG at low dosage. Randomized, controlled trials are necessary to prove that low-dose, long-term administration of FK506 is efficacious and safe in MG and may be appropriate therapy for "refractory" patients.
**Case 3: Thymectomy – To Do or Not To Do?**

A 24 y/o Hispanic female with a five year history of oculo-bulbar myasthenia gravis presents to your office for a second opinion. Her symptoms have been relatively well controlled on prednisone 20mg qod, however, attempts to wean her dose in the past have resulted in severe relapses. She has been reluctant to consider thymectomy due to her concern regarding the scar that would result from the procedure. She wants to know what her chance of going into remission would be if she decided to proceed with the surgery and whether a less invasive procedure could be done. What advice can you give her?


Thymectomy has gained widespread acceptance as a form of treatment of non-thymomatous autoimmune MG, however its role remains uncertain due the absence of a definitive prospective, randomized trial. Key questions regarding thymectomy continue to include: (1) which patients are most likely to respond; (2) when should thymectomy be performed; (3) which patients should undergo the procedure; and (4) which type of surgical procedure is most effective. Unfortunately, all studies that address the effectiveness of thymectomy are retrospective or case control series. Gronseth and Barohn (7) published an AAN Practice Parameter based upon an evidence-based review of 28 articles describing outcomes in 21 MG cohorts from 1953 to 1998. Patients who underwent thymectomy were more likely to achieve medication-free remission, become asymptomatic, or show clinical improvement compared with patients who did not have thymectomy (median relative rates: 2.1, 1.6, and 1.7, respectively). However, among the patients who had undergone thymectomy, the median rates of remission, asymptomatic state or improvement were only 25%, 39%, and 70%, respectively (the mean rates are approximately 50% lower for each). Therefore, although a patient who undergoes thymectomy may be two times more likely to experience improvement, the majority of patients who have this operation will not experience remission or become completely asymptomatic. Peri-operative mortality rates were consistently less than 1% since 1970. Common morbidities included acute myasthenic respiratory failure in 6%, infection in 11%, and permanent nerve injury (recurrent laryngeal or phrenic nerve) in 2%.

The few controlled trials comparing outcomes in MG patients undergoing thymectomy with different surgical techniques demonstrate inconsistent results. In all of these studies, there were numerous confounding differences between MG patients in each technique group. Therefore, controlled trials currently do not provide convincing evidence that one thymectomy technique is superior. Based upon this evidence based review, the AAN Practice Parameter states that for patients with non-thymomatous autoimmune MG, thymectomy is recommend as an option to increase the probability of remission or improvement (Class II). A prospective, randomized trial of thymectomy is currently being planned as an international collaboration.

**Case 4: Treatment of MG Crisis**

A 32 y/o white female with a history of generalized MG presents to the emergency room due to a 3 day history of worsening dysphagia, proximal weakness, and shortness of breath. She is currently being treated with prednisone 20mg qod and pyridostigmine 60mg TID. Over the past 24 hours, she has been unable to swallow liquids without choking. Her forced vital capacity is 1.2 liters (25% of predicted). What treatment(s) are you going to recommend?


The treatment of MG crisis has traditionally included either plasma exchange (PE) or high-dose intravenous immunoglobulin (IVIG). Unfortunately, there is limited information regarding a comparison of their efficacy. Qureshi et al (8) performed a retrospective multi-center study to compare the efficacy and safety of PE and IVIG in a series of 54 episodes of MG crisis. In the PE group (28 episodes), five or six cycles were performed on alternate days with 25-45 cc/kg exchanged per session. In the IVIG group (26 episodes), patients received
400mg/kg/d for 5 days. The complication rate was higher with PE compared with IVIG (13 versus 5 episodes, p=0.07) and consisted of infections (6), CV instability (6), and coagulopathy (1). One week after initiation of treatment, the MG severity scores in the IVIG group improved from 7.5±1.7 to 10.3±3.2 (p=0.054) and in the PE group from 6.9±1.7 to 11.1±2.5 (p=0.009). After adjustment for other variables, PE (compared to IVIG) was associated with a superior ventilatory status at 2 weeks (p=0.02) and 1 month functional outcome (p=0.04). These observations suggest that PE is more effective than IVIG in the treatment of MG crisis, however IVIG provides a good alternative treatment, particularly in patients at risk for hemodynamic complications.

MG patients developing acute respiratory failure are generally treated with mechanical ventilation, however prolonged endotracheal intubation is associated with discomfort and correlates with ventilator-associated complications. Rabinstein and Wijdicks (9) retrospectively evaluated the use of non-invasive bi-level positive pressure ventilation (BiPAP) in the management of patients with respiratory failure caused by MG crisis. The authors treated 11/36 episodes of MG exacerbation with BiPAP in order to prevent endotracheal intubation. With a single exception, all patients were also treated with either PE or IVIG. The mean BiPAP pressures were 13/5 mm Hg (inspiratory/expiratory; range 10 to 16/4 to 6 mm Hg). Oxygen supplementation was provided as necessary to keep SaO2 above 90 mm Hg (range 2 to 10 L per minute). BiPAP failure was defined as hypoxemia (PO2 < 60 mm Hg), hypercapnia (PCO2 > 50 mm Hg), poor tolerance, or persistent air hunger. BiPAP prevented intubation in seven of the 11 trials. The presence of hypercapnia at the institution of BiPAP was the only predictor of failure (p<0.01). Bedside pulmonary function studies (vital capacity, maximal inspiratory and expiratory pressures) did not predict the outcome of the BiPAP ventilation trials. Vital capacities were consistently below 10 mL/kg in all patients treated with BiPAP. Respiratory rate was greater then 20 breaths per minute in all cases and was not significantly different between successful and failed episodes. The length of hospital stay was significantly lower for episodes successfully treated with BiPAP (mean 7 +/- 5 days vs. 23 +/- 16 days; p=0.03). Results of this study suggest that BiPAP could be tried first in patients with acute respiratory failure from MG crisis while awaiting improvement from IVIG or PE therapy and may eliminate the need for endotracheal intubation in as many as 70% of patients. BiPAP trials should probably not be attempted, however in patients with overt hypercapnea.

**Case 5: Treatment of the MuSK positive Patient**

A 40 y/o Hispanic female presents with a 3 month history of fluctuating ptosis, dysphagia, nasal speech, and head drop. Repetitive nerve stimulation studies showed a 16% decrement with ulnar nerve stimulation recording over the adductor digiti minimi however, her acetylcholine receptor antibody titer was negative. The patient was started on Mestinon 60 mg TID with subsequent worsening of her symptoms. In the interim, a MuSK antibody returned positive. What treatment(s) are you going to recommend?


Recent reports have suggested that as many as 70% of “seronegative” MG (SNMG) patients may have detectable levels of antibodies to muscle-specific tyrosine kinase (MuSK), a surface membrane receptor essential for the development of the neuromuscular junction. Anti-MuSK antibodies have not been found in either ocular MG or in patients with antibodies to the AchR. Sanders et al (10) reported the clinical aspects of MuSK antibody positive SNMG in 12 patients identified at Duke University. These patients were identified from a group of 32 generalized MG patients who were AchR-Ab negative. All 12 patients were women, with onset between 21 and 59 years of age. Five patients had fluctuating ocular and oropharyngeal weakness typical of MG. The other seven MuSK-positive patients initially had proximal weakness or respiratory insufficiency without ocular symptoms. Most of these patients had a restricted pattern of weakness limited to a few muscles, particularly involving the neck extensors and shoulder girdle musculature.

Electrodiagnostic features of the MuSK-positive patients were unusual. In five patients, EMG findings suggested a necrotizing myopathy in proximal muscles, although biopsy of the deltoid muscle in four of these patients showed only muscle fiber atrophy. In addition, in three patients, increased jitter was found only or predominantly in neck extensor or shoulder muscles. This distribution is different from MG, in which abnormal jitter is almost always found in arm or face muscles, or both.

The response to treatment in the MuSK-positive patients was also not typical of MG. Only five MuSK-positive patients improved on pyridostigmine; three did not and one became worse. Thymectomy was performed in seven patients, however no definite clinical benefit was seen after 8 months of follow-up. Ten patients received
plasma exchange and all showed a dramatic benefit. Further studies will need to be performed to provide additional guidance in making therapeutic decisions regarding thymectomy and immunosuppressive therapy in MusK-positive patients.
Case 1: Initiation of Immunosuppressive Therapy

- 63 y/o WM presents with 2 month hx of fatigable ptosis, diplopia, slurred speech, and proximal muscle weakness.
- Positive AchR-Ab and RS studies.
- Following treatment with Mestinon 60mg q 4h, patient remains unable to arise from a chair and cannot read/drive due to persistent diplopia.

What are your therapeutic options at this point?
Myasthenia Gravis: Treatment

- Increase acetylcholine:
  - Mestinon
- Decrease antibodies against the acetylcholine receptor:
  - Prednisone
  - Azathioprine (Imuran)
  - Cyclosporine (Sandimmune)
  - Plasmapheresis/Intravenous gammaglobulin
  - Thymectomy

Goals of Immunotherapy in MG

- To make the patient as functionally normal as possible
- To produce the fewest side effects
- To achieve remission as quickly as possible
- To provide the simplest regimen at a reasonable cost
General Guidelines for Immunotherapy in MG

- Immune-modulating treatments should be individualized based on a variety of factors:
  - Severity of symptoms
  - Co-existing diseases/medications
  - Age and sex
  - Patient’s lifestyle and profession
  - Ability to comply with monitoring requirements
  - Ability to pay for medications

MG Medication Costs per month

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Cost per month</th>
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</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>60 mg q d</td>
<td>$13-15</td>
</tr>
<tr>
<td></td>
<td>10 mg qod</td>
<td>$1.50</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>150 mg q d</td>
<td>$97-186</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>150mg BID</td>
<td>$390-566</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>1 g BID</td>
<td>$516-539</td>
</tr>
<tr>
<td>IVIG</td>
<td>140 grams</td>
<td>$6,650-16,282</td>
</tr>
<tr>
<td>PE</td>
<td>4 exchanges</td>
<td>$8,000-26,688</td>
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</tbody>
</table>
### MG Therapy: Time to Initial Response

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edrophonium</td>
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</tr>
<tr>
<td>Pyridostigmine</td>
<td>10-15 minutes</td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>1-14 days</td>
</tr>
<tr>
<td>IVIG</td>
<td>1-4 weeks</td>
</tr>
<tr>
<td>Prednisone</td>
<td>2-8 weeks</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>2-6 months</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>2-6 months</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>3-18 months</td>
</tr>
<tr>
<td>Thymectomy</td>
<td>Several mos to yrs</td>
</tr>
</tbody>
</table>

### Prednisone: Efficacy

- Cohort study of 116 patients treated with prednisone (60-80 mg/d with taper to qod) followed from 8 months - 17 years.
  - 28% pharmacologic remission
  - 52% marked improvement
  - 15% mild to moderate improvement
  - 5% no response
- Only 14% maintained improvement after discontinuation of treatment

*Pascuzzi et al, Ann Neurol 1984*
Prednisone: “High dose” regimen

- Start at 100mg/day (1.5 mg/kg/d) for 2-4 weeks, then taper to 100mg qod.
- Maintain same dose until significant improvement (preferably remission) is achieved.
- Improvement usually begins in 2-4 weeks.
- Maximum benefit seen in 4-6 months.

High-dose prednisone: Warning!

- Exacerbation occurs in 30%-50% of patients within the first week of therapy and typically lasts 3-6 days.
- 10% of patients experiencing an exacerbation will require mechanical ventilation or a feeding tube.
- Patients with significant oropharyngeal or respiratory involvement should be hospitalized for plasma exchange during the initiation of high dose prednisone.
Prednisone:  
“Low and slow” regimen

- Start at 25mg qod and increase by 12.5mg every third dose (about every 5 days) to a maximum dose of 100mg qod.
- Another option is to start at 10 mg/d and increase dose by 5 mg every 3-5 days.
- Clinical improvement begins within one month.
- Frequency and severity of early exacerbation is less than high dose daily regimens.
- Onset of improvement is less predictable and the ultimate response may be less complete.

Prednisone:  
Tapering Schedule

- Once remission or significant improvement is obtained, taper by 5-10 mg every 2 weeks to 60 mg qod, then 5 mg every 2 weeks to 20 mg qod.
- Below 20 mg qod, taper by 2.5 mg/month until discontinued or relapse of symptoms occurs.
- “Remission” is frequently steroid dependent requiring a dose of 5-10 mg qod.
- The more rapid the taper, the more likely a relapse will occur.
**Prednisone:**
Potential Side Effects

- Cushingoid appearance
- Weight gain
- Hypertension
- Osteoporosis
- Cataracts/glaucoma
- Insomnia
- Mood changes
- Glucose intolerance
- Hypokalemia
- Gastritis/PUD
- Aseptic hip necrosis
- Myopathy
- Acne
- Easy bruiseability
- Activation of TB
- Infection

**Prednisone:**
Collateral program

- 1800 calorie/ low carbohydrate/4 gram Na diet
- Vitamin D 400-800 IU/day
- Calcium supplementation
  - 1000mg/d pre-menopausal or male
  - 1500mg/d post-menopausal (with estrogen)
- DEXA studies q 6-12 months - initiate treatment with alendronate if evidence of bone loss.
- H2 antagonists if history of PUD or symptoms of gastritis
Azathioprine (Imuran)

- Cyotoxic purine analog which blocks cellular proliferation.
- Can be used as initial therapy if prednisone is contraindicated or a less rapid response is acceptable.
- May also be used as a “steroid-sparing” agent.
- Starting dose: 50 mg/day x 1 week.
- If tolerated and CBC/LFTs are stable, increase by 50 mg every 1-2 weeks up to 2-3 mg/kg/d (typical dose = 150 mg/d).

Azathioprine (Imuran): Potential Side Effects

- Systemic flu-like reaction (15%)
- Leukopenia (25%)
- Thrombocytopenia
- Macrocytic anemia
- Hepatotoxicity (5-10%)
- Infection (5%)
- Pancreatitis
- Toxic interaction with allopurinol
- Malignancy
- Teratogenicity
Azathioprine (Imuran): Monitoring

- WBC and LFTs each week for the first month, then monthly for the first year. Monitoring should then continue every 2-3 months.
- Laboratory Targets:
  - WBC > 4,000 per mm$^3$
    - If WBC 3,000-4,000 per mm$^3$, reduce dose by 50mg/d
    - If WBC < 3,000 per mm$^3$ or absolute lymphocyte count falls below 1000 per mm$^3$, discontinue temporarily
  - MCV increased by 10 units above baseline
  - LFTs < 2x baseline levels

Azathioprine (Imuran): Efficacy

- 70-90% improve whether used as a first or second line therapy.
  - Matel et al, Ann NY Acad Sci 1987
  - Sanders et al, Neurol Clin 1994
- Onset is generally not seen for 3-12 months.
- Relapse after discontinuation occurs in over 50% of patients, usually within one year.
**A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis**

J. Palace, BM, DM; J. Newsom-Davis, MD, FRS; B. Lecky, MD, FRCP; and the Myasthenia Gravis Study Group

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**Article abstract**—We compared prednisolone (PRED) and azathioprine (AZA) versus prednisolone alone in the treatment of MG. Prednisolone alone or combined with azathioprine is widely used in the treatment of MG, but no randomised placebo-controlled comparative trial data are available. The prednisolone dose and clinical outcome were compared in a multicenter randomized double-blind study of 34 MG patients who were followed up for 3 years. One group (PRED + AZA) received prednisolone (on alternate days) plus azathioprine (2.5 mg/kg); the other group received prednisolone on alternate days plus placebo (PRED + PLAC). Initial high-dose prednisolone (1.5 mg/kg on alternate days) was tapered at remission to the minimal dose required to maintain remission. The prednisolone dose did not differ significantly between the two groups at 1 year (median values: PRED + AZA, 37.5 mg on alternate days; PRED + PLAC, 45 mg on alternate days) but was reduced at 2 and 3 years in the PRED + AZA group (median value at 3 years: PRED + AZA, 0 mg on alternate days; PRED + PLAC, 45 mg on alternate days; p = 0.02). Relapses and failures to remit over the 3 years were more frequent in the PRED + PLAC group. There was a sharp rise in the anti-acetylcholine receptor (AChR) titer in the PRED + PLAC group at 2 years. Incidence of side effects was slightly less in the PRED + AZA group. Azathioprine as an adjunct to alternate day prednisolone in the treatment of antibody-positive generalized MG reduces the maintenance dose of prednisolone and is associated with fewer treatment failures, longer remissions, and fewer side effects.

*Neurology* 1998;50:1778-1783.

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**Azathioprine plus Prednisone**

- Randomized, double blind trial of prednisone + placebo vs. prednisone + AZA in 34 MG patients followed for 3 years.
- Prednisone was initiated at 100mg qod or 1.5 mg/kg qod. Initial dose was maintained until remission and then dose was tapered.
- Patients randomized to AZA were treated with 2.5 mg/kg/d.

Azathioprine plus Prednisone for MG

Azathioprine plus Prednisone for MG


Cyclosporine

- Fungal cyclic polypeptide which inhibits predominantly T lymphocytic-dependent immune responses by suppressing IL-2 activity.
- May be used as monotherapy or as a “steroid sparing” agent.
Cyclosporine

- Obtain baseline renal function tests prior to initiation of treatment. Avoid if creatinine is greater than ULN.
- Dose: 3-6 mg/kg/day divided BID
- Onset is 1-2 months
- Maximal improvement occurs in 3-4 months

Cyclosporine:
Potential Side Effects

- Nephrotoxicity
- Hypertension
- Hirsuitism
- Tremor
- Gum Hyperplasia
- Hepatotoxicity
- Paresthesias
- Seizures
- Hallucinations
- Malignancy

Drug interactions
- Antibiotics
- Antifungals
- Acyclovir
- H2 blockers
- NSAIDs
- Anti-hypertensives
- Anti-convulsants
**Cyclosporine: Monitoring**

- Obtain trough cyclosporine level every 2 weeks until level of 100-200 ug/L is achieved, then monthly.
- Check blood pressure every 2 weeks for 3 months, then monthly.
- Check serum electrolytes monthly.
- Check 24-hour creatinine clearance if elevation in creatinine is noted. Drug should be stopped if creatinine increases more than 30% from baseline.

**Cyclosporine: Efficacy**

- In a retrospective analysis of 57 patients taking cyclosporine for average of 3.5 years, 55 (96%) had clinical improvement.
- Mean time to best clinical response was 7 months.
- Corticosteroids were discontinued or decreased in 95% of 38 patients.

*Ciafaloni et al. Neurology 2000*
Intravenous Immunoglobulin: Dosing

- Initial dose: 2 g/kg over 2-5 days
  - 5% solution on day 1
  - 10% solution thereafter
- Maintenance dose: 0.4 g/kg every 4-8 weeks

Intravenous Immunoglobulin: Potential Side Effects

- Fever/chills
- Nausea/vomiting
- Headache
- Myalgias
- Hypotension
- Hypertension
- CHF
- Hepatitis C
- Anaphylaxis in IgA deficiency
- Aseptic meningitis
- Renal failure
- Stroke
- DVT
- Allergic reactions
11 patients with positive AChR-Ab titers and significant bulbar or respiratory compromise were treated with either oral azathioprine (150-200 mg/d) or CellCept (2-3 g/d) 

IVIG (2 g/kg the first month and 1 g/kg the following 3-4 months) was given to avoid corticosteroid use.

Patients were evaluated monthly with the Drachman scale (D5 being the most compromised and D0 = normal) and the MGFA Clinical Classification.

Koski, C.L. Neurology. 2003; 60, (Supplement 1): A419-S50. 004.
**IVIG and Steroid Sparing for MG**

- Vital capacity improved to >80% in all patients
- 10/11 patients had normal bulbar function
- MGFA classification at one year: 0 (N=2), I (N=4), or II (N=5)
- Mean Drachman SS improved from D3.82 to D0.9

**Mycophenolate mofetil**

- Inhibits proliferative responses of T- and B-lymphocytes by blocking purine synthesis
- Prevents B cell antibody production
Mycophenolate mofetil:
Dosing

- Start with 1000mg BID
- Monitor CBC weekly for the first month, twice monthly for the second and third months, then monthly through the first year.
- Response usually occurs within 6 weeks.
- May increase up to 1500mg BID if no benefit in 2 months.
- Renally excreted - dose should not exceed 1000 mg in patients with renal insufficiency

Mycophenolate mofetil:
Potential Side Effects

- Diarrhea
- Leukopenia
- Nausea/vomiting
- Abdominal discomfort
- Fever
- Peripheral edema
- Infection
- Malignancy
- Allergic reaction
Mycophenolate mofetil: Efficacy

- Cohort study of 32 MG patients treated for an average of 12 mos (4 on monotherapy)
- 22/32 (69%) improved either in functional status or in their ability to reduce steroid dose.
- Mean time to improvement: 5 months
- No serious adverse effects
  
  Chaudhry et al. Neurology 2001

Mycophenolate mofetil: Efficacy

- Open label, 6 month study of 12 MG patients with refractory MG on steroids.
- 8/12 (67%) improved either in functional status or in their ability to reduce steroid dose.
- Time to improvement: 2 weeks - 2 months
- No serious adverse effects

  Ciafaloni et al. Neurology 2001
Mycophenolate Mofetil for myasthenia gravis
An analysis of efficacy, safety, and tolerability

M.N. Meriggioli, MD; E. Ciafaloni, MD; K.A. Al-Hayk, MD; J. Rowin, MD; B. Tucker-Lipscomb, RN; J.M. Massey, MD; and D.B. Sanders, MD

Abstract—The authors report a retrospective analysis of the use of mycophenolate mofetil (MyM) in 85 patients with autoimmune myasthenia gravis. The Myasthenia Gravis Foundation of America (MGFA) postintervention status (PIS) was used to characterize the treatment response in each patient. Sixty-two patients (73%) achieved a PIS status indicating improvement. Quantitative strength testing performed on the majority of patients before and after treatment also improved. Side effects to MyM were observed in 27% of patients but required discontinuation in only 6%.

NEUROLOGY 2003;61:1438-1440

Mycophenolate Mofetil: Efficacy

- Retrospective analysis of the use of MyM (1-3 g/d) in 85 MG patients
- 62 patients (73%) reached a PIS status of pharmacologic remission, minimal manifestations or improved
- MMT and QMG scores were all significantly improved
- Corticosteroid dose was decreased by at least 50% in 23 patients (37%) and by less than 50% in 13 (21%)

Mycophenolate Mofetil: Efficacy

- Mean time to onset of subjective improvement was 8.8 weeks
- Mean time to objective improvement was 10.8 weeks
- Mean time to maximal objective improvement was 26.7 weeks (range 8-104 weeks)


Mycophenolate Mofetil: Efficacy

- No significant differences in response based on AChR-Ab or thymectomy status, duration of therapy, or disease severity except that 38% of 13 patients graded MGFA class IV did not improve
- MyM was discontinued due to side effects in only 6%, usually due to GI intolerance

Myasthenia Gravis: Treatment Recommendations

- Treatment algorithm difficult to develop due to:
  - Few direct comparisons between different immunosuppressive agents
  - Lack of standardized outcome measures
  - Need to individualize treatment based on patient variables
    - Disease severity
    - Functional disability
    - Co-existing diseases
    - Insurance coverage for medication costs

MG: “Traditional” Treatment Recommendations

- If symptoms are uncontrolled on Mestinon, use immunosuppressive agents:
  - Prednisone if severe or urgent
  - Azathioprine, cyclosporine or mycophenolate mofetil if:
    - Prednisone contraindicated (severe obesity, DM, uncontrolled HTN, PUD, osteoporosis)
    - Prednisone failure
    - Excessive prednisone side effects
Muscle Nerve
Issues and Opinions 2002

Rivner
- Steroids are over utilized; side effects
- Other IS Rx can work alone
  Ex: cyclosporine, azathroprine, ? mycophenolate

Bedlack & Sanders
- Use steroids in All MG with > minimal weakness, even ocular
- Begin 60 mg/day
- If bulbar, give PE or IVIG 1st
- Add other IS Rx if prednisone alone is not adequate

Myasthenia Gravis:
Treatment Recommendations

- If symptoms are severe:
  - Prednisone + azathioprine
  - IVIG + mycophenolate mofetil
  - IVIG + azathioprine
  - Prednisone + mycophenolate

- If symptoms are mild/moderate:
  - Prednisone
  - Cyclosporine
  - Mycophenolate mofetil
Case 2: Treatment of the “Refractory” Patient

- 45 y/o BF with a hx of AchR-Ab positive generalized MG presents for a second opinion.
- Previous treatments with prednisone, azathioprine, cyclosporine, and mycophenolate mofetil have either been poorly tolerated or ineffective.

What are your therapeutic options in this “refractory” patient?
IVIG for “Refractory” MG

- Open label study of IVIG (0.4g/kg/d x 5 days q 6 weeks) in 10 patients with severe generalized MG refractory to high dose prednisone (30-60 mg/d, 9 pts) and/or azathioprine (100-300 mg/d, 5 pts)
- Following one year of treatment, the severity of disease decreased by 2.5 grades on the Osserman scale (p<0.001) in parallel with a reduction in immunosuppressive therapy (p<0.005)
- Attempts to discontinue IVIG maintenance treatment were successful in 7/10 patients within 1.5 to 3 years


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**FIGURE 1.** Individual Osserman scores for the 10 patients throughout the study.

**IVIG for Refractory MG**


![Graphs showing mean dose of concurrent medications throughout the study period](image)

(A) Azathioprine, (B) Prednisone, (C) Pyridostigmine.

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**Treatment of Refractory Myasthenia: “Rebooting” with High-Dose Cyclophosphamide**

Daniel B. Drachman, MD, Richard J. Jones, MD, and Robert A. Brodsky, MD

Patients with myasthenia gravis (MG) who do not respond to conventional immunotherapeutic agents, or cannot tolerate their side effects, are considered “refractory.” Ablation of the immune system followed by bone marrow transplant has been shown to cure experimental MG in rats. It is now known that immunosuppressive treatment with high-dose cyclophosphamide does not damage hematopoietic “stem cells,” permitting repopulation of the immune system without bone marrow transplant. Recent evidence indicates that this treatment can induce durable remissions in autoimmune diseases. We treated three myasthenic patients, for whom treatment with thymectomy, plasmapheresis, and conventional immunotherapeutic agents failed, by using high-dose cyclophosphamide (50mg/kg/day intravenously for 4 days) followed by granulocyte colony stimulating factor. All three patients tolerated the treatment well and have had marked improvement in myasthenic weakness, permitting reduction of immunosuppressive medication to minimal levels. Acetylcholine receptor (AChR) antibody levels decreased in two AChR antibody-positive patients, and anti-MuSK antibody levels decreased in one “AChR antibody-negative” patient. The patients have been followed for up to 3.5 years, with no recurrence of symptoms. High-dose cyclophosphamide treatment appears to be an effective and safe treatment for selected patients with refractory MG. Further follow-up of these and additional patients will be needed to determine whether the benefit is durable.

“Rebooting” with Cyclophosphamide for MG

- Open label study of IV cyclophosphamide (50 mg/kg ideal BW qd x 4 days) in 3 MG patients refractory to PE, thymectomy, and IS agents
- IV ondansetron was used for prophylactic treatment of nausea
- IV mesna (10 mg/kg) was administered 30 min prior and 3, 6, and 8 hrs after infusion to prevent interstitial cystitis
- Prophylactic antibiotics were given 1 day after the last dose and continued until the neutrophil count exceeded 0 cells/mm³


“Rebooting” with Cyclophosphamide for MG

- Granulocyte colony SF (5 ug/kg q d) was started on day 6 after the last dose of cyclophosphamide until the neutrophil count was 1,000/mm³ for 2 consecutive days
- Improvement was seen in all 3 patients within 2 months of therapy
- After follow-up of 7-40 months, all 3 patients had returned to fully active lives and IS medications had been substantially minimized (prednisone doses ranged 2.5-10 mg/d)

Tacrolimus (FK-506)

- Reduces proliferation of activated T cells by inhibition of the calcium-calcineurin pathway (same class as cyclosporine).
- Dose: 0.05 mg/kg BID
- Recommended trough level: 5-15 ng/ml
- Onset: 2-3 weeks

Tacrolimus (FK-506):
Potential Side Effects

- Insulin-dependent DM (20% in kidney transplant)
- Nephrotoxicity
- Hyperkalemia
- Thrombocytopenia
- Tremor
- Headache

- Seizures
- Delerium
- Anaphylaxis
- Hypertension
- Myocardial hypertrophy
- Drug interactions
Case report of a single MG patient with hepatitis C, type 2 diabetes, and cyclosporine induced renal failure who was treated with Tacrolimus.

Improvement was noted in 2 weeks

Pharmacologic remission was achieved in 3 months which was sustained throughout a one year follow-up.

Evoli et al, Muscle Nerve 2002
Tacrolimus (FK-506): Efficacy

- Open label trial of FK506 (3-5 mg/d) in 19 MG patients for 16 weeks
- 18/19 patients were receiving steroid therapy and all patients had previously undergone thymectomy
- All patients had an MG ADL score of >2
- Serum levels of FK506 were less than 10 ng/ml in all but 1 patient, in whom it was 12 ng/ml
- Increases in neutrophil counts and decreases in lymphocyte counts were commonly seen, but not serious.


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Tacrolimus (FK-506): Efficacy

- No increase in creatine or HbA1c levels
- Clinical improvement was observed by 2 weeks in lower limb strength
- MG scores measuring strength (range 0-27) improved by >3 points in 37%
- MG ADL scores (range 0-6) improved by >1 point in 42%
- 12/19 patients elected to continue therapy for up to 2 years without serious side effects

**Recommendations for Therapy of the “Refractory” MG patient**

- IVIG seems to be highly potent for inducing rapid improvement as well as for maintaining remission.
- High dose cyclophosphamide appears to be an effective and safe treatment for selected patients.
- FK506 could safely serve as an adjunct to steroid therapy.
- Rituximab has been shown in isolated case reports to be effective.
- Consider repeat thymectomy.
- Be sure you have the correct diagnosis!
Case 3: Thymectomy - To Do or Not To Do?

- 24 y/o hispanic female with a 5 year hx of oculobulbar MG well controlled on prednisone 20mg qod.
- Prior attempts to wean off of prednisone have resulted in severe relapses.
- Reluctant to consider thymectomy due to concern regarding sternal scar and wants to know if a less invasive procedure can be done.

What advice can you give her?

Practice parameter: Thymectomy for autoimmune myasthenia gravis (an evidence-based review)

Report of the Quality Standards Subcommittee of the American Academy of Neurology

Gary S. Gronseth, MD; and Richard J. Barohn, MD
Thymectomy?

- Evidence-based review of 28 articles describing outcomes in 21 MG cohorts from 1953-1998
- All articles provided Class II evidence (non-randomized, non-prospective)
- Peri-operative mortality rates were consistently less than 1% since 1970
- Common morbidities included acute respiratory failure (6%), infection (11%), and permanent recurrent laryngeal or phrenic nerve injury (2%)


Thymectomy?

- Patients who underwent thymectomy were more likely to achieve:
  - Medication-free remission (RR 2.1, median rate = 25%)
  - Asymptomatic (RR 1.6, median rate = 39%)
  - Clinical improvement (RR 1.7, median rate = 70%)
- Trials comparing outcomes using different surgical techniques demonstrated inconsistent results.

Effect of Thymectomy on Strength in MG

Clinical Trials: Thymectomy vs Natural Hx

<table>
<thead>
<tr>
<th></th>
<th>Natural Hx %</th>
<th>Thymectomy %</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>6 – 34</td>
<td>12 – 52</td>
<td>1.4 – 3.3</td>
</tr>
<tr>
<td>Improved</td>
<td>24 – 100</td>
<td>44 – 96</td>
<td>0.8 – 3.2</td>
</tr>
</tbody>
</table>
**Recommendations regarding Thymectomy**

- AAN Practice Parameter states that for patients with non-thymomatous autoimmune MG, thymectomy is recommended as an *option* to increase the probability of remission or improvement.
- Current trials do not provide convincing evidence that one technique is superior.
- Generally *not* recommended in patients with only ocular disease or patients over 60 years of age.
- Prospective, randomized trial is currently being planned as an international collaboration.

**Case 4: Treatment of MG Crisis**

- 32 y/o white female with hx of generalized MG presents to the ER due to 3 day hx of worsening dysphagia, proximal weakness, and shortness of breath.
- Current treatment includes prednisone 20mg qod and pyridostigmine 60mg TID.
- Over the past 12 hours, she has been unable to swallow liquids without choking.
- FVC = 1.2 liters (25% predicted)  
  *What treatment(s) are you going to recommend?*
87 patients with acute MG crisis were randomized to 0.4 gm/kg of IVIG daily x 3 days (N=23) or 5 days (N=23), or PE (N = 41).

Primary endpoint: Myasthenic Muscular Score (MSS) through day 15.

MSS variation was 18 in the PE group and 15.5 in the IVIG group.

Side effects occurred in 8 PE patients compared with 1 who had received IVIG.


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**IVIG vs PE in Acute Exacerbation of MG**

![Graph showing MSS over days for IVIG and PE groups](image_url)
Treatment of MG Crisis

- Retrospective, multi-center study comparing PE and IVIG in a series of 54 episodes of MG crisis
- PE group (28 episodes) received 5-6 cycles on alternate days (25-45 cc/kg per session)
- IVIG group (26 episodes) received 400mg/kg/d for 5 days

Qureshi AI et al. Neurology 1999;52:629-632

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**Plasma exchange versus intravenous immunoglobulin treatment in myasthenic crisis**

**Article abstract**—We performed a retrospective multicenter chart review to compare the efficacy and tolerance of plasma exchange (PE) and intravenous immunoglobulin (IVIg) in treatment of 54 episodes of myasthenic crisis. After adjustment for other variables, PE (compared with IVIg) was associated with a superior ventilatory status at 2 weeks (partial F = 6.2, p = 0.02) and 1 month functional outcome (partial F = 4.5, p = 0.04). However, the complication rate was higher with PE compared with IVIg (13 versus 5 episodes, p = 0.07).

NEUROLOGY 1999;52:629-632

A.I. Qureshi, MD; M.A. Choudhry, MD; M.S. Akbar, MD; Y. Mohammad, MD; H.C. Chua, MD; A.M. Yahia, MD; J.A. Ulatowski, MD, PhD; D.A. Krendel, MD; and R.T. Leshner, MD
Treatment of MG Crisis

- Complication rate was higher with PE compared to IVIG (13 vs. 5 episodes)
- MG Severity Scores at one week improved in both IVIG (p=0.054) and PE (p=0.009)
- PE was associated with superior ventilatory status at 2 weeks (p=0.02) and 1 month functional outcome (p=0.04)


Treatment of MG Crisis: IVIG vs. PE

BiPAP in acute respiratory failure due to myasthenic crisis may prevent intubation

Alejandro Rabinstein, MD; and Eelco F.M. Wijdicks, MD

Abstract—Noninvasive mechanical ventilation using bilevel positive pressure ventilation (BiPAP) has not been studied in acute respiratory failure caused by MG. Eleven episodes in nine patients were initially managed with BiPAP, and endotracheal intubation was avoided in seven of these trials. Presence of hypopneas (PaCO₂ greater than 50 mm Hg) at onset predicted BiPAP failure and subsequent intubation. Results of this preliminary study suggest that a trial of BiPAP may prevent intubation in patients with myasthenic crisis without overt hypopneas.

NEUROLOGY 2002;59:1047-1049
Treatment of MG Crisis

- Treated 11/36 episodes of MG crisis with BiPAP to prevent endotracheal intubation
- 10/11 patients received IVIG or PE
- Mean BiPAP pressures were 13/5 mm Hg ( inspiratory/expiratory; range 10-16/4-6)
- Oxygen supplementation was provided to keep SaO$_2$ above 90 mm Hg (range 2-10 L per minute)


Treatment of MG Crisis

- BiPAP prevented intubation in 7/11 trials
- Presence of hypercapnia (pCO$_2$>50 mm Hg) was the only predictor of BiPAP failure
- Bedside PFTs and respiratory rates did not predict the outcome
- Length of hospital stay was significantly lower for episodes treated with BiPAP (mean 7 vs. 23 days; p=0.03)

Recommendations for Therapy in MG Crisis

- PE should be considered the treatment of choice for MG crisis except:
  - Hemodynamic instability
  - Sepsis/pulmonary infection
  - Coagulopathy
  - Experienced unit unavailable
  - First trimester of pregnancy
- BiPAP should be initiated to avoid endotracheal intubation except in the presence of hypercapnia

Case 5: Treatment of the MuSK positive patient

- 40 y/o Hispanic female presents with a 3 month history of fluctuating ptosis, dysphagia, nasal speech and head drop.
- RNS showed a 16% decrement; AchRAb was negative
- Mestinon 60mg TID resulted in worsening.
- MuSK antibody returned positive

What treatment(s) are you going to recommend?
MuSK Antibody

- MuSK is a muscle specific protein essential for the development of the NMJ.
- Seen in 40-70% of generalized MG patients who are acetylcholine receptor Ab negative.

CME Clinical aspects of MuSK antibody positive seronegative MG

D.B. Sanders, MD; K. El-Salem, MD; J.M. Massey, MD; J. McCorville, MRCP; and A. Vincent, FRCPaPath

Abstract—Serum antibodies to muscle-specific receptor tyrosine kinase were detected in 12 of 32 patients with generalized seronegative MG. All were women, with onset between ages 21 and 59 years. Seven had prominent neck, shoulder, or respiratory muscle weakness and little or delayed ocular muscle involvement. The response to cholinesterase inhibitors was variable, and electromyographic findings suggested myopathy in several. None improved after thymectomy. All patients improved after plasma exchange, and most had a good response to selected immunotherapy. MuSK antibody status should help diagnose MG with atypical presentations and ensure appropriate patient treatment.

Clinical Aspects of MuSK positive MG

- MuSK antibody was found in 12/32 generalized MG patients who were AchR-Ab negative
- All patients were women; disease onset between 21-59 years of age
- MuSK Clinical Phenotypes:
  - 5 patients had fluctuating ocular/oropharyngeal weakness typical of SPMG
  - 7 patients initially had proximal weakness or respiratory insufficiency without ocular symptoms. Weakness was generally restricted to neck extensors and shoulder girdle muscles

MuSK-positive Phenotypes

<table>
<thead>
<tr>
<th>Patient</th>
<th>Onset age</th>
<th>Weaknesses at onset</th>
<th>Ocular onset</th>
<th>Maximum MGFA class</th>
<th>MGFA postintervention status</th>
<th>MuSK antibody (nM)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>42</td>
<td>Neck extension</td>
<td>2 yr</td>
<td>IIIB</td>
<td>Imp</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>Shoulders, neck ext</td>
<td>2 yr</td>
<td>IIA</td>
<td>Imp</td>
<td>8</td>
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<tr>
<td>3</td>
<td>30</td>
<td>Diplopia, ptosis, dysphagia</td>
<td>Initial</td>
<td>V</td>
<td>MM</td>
<td>12</td>
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<tr>
<td>4</td>
<td>42</td>
<td>Diplopia, dysarthria</td>
<td>Initial</td>
<td>IIIB</td>
<td>MM</td>
<td>44</td>
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<tr>
<td>5</td>
<td>48</td>
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<td>PR</td>
<td>2</td>
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<td>6</td>
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<td>Respiratory insufficiency</td>
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<td>MM</td>
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<tr>
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<td>32</td>
<td>Respiratory failure</td>
<td>6 mo</td>
<td>V</td>
<td>Imp</td>
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<tr>
<td>8</td>
<td>18</td>
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<td>V</td>
<td>Imp</td>
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<td>60</td>
<td>Diplopia, ptosis, dysphagia</td>
<td>Initial</td>
<td>IIIB</td>
<td>Imp</td>
<td>20</td>
</tr>
</tbody>
</table>

* Normal, <5.0 nM.

MGFA = Myasthenia Garris Foundation of America; Imp = significantly improved from pretreatment status; MM = minimal manifestations (no myasthenic symptoms or dysfunction, but clinically insignificant weakness on examination); PR = pharmacological remission (no myasthenic symptoms for one year, no weakness on examination).

Electrodiagnostic Features of MuSK-positive MG

- EMG findings in 5/12 patients suggested a necrotizing myopathy in proximal muscles
- Muscle biopsy in 4 of these 5 patients showed muscle fiber atrophy
- Single fiber EMG in 3 patients identified abnormal jitter only in neck extensors or shoulder girdle muscles


Treatment Considerations with MuSK-positive MG

- Pyridostigmine
  - 5 patients improved
  - 3 patients showed no improvement
  - 1 patient became worse
- Thymectomy
  - 7/7 patients showed no improvement at 8 mo
- Plasma Exchange
  - 10/10 patients demonstrated dramatic benefit

Recommendations for Therapy in MuSK-positive MG

- Consider checking MuSK antibody in all AChR-Ab negative MG patients
- Remains unclear if there is a “typical” phenotype
- Be aware that pyridostigmine may be ineffective or result in clinical worsening
- Approach IS therapy like any MG patient
- Role of thymectomy will require further study, although limited data suggests it may be ineffective