Management of Neuromuscular Junction Disorders

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- Dr. Sanders has received financial support through his institution from Roche Laboratories and Aspreva Pharmaceuticals for research of mycophenolate mofetil in MG.

- Off-label use of some medications will be discussed.
Treatment of Myasthenia Gravis
The Goals of MG Treatment

To achieve normal function
- with fewest side-effects,
- as quickly as possible,
- at the lowest cost,
- using the simplest regimen.
Treatment of MG: keep these concepts in mind

- No single treatment or regimen is best for every patient.
- Patients who are not in virtually complete remission are at risk for exacerbations, even crisis, with infections, surgery or other stress.
- If left untreated, the weakness of MG may become fixed.
The evaluation of MG treatment is challenging because:

- Severity varies among patients.
- Spontaneous improvement is common.
- Controlled treatment trials using standardized measures of severity and response are lacking.
Treatments for MG

- Improve neuromuscular transmission: anticholinesterase
- Remove antibodies: plasmapheresis
- Suppress immune response: steroids, immunosuppressants, IVIg
- Thymectomy
The role of anticholinesterase

- Diagnostic – Tensilon/prostigmin test, therapeutic trial
- Symptomatic treatment
  - Initial treatment in most patients
  - Ancillary treatment in many
  - Sole therapy in some
- Not needed when response to immunotherapy is optimal
How to use pyridostigmine (Mestinon®)

- Dose requirements vary: start low, titrate up
- Optimize response in the most critical muscles
- Individualize dose schedule per patient needs
- Aim for observable improvement after each dose
- Alert patient to overdose symptoms
- Re-assess dosage periodically
- Reduce/discontinue when possible
How to use pyridostigmine

- **In hospital**
  - maintain patient’s home schedule
    - *Order for specific times*
    - *Keep at bedside, if necessary*

- **In crisis**
  - discontinue in intubated patients
  - resume at lower dose, titrate up
Why try to discontinue anticholinesterase?

- Not needed when other treatment (steroids, thymex, immunorx) is optimal.
- No antichol requirement thus confirms optimal response to other treatments.
- Patients who require antichols are at risk for exacerbations, even crisis, with infections, surgery or other stress.
Thymectomy in MG

**Pros**
- Followed by sustained improvement, even CSR, in some patients with MG
- Excludes or removes thymoma
- No chronic side-effects

**Cons**
- Operative risks
- Value not proven
- Questionable value in late onset MG
How many neurologists on the MGFA MAB recommend thymectomy for:

- Ocular MG: "Few"
- Thymoma with MG: 100%
- All generalized MG: 5%
- Selected generalized MG: 95%
- "Disabling" MG only: 38%
- Unresponsive to antichols: 25%
- Recent onset MG only: 21%

Lanska, Neurology 40:1828, 1990
Thymectomy is an option for the treatment of autoimmune MG.

Prospective treatment trial is necessary to prove benefit.
Prospective trial of thymex in MG

Newsom-Davis et al

- Does extended thymectomy reduce the dose of prednisone required to maintain minimal manifestations over a three-year period?
- 200 patients from 59 centers worldwide
- Thymex + prednisone vs prednisone alone
Treatment of Thymoma

- Surgical removal in almost all patients
  - Remove all thymus tissue as well
- Post-op radiation if invasive (?)
- Immunosuppression as needed pre and post-op
- Does not usually improve the MG
Immunosuppression in autoimmune MG
Immunotherapy

- Few MG patients achieve sustained remission without it.
- Most achieve and maintain sustained remission with optimum immunotherapy.
  - But only if it is continued.
- No one regimen is best for all patients.
- Requires close and long-term monitoring.
Immunosuppressives

- Prednisone
- Azathioprine
- Mycophenolate mofetil
- Cyclosporine
- Cyclophosphamide
- Methotrexate
- Rituximab
Immunosuppression questions

- Low-dose vs high-dose prednisone?
- Which immunosuppressant to use first?
- When to discontinue?
- Use during pregnancy?
- What are long-term side-effects?
Which immunosuppressant?

- Most patients respond to any.
- Those who don't respond to one, may respond to another,
  thus
- Don't quit if the first one doesn't work.
- Most work better with prednisone, at least initially.
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

**Pros**
- fastest
- cheapest
- most effective

**Cons**
- SIDE EFFECTS
- exacerbations
How I use prednisone:
mild-moderate generalized MG

- 60 mg/day until definite improvement (usually <2 weeks)
- Taper on alternate day to AD schedule
  - Faster taper if good prompt response, eg to 60 AD over 1 month
  - SLOW taper thereafter to minimal effective AD dose, eg to 10 AD over 6 months
Prednisone-induced exacerbation

- Exacerbation occurs in 30%-50% of patients within the first week of high-dose prednisone and typically lasts 3-6 days.
- 10% of patients experiencing an exacerbation will require mechanical ventilation or a feeding tube.
- May be prevented by plasma exchange (and possibly IVIg) before or while starting prednisone.
How I use prednisone:
bulbar/respiratory weakness

- PLEX in hospital until definite improvement
- 60 mg/day, taper, etc as tolerated
High-dose daily vs incrementing prednisone

- **HDDP**
  - Faster response
  - Non-responders identified sooner
  - Exacerbations within predictable time
  - Frequently requires lower cumulative dose
Azathioprine

- **Pros**
  - usually effective
  - easy to monitor
  - few long-term side effects
  - extensive experience

- **Cons**
  - slow onset (up to 6 months)
  - frequent idiosyncratic reactions (10-15%)
  - increased risk of skin cancer
  - teratogenicity (??)
When do I use azathioprine?

- When prednisone is ineffective or contraindicated, and delayed response is acceptable
- With prednisone as initial immunotherapy
- As steroid-sparing agent
- Avoid during pregnancy (?)
How I use azathioprine

- Begin 50mg/day x 7 days, increase by 50mg/day q 7 days to 150-200mg/day
- Give on QD schedule
- Monitor for:
  - Idiosyncratic, flu-like reaction (10-14 days)
  - Elevated LFT (1-2 months)
  - Leukopenia, anemia (any time)
  - ? Adjust to macrocytosis
- After optimal response, taper SLOWLY to minimal effective dose
MMF in MG - summary

- >200 pts in literature (pilot, retrospective, & case reports)
- 60-90% benefited from MMF
- Pts with shorter disease duration did better
- Typical dose 1 g bid
**Mycophenolate mofetil**

- **Pros**
  - Usually effective
  - Few side-effects
  - Onset 2-6 months

- **Cons**
  - Very expensive
  - Increased cancer risk (?)
  - Teratogenetic
When do I use MMF?

- As initial immunosuppressant, usually with steroids, when rapid response is needed or other immunosuppression is contraindicated.

- As steroid-sparing agent when other immunosuppressants are contraindicated or have been ineffective.

- D/c during pregnancy. Advise pts of potential risk.
How I use mycophenolate

- Begin 1g q 12 hours
- Monitor CBC periodically (optional necessary)
- If inadequate response after >6mos, consider increased dose to 3g/d.
- After optimum response, taper SLOWLY to minimum effective dose.
- Advise pts of child-bearing potential to use effective contraception, d/c if pregnant.
Conclusions from two recent studies of MMF in MG

- MMF is not better than prednisone alone as initial treatment in mild-moderate MG, and has no steroid-sparing effect within the time frame of these studies.
- It may take longer than predicted to see benefit from MMF.
- MMF may have a beneficial effect in certain MG patients the characteristics of which need to be better identified.
Conclusions

- Prednisone is more effective than predicted, and at a lower dose than expected.
- Exacerbations after prednisone may also occur at lower doses than previous thought.
**Cyclosporine**

**Pros**
- Usually effective
- Relatively rapid onset (2-3 months)
- Relatively safe if monitored

**Cons**
- Side effects
  - cumulative renal toxicity
  - hypertension
- Expensive
- Multiple drug interactions
- Requires close monitoring
- Potentially teratogenetic
- Increased cancer risk (?)
When do I use cyclosporine?

- When other immunosuppression is ineffective or contraindicated, or with prednisone as initial immunosuppression.
- As steroid-sparing agent
- Avoid during pregnancy
How I use cyclosporine

- Begin 5-6 mg/kg/day (~200mg) q 12 hrs
- Check trough level in 1 month, adjust dose to 75-150 ng/ml
- Monitor BUN/Cr, CBC, BP q 1 mo
- Adjust dose to keep creatinine <150% baseline
- After optimum response, SLOWLY taper to minimal effective dose
- Monitor potential interacting medications (and they are many!)
## MG Therapy: Time to Initial Response

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time to Initial Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edrophonium</td>
<td>1-2 minutes</td>
</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>
How I treat generalized MG: summary

- If symptoms are uncontrolled on pyridostigmine (almost all patients), treat with:
  - Prednisone if severe or urgent
  - Azathioprine, mycophenolate or cyclosporine if:
    - Prednisone contraindicated (severe obesity, DM, uncontrolled HTN, osteoporosis)
    - Prednisone failure
    - Excessive prednisone side effects
- Recommend thymex for age < 50-60
How I treat ocular MG

- Pyridostigmine
- If not satisfactory (usually), prednisone
  - High dose daily vs
  - Low dose, incrementing
  - Consider additional immunosuppressant if ineffective
  - Thymectomy (?)
- Symptomatic maneuvers
  - Dark glasses or patching for diplopia
  - Eyelid crutches or tape for ptosis
- Avoid ocular surgery!
- Observe for generalization
When to use plasma exchange?

- To induce temporary improvement
  - in crisis or impending crisis
  - before thymectomy or other surgery
  - when beginning immunosuppression

- To prevent steroid-induced exacerbations

- When other immunosuppression has failed
When to use IVIg?

- Need for temporary improvement when PLEX not available or contraindicated (e.g. children, poor venous access)
  - Crisis or impending crisis
- Significant weakness unresponsive to other treatment
PLEX or IVIg?

- Some reports that PLEX gives better response in crisis.
- PLEX may induce improvement when IVIg did not.
- Major difference is side-effects
  - mainly due to access issues with PLEX
Annual Cost Comparison
PLEX vs IVIg

Plasmapheresis (6 courses of 6 exchanges, OP)
$40,032

IVIg 10% (6 courses of 2gm/kg)
Home Health $97,692
Duke OP $83,104
My overall treatment approach

- **If symptoms are severe:**
  - PLEX + Prednisone + immunosuppressant

- **If symptoms are mild/moderate:**
  - Prednisone
  - Azathioprine
  - Mycophenolate mofetil
How I treat MG Crisis

- PLEX is 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.
BiPAP in MG Crisis
Rabinstein & Wijdicks. Neurology 2002

- BiPAP prevented intubation in 7/11 trials.
- Hypercapnia (pCO₂ > 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.)
Muscle Specific Receptor Kinase (MuSK) antibody positive MG
MuSK+ MG

- ~50% of generalized SN-MG have anti-MuSK antibodies
  - Some patients with ocular MG also
- MuSK+ MG may look like typical MG or have limited distribution of weakness suggesting other diseases.
- MG may not be suspected in the latter patients unless EMG is performed in weak muscles.
Treatment of MuSK+ MG

- Frequently don’t improve with cholinesterase inhibitors
  - some patients actually get worse, and have profuse fasciculations.
- Many respond well to selected therapy (prednisone, plasmapheresis, IVIg, MMF).
- Benefit of thymectomy is uncertain.
# Response to treatment

**32 MMG pts**

<table>
<thead>
<tr>
<th>Rx</th>
<th>Improved/Treated</th>
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<tbody>
<tr>
<td>Edrophonium</td>
<td>9/16 (56%)</td>
</tr>
<tr>
<td>Pyridostigmine</td>
<td>16/30 (53%)</td>
</tr>
<tr>
<td>Prednisone</td>
<td>17/22 (77%)</td>
</tr>
<tr>
<td>Azathioprine*</td>
<td>7/13 (54%)</td>
</tr>
<tr>
<td>Cyclosporine*</td>
<td>9/10 (90%)</td>
</tr>
<tr>
<td>Mycophenolate*</td>
<td>17/20 (88%)</td>
</tr>
<tr>
<td>PLEX</td>
<td>21/24 (91%)</td>
</tr>
<tr>
<td>IVIg</td>
<td>5/10 (50%)</td>
</tr>
<tr>
<td>Rituximab*</td>
<td>1/1</td>
</tr>
</tbody>
</table>

*Alone or with other immunosuppressants*
Lambert-Eaton myasthenic syndrome (LEMS)
How I treat LEMS

- Evaluate for underlying cancer. Treat if found,
- Assess response to antichols
- 3,4-Diaminopyridine
- Consider prednisone, immunosuppressants, PLEX, IV-IG
- Periodically re-evaluate for cancer
3,4-Diaminopyrididine

- Blocks voltage-dependent fast K⁺ channels (when closed)
- Prolongs falling phase of APs
- Enhances Ca²⁺ entry into nerve terminals & transmitter release
DAP in LEMS

Before                1° after 15mg DAP
3,4-Diaminopyrididine in LEMS

- 80% of patients have significant clinical benefit
- No significant side-effects at usual clinical doses
- Complemented by pyridostigmine
- Available only on “treatment use” protocol with IND
3,4-Diaminopyrididine

Side Effects

- Perioral & digital paresthesias
- Enhanced cholinergic symptoms
- Insomnia
- Seizures (high doses only)
## Response to treatment
### 70 LEMS pts

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<tr>
<td>Pyridostigmine</td>
<td>3/54 (6%)</td>
</tr>
<tr>
<td>DAP</td>
<td>41/49 (84%)</td>
</tr>
<tr>
<td>Cancer Rx</td>
<td>5/20 (25%)</td>
</tr>
<tr>
<td>Guanidine</td>
<td>5/8 (63%)</td>
</tr>
<tr>
<td>Prednisone</td>
<td>9/30 (30%)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>2/10 (20%)</td>
</tr>
<tr>
<td>PLEX</td>
<td>9/18 (50%)</td>
</tr>
<tr>
<td>IVIg</td>
<td>10/16 (63%)</td>
</tr>
</tbody>
</table>
Conclusions: Rx of LEMS

- Treating SCLC produces marked, sustained improvement in some patients.
- Pyridostigmine alone is usually ineffective.
- DAP is usually beneficial, and is usually enhanced by pyridostigmine.
- PLEX/IVIg frequently gives marked, but temporary improvement.
- Immunosuppression rarely gives marked benefit.

(Contraindicated in cancer?)