An Overview of the Treatment of Autoimmune Neuromuscular Disease

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NEUROMUSCULAR DISEASES IN WHICH IMMUNOSUPPRESSIVE & IMMUNOMODULATING THERAPY IS USED

• Neuropathies
  – GBS
  – CIDP & Variants
    o Multifocal Motor Neuropathy – MMN
    o MADSAM
    o DADS
  – Vasculitis

• Neuromuscular Junction
  – Myasthenia Gravis
  – Lambert-Eaton Syndrome

• Myopathy
  – Polymyositis/Dermatomyositis
  – Necrotizing Myopathy
  – ? IBM
  – ? Duchenne’s Muscular Dystrophy
IMMUNOTHERAPEUTIC OPTIONS IN NEUROMUSCULAR DISEASE

• Corticosteroids
• Azathioprine
• Cyclophosphamide
• Methotrexate
• Mycophenylate
• Cyclosporine

• IVIg / SQIg
• Plasmapheresis
• Mycophenolate
• Rituximab
• Thymectomy
<table>
<thead>
<tr>
<th>THERAPY</th>
<th>TIME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasmapheresis</td>
<td>Days (1-14d)</td>
</tr>
<tr>
<td>IVIG</td>
<td>Days (1-14d)</td>
</tr>
<tr>
<td>Prednisone</td>
<td>Weeks (2-8 wks)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Months (2-6 mos)</td>
</tr>
<tr>
<td>Cyclophosphamidide</td>
<td>Months (2-6 mos)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Months (2-6 mos)</td>
</tr>
<tr>
<td>Mycophenylate</td>
<td>Months (2-6 mos)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Months (3-18 mos)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Months (? How many)</td>
</tr>
<tr>
<td>Thymectomy</td>
<td>Months (? Years)</td>
</tr>
</tbody>
</table>
GLUCOCORTICOIDS MECHANISM OF ACTION

SUBCELLULAR

• Binds to Receptor in Cytoplasm
• Moves to Nucleus
• Turns Genes On or Off
• Modifies Transcription of RNA
• Control Rate of Protein Synthesis
• Inhibit NF-κB
STEROID RESPONSIVE NEUROMUSCULAR DISORDERS:

- Myasthenia gravis*
- CIDP* & variants
- Peripheral nerve vasculitis
- Inflammatory/autoimmune myopathy – PM/DM/NM
- Duchenne Muscular Dystrophy*

* RCT
DOsing PREDnISONE

• 60 to 100 mg/day x 2-4 weeks (1-1.5 mg/kg)
• Then switch to alternate-day
  – Or stay daily at a lower level
• Give single dose in a.m.
• Maintain at 60 to 100 mg qod for 4-6 months
• Then taper 5 mg qod 2 weeks
• Measure response to Rx in terms of wks
  – Or (esp. in MG)
    • Go low and slow
    • 5 or 10 mg/day and increase by 5 to 10 mg/day each week
  – Or 20 mg/day initial dose & maintain
BENEFIT FROM ALTERNATE-DAY PREDNISONE IN MYASTHENIA GRAVIS

Abstract

Five adults with myasthenia gravis of varying severity and duration were treated with long-term, high-single-dosage (100 mg) alternate-day oral prednisone. Improvement in muscle function appeared 24 to 72 hours after the initiation of therapy and has been maintained from six to 17 months. Complete remission of symptoms was obtained in one patient in four months and has been maintained for 18 months.

Myasthenia gravis is a disease involving impaired neuromuscular transmission. Death may result from respiratory weakness or aspiration pneumonitis caused by dysphagia. The ordinary therapy with cholinesterase inhibitors at frequent, precisely spaced intervals during the day provides only symptomatic improvement lasting but a few hours, which is usually incomplete and which may greatly diminish after months to years. In some patients favorable longer-term results may follow dapsone therapy,1 short-term courses of massive amounts of ACTH,2 or long-term periodic ACTH injections.

In five consecutively studied adults with myasthenia gravis of varying length and severity of involvement lasting improvement, without initial worsening, was achieved with long-term, high-single-dosage (100 mg), alternate-day oral prednisone therapy. Prednisone was given as an 8 A.M. single dose, without anticholinesterase medication, in a program including potassium supplements (15 to 30 mEq of potassium ion four times a day), antacids throughout each day, a diet low in sodium and carbohydrates, close scrutiny for drug-related side effects, and evaluation of respiratory and nursing attention during the early phase of treatment.

Case Reports

Case 1 (NH 07-26-72). A 44-year-old man had had mild oculomotor and limb muscle weakness for 8 years. Loss of consciousness after 1 dose each of etorphine and meptazinol had preceded anticholinesterase therapy. During the 7 months before admission to the National Institutes of Health, steadily increasing bulbar and extremity weakness and fatigability developed, culminating in aspiration pneumonitis, requiring tracheotomy, assisted ventilation and amiphenazole therapy, and such severe generalized weakness that he had severe dysphagia and could not lift his arms from the bed. Supramaximal alternate nerve stimulation at 2, 5, 10 and 50 per second demonstrated a markedly declined in amplitude over the first several potentials (determining response) evoked from adductor pollicis and posterior tibial faradic stimulation and exhaustion. From 72 hours after the beginning of prednisone therapy his strength and endurance began gradually to improve, first in swallowing and in proximal limb muscles and then in facial, bulbar and extremitas muscle strengths. Improvement continued steadily until, by day 50, only mild proximal-retract and minimal limb weakness remained, and the patient returned to full work. From 9 months to the present, 17 months into continued therapy, no exacerbation has been detectable. He now walks 5 miles a day as his work.

Case 2 (NH 68-73-20). A 19-year-old girl, with 7 months of fluctuating moderate weakness and fatigability of eye, extraocular, facial and limb muscles and reduced vital capacity, had received partial and variable relief of symptoms from 150 mg of pyridostigmine bromide at 4-hour intervals that was discontinued before study. A prominent deteriorating response of orbicularis oculi and adductor pollicis to supramaximal nerve stimulation at 2, 5, and 10 per second was found, with less than 20 per cent response. 1/80th 8-0058 mg per kilogram intravenously of a suraminlike dose of d-sodium caused a marked decline in vital capacity and increased weakness of eye abductors and limb muscles. Pred-

• 5 MG Pts
• Prednisone 100mg every other day
  • Single AM dose
    – With daily K⁺, antacids, low Na/carb diet
• All improved in 24-72 hrs
• 1 complete remission

Remission in Ocular MG

- Planned 88 patients
- 11 randomized (6 pred/5 plac)
- Up to 60 mg/day
- Failure to reach remission
  - 100% PLAC
  - 17% PRED
- NNT 1.2

SIDE EFFECTS OF PREDNISONE

• Type 2 muscle fiber atrophy
• But true steroid myopathy **rare**
• Hypertension
• Glucose intolerance (diabetes)
• Low potassium
• Fluid retention and weight gain
• Cataracts
• Risk of infection
• Osteoporosis, aseptic femoral necrosis
CONCURRENT MANAGEMENT ON PREDNISONE

• Chest X-ray and PPD or Quantiferon TB blood test prior to treatment
• Vitamin D and calcium supplementation for prophylaxis against osteoporosis
• Baseline bone density DEXA scan and then annual
• Alendronate (Fosamax) as needed
• Dietary consult to instruct on low carbohydrate, low sodium diet
• Check potassium, glucose, blood pressure, eyes on follow-up
AZATHIOPRINE (IMURAN)

- Purine analog - blocks DNA/RNA synthesis and cell proliferation
- Response is slow - up to 18 months
- Dose: Begin 50 mg/day x 1 week, Then, 2-3 mg/kg/day
- Typical dose 150 mg/day (single dose)
- Toxicity
  - Systemic “flu-like” reaction
  - Leukopenia
  - Hepatotoxicity
- Monthly CBC/LFTs
- We do not use Thiopurine Methyltransferase (TPMT) test

Palace et al 1998 MG RCT

$\rho = 0.02$ at 24 mo
AZATHIOPRINE

INDICATIONS

• Second line therapy for:
  – MG
  – LEMS
  – CIDP
  – PM/DM

• Useful for:
  – Relapses or non-response to steroids, “steroid-sparing” properties
AZATHIOPRINE: PRECAUTIONS

• Monthly CBC/LFTs
• Reduce dose if WBC 3000-4000 mm$^3$
• Stop drug if WBC < 3000 mm$^3$ or poly < 1000
• If LFTs increase, discontinue drug; can attempt rechallenge when LFTs return to normal
• Avoid allopurinol (inhibits xanthine oxidase, potentiates toxicity)
• Selective/reversible on T-cells
  – Inhibit IL-2 and interferon γ
  – Inhibits cytotoxic/express supp Ts

• 1987 - CSA Effective in non-immunosuppressed MG*
  – 20 patients

• 1993 - CSA Effective in Steroid-Dep MG*
  – 39 patients

• QMG - Primary End-Point

• In 1993 Study:
  – Mean Dec QMG 3.5 in CSA
  – Mean Dec QMG 0 in Placebo

• Sandoz industry study: results never released

*Tindall et al 1987 & 1993
CYCLOSPORINE

**INDICATIONS**

- Second or Third Line Therapy For:
  - MG
  - LEMS

- Third or Fourth Line Therapy For:
  - CIDP
  - PM/DM
CYCLOSPORINE

**Dose**

3-6 mg/kg/day in divided dose - b.i.d. Gelatin capsules (25 or 100 mg) or solution (100 mg/ml)

**Precautions**

Monitor CSA levels - maintain trough level < 300 ng/ml

Monitor creatinine/BUN/LFTs, BP. Maintain serum creat no more than 30% above baseline; do not exceed 50%

Patients with renal impairment or hypertension require careful monitoring
MYCOPHENOLATE MOFETIL (CELLCEPT)

• Prodrug of mycophenolic acid
• Inhibits DNA precursor synthesis by blocking de novo pathway only
• Selective, reversible and potent cytostatic effect on stimulated T and B lymphocytes
MYCOPHENOLATE MOFETIL

• Neuromuscular diseases used for:
  – MG
  – CIDP
  – DM/PM
MYCOPHENOLATE MOFETIL
RAND/CONTROL TRIALS IN MG

- Sanders & colleagues (MSG Neurology 2008;71:394)
  - Investigator initiated funded by FDA-ODG
  - Must be AChR-Ab pos
  - No prior IS Rx
  - 2.5 gm MM vs. plac
  - All placed on pred 20
  - 1° – QMG 3 mos
  - 2° – MMT, MG-ADL
  - AChR-Ab, SFEMG
  - 80 subjects

- Aspreva sponsored-138 subjects (Sanders et al Neurol 2008;71:400)
  - Can already be on prednisone
  - 9 month trial
MYCOPHENOLATE MOFETIL RAND/CONTROL TRIALS IN MG

Sanders & colleagues (MSG Neurology 2008;71:394)

Aspreva sponsored-138 subjects (Sanders et al Neurol 2008;71:400)

RESULTS FOR BOTH: NO SIGNIFICANT DIFFERENCE!
MYCOPHENOLATE MOFETIL RAND/CONTROL TRIALS : WHY NEGATIVE?

• Drug does not work
• Prednisone improved all pts and masked MM effect
• Studies were not long enough
• Endpoints were not good enough
• Non-homogenous populations enrolled
MYCOPHENOLATE MOFETIL

• Dosing:
  – 500 mg bid; increase to 2.5 to 3.0 gm per day (bid dosing).
  – Comes in 250 mg and 500 mg pills

• Monitor CBC
METHOTREXATE

• Folic Acid Antagonist
• Inhibits DNA/RNA
• Net Effect:
  – Block cell proliferation
• Uses:
  – Used as 2\textsuperscript{nd} or 3\textsuperscript{rd} line tx for DM/PM
  – Use in MG recently studied as steroid sparing agent
METHOTREXATE: Dose

• P.O. or I.V. or I.M.
• Intermittent - give 1 day per week.
• P.O. regimen:
  – 7.5-20 mg/wk in 3 divided doses over 24 hrs. Comes in 2.5 mg tab.
  – Begin with 2.5 or 5 mg/wk p.o. and inc by 1 tab/wk to 15 mg (6 tabs over 24 hrs or single dose).
• - I.V./I.M. doses are higher (20-50 mg/wk or approx. 0.5-0.8 mg/kg) and usually used when giving over 20 mg/wk.
**PHASE II TRIAL OF METHOTREXATE IN MG**

Pasnoor, Barohn and Muscle Study Group FDA OPD R01 FD003538/IND #101,306

- A randomized, double-blind, placebo-controlled study

- 50 patients
  - 25 receiving MTX; 20mg/week
  - 25 receiving placebo/12 mo study

- Hypothesis – adding MTX therapy will improve the MG manifestations so that prednisone dose can be reduced and clinical measures of MG severity will improve

- The primary measure of efficacy: 9-month prednisone area under the curve (AUC)

- Secondary: QMG, MG ADL, MG Comp, MG QOL15


- **Conclusion: NEGATIVE STUDY**

A randomized controlled trial of methotrexate for patients with generalized myasthenia gravis

ABSTRACT

Objective: To determine the steroid-sparing effect of methotrexate (MTX) in patients with symptomatic generalized myasthenia gravis (MG).

Methods: We performed a 12-month multicenter, randomized, double-blind, placebo-controlled trial of MTX 20 mg orally every week vs placebo in 50 acetylcholine receptor antibody-positive patients with MG between April 2009 and August 2014. The primary outcome measure was the prednisone area under the dosing-time curve (AUDTC) from months 4 to 12. Secondary outcome measures included 12-month changes of the Quantitative Myasthenia Gravis Scores, the Myasthenia Gravis Composite Score, Manual Muscle Testing, the Myasthenia Gravis Quality of Life, and the Myasthenia Gravis Activities of Daily Living.

Results: Fifty-eight patients were screened and 50 enrolled. MTX did not reduce the month 4–12 prednisone AUDTC when compared to placebo (difference MTX – placebo: –488.0 mg, 95% confidence interval –2,443.4 to 1,467.3, p = 0.266); however, the average daily prednisone dose decreased in both groups. MTX did not improve secondary measures of MG compared to placebo over 12 months. Eight participants withdrew during the course of the study (1 MTX, 7 placebo). There were no serious MTX-related adverse events. The most common adverse event was nonspecific pain (1.9%).

Conclusions: We found no steroid-sparing benefit of MTX in MG over 12 months of treatment, despite being well-tolerated. This study demonstrates the challenges of conducting clinical trials in MG, including difficulties with recruitment, participants indicating on prednisone alone, and the need for a better understanding of outcome measure variability for future clinical trials.

Classification of evidence: This study provides Class I evidence that for patients with generalized MG MTX does not significantly reduce the prednisone AUDTC over 12 months of therapy.

GLOSSARY

AUC = area under the curve; AUDTC = area under the dosing-time curve; CI = confidence interval; LOCF = last observation carried forward; MG = myasthenia gravis; MGADL = Myasthenia Gravis Activities of Daily Living scale; MGFS = Myasthenia Gravis Foundation of America; MMT = manual muscle testing; MTX = methotrexate; QMSS = Quantitative Myasthenia Gravis Score.

Myasthenia gravis (MG) is the most prevalent (7.8/100,000) acquired disorder of the neuromuscular junction, causing significant morbidity. Symptoms include difficulties with vision, speech, swallowing, breathing, and strength. The mainstay of treatment is disease-modifying agents corticosteroids alone or in combination with immunosuppressive drugs. The only immunosuppressive drugs shown to be effective for MG in randomized placebo-controlled studies are azathioprine and cyclosporine. Azathioprine’s steroid-sparing benefit was
Intent-to-treat analysis using multiple imputation method

- Mean Prednisone dose in:
  - Methotrexate group: $3340.54 \pm 2404.61$
  - Placebo: $3811.62 \pm 1971.4$
  - P-value: 0.14

- Average daily prednisone dose
  - Methotrexate group: $13.26 \pm 9.54$
  - Placebo group: $15.13 \pm 7.82$
**MG MTX TRIAL: SECONDARY OUTCOME MEASURES**

<table>
<thead>
<tr>
<th></th>
<th>Methotrexate Mean change</th>
<th>Placebo mean change</th>
<th>Difference between Placebo and MTX</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QMG</td>
<td>-1.6 ±3.5</td>
<td>.28 ± 4.5</td>
<td>1.88</td>
<td>0.08</td>
</tr>
<tr>
<td>MGMMT</td>
<td>-5.6 ± 4.6</td>
<td>-3.7 ± 7.7</td>
<td>1.9</td>
<td>0.14</td>
</tr>
<tr>
<td>MGQOL</td>
<td>-4.3 ±9.2</td>
<td>-4.8 ± 11.4</td>
<td>0.5</td>
<td>0.38</td>
</tr>
<tr>
<td>MGADL</td>
<td>-1.4± 2.3</td>
<td>-0.26± 2.9</td>
<td>1.14</td>
<td>0.059</td>
</tr>
<tr>
<td>MG Composite</td>
<td>-4.8 ±4.4</td>
<td>-2.5± 5.4</td>
<td>2.3</td>
<td>0.052</td>
</tr>
</tbody>
</table>

*Intent-to-treat analysis using multiple imputation*
MG MTX TRIAL: IS IT “NEGATIVE”? WHY?

• Prednisone probably works too well
  – Maybe hard to do MG studies with patients on prednisone
• Methotrexate does not work
• Underdose methotrexate
• High number of placebo drop outs
• Not enough patients (underpowered)
• Statistical handling of dropouts
METHOTREXATE: Precautions

• Baseline LFTs, CXR
• Monitor:
  – Monthly CBC, LFTs
  – In IM/DM cases, also check GTT
• All patients go on folic acid 1mg/day
CYCLOPHOSPHAMIDE

- Nitrogen Mustard
- Alkalating Agent
- Net Effect:
  - Block cell proliferation

- P.O. dose
  - 1.5-2 mg/kg/day
  - Single dose
  - Supplied as 50 mg tablet

- Precautions:
  - Keep WBC > 3,000 cells/mm³
  - Keep polys > 1,000 cells/mm³
  - Keep well hydrated

- Monitor monthly CBC and UA
CYCLOPHOSPHAMIDE

INDICATIONS

• First Line Therapy (with Pred) for:
  – Vasculitis

• Second or Third Line Therapy for:
  – MNN
  – CIDP
  – PM/DM
  – MG
CYCLOPHOSPHAMIDE

I.V. ADMINISTRATION

• Infrequently Used in Neuromuscular Disease:
  – MMN not responsive to IVIG
  – Severe vasculitis not responding to P.O. CTX/Pred
  – Rarely: severe MG, PM/DM, CIDP
CYCLOPHOSPHAMIDE

I.V. ADMINISTRATION

• How Given:
  • 0.25-1 gm/m² in single dose, often monthly
  • or can “pulse”: 3 gm/m² divided over 10 days qod (MS protocol)
  • Example:
    For 180 lb/70 inch adult
    body surface area = 2 m²
    therefore, 1 gm/m² = 2 gm
IVIG TREATMENT IN NEUROMUSCULAR DISEASE INDICATIONS

• First Line Rx In:
  – GBS (off label)
  – CIDP (FDA approved)
  – MMN (FDA approved)

• Second Line Rx In:
  – DM (off label)
  – MG (off label)
INTRAVENOUS IMMUNOGLOBULIN (IVIg)

• Polyvalent antibody from pooled plasma from donors.

• Possible mechanisms of action:
  – Fc receptor blockade
  – Block autoantibody binding in target tissues
  – Anti-idiotypic antibody effect
  – Suppresses formation of autoantibodies
  – Complement absorption
  – Enhancement of suppressor T cells
IVIG RX IN NEUROMUSCULAR DISEASE DOSING

• Induction Dose: 2 gm/kg
  – Either: 0.4 gm/kg x 5 days or
  – 0.6 / 0.7 / 0.7 gm/kg over 3 days or
  – 1.0 gm/kg x 2 days

• Maintenance Dose (For Chronic Diseases)
  – 0.4 to 1.0 gm/kg every 3 to 4 weeks
  – But may need infusion q 2 weeks or only q 8 weeks
PLASMAPHERESIS

• Directly removes humoral factors such as autoantibodies, immune complexes, complement and other nonspecific inflammatory mediators.

• Remove 3-6 liters of plasma over several hours. Replace with albumin or purified protein fraction (PPF).

• Indications:
  – MG: crises; pre-thymectomy; severe MG (not in crises) when initiating or increasing oral immunosuppressive drugs
  – GBS/CIDP
  – LEMS
Plasmapheresis and Guillain-Barré Syndrome: Analysis of Prognostic Factors and the Effect of Plasmapheresis

G. M. McKhann, MD, J. W. Griffin, MD, D. R. Cornblath, MD, E. D. Mellits, ScD, R. S. Fisher, MD, PhD, S. A. Quaskey, BS, and The Guillain-Barré Syndrome Study Group*

The time course of recovery in the Guillain-Barré syndrome is known to vary widely, but factors associated with differences have not been previously defined. In this study we used multivariate analysis to identify such factors and to determine whether the presence or absence of specific factors would influence treatment decisions, particularly the use of plasmapheresis. Data from 245 patients randomized into conventional and plasmapheresis arms were used to assess the time to walk independently (Grade 2), the time to improve one grade, and the percentage improved at 4 weeks. Individually, many factors were associated with outcome. In the multivariate analysis, four factors correlate with poorer outcomes: mean amplitude of compound muscle action potential on stimulating distally of 20% of normal or less, older age, time from onset of disease of 7 days or less, and need for ventilatory support. The most powerful predictor of outcome was the abnormal mean amplitude of compound muscle action potential on stimulating distally. Plasmapheresis, the only variable the physician can influence, has a beneficial effect over and above any or all of these factors. The plasmapheresis patients on continuous flow machines had better outcomes than those on intermittent flow machines. From these data, tables of expected outcome probabilities have been developed.

GBS

Plasmapheresis
North American Study
(Neurology 1985; 35:1096)

• 245 pts/21 centers
• Randomized/Not Blinded
• Time to Walk Unaided
  – Pheresis pts dec. time by: 32 days (all)
  – 72 days (respirator)
• Average Time on Vent. Dec. by 12 Days
### GBS: DUTCH IVIG VS. PLASMAPHERESIS STUDIES COMPARED TO THE NORTH AMERICAN PLASMAPHERESIS STUDY

<table>
<thead>
<tr>
<th></th>
<th>Dutch</th>
<th>Dutch</th>
<th>North American</th>
<th>North American</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IVIG</td>
<td>PE</td>
<td>PE</td>
<td>Control</td>
</tr>
<tr>
<td>Total patients</td>
<td>74</td>
<td>73</td>
<td>108</td>
<td>120</td>
</tr>
<tr>
<td>Improved 1 grade (4 wk)</td>
<td>53%</td>
<td>34%</td>
<td>59%</td>
<td>39%</td>
</tr>
<tr>
<td>Median days to 1 grade ^</td>
<td>27</td>
<td>41</td>
<td>19</td>
<td>40</td>
</tr>
<tr>
<td>Days grade 2</td>
<td>55</td>
<td>69</td>
<td>19</td>
<td>40</td>
</tr>
<tr>
<td># multiple complications</td>
<td>5</td>
<td>6</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Ventilator by week 2</td>
<td>27%</td>
<td>42%</td>
<td>--</td>
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</tbody>
</table>

# PE, IVIG, AND PE + IVIG FOR GBS

<table>
<thead>
<tr>
<th></th>
<th>PE (N=121)</th>
<th>IVIG (N=130)</th>
<th>PE + IVIG (N=128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in disability</td>
<td>.9</td>
<td>.8</td>
<td>1.1</td>
</tr>
<tr>
<td>Number of patients ventilated</td>
<td>28</td>
<td>29</td>
<td>21</td>
</tr>
<tr>
<td>Days to stopping ventilation</td>
<td>29</td>
<td>26</td>
<td>18</td>
</tr>
<tr>
<td>Days to unaided walking</td>
<td>49</td>
<td>51</td>
<td>40</td>
</tr>
<tr>
<td>Days to hospital discharge</td>
<td>63</td>
<td>53</td>
<td>51</td>
</tr>
<tr>
<td>Days to returning to work</td>
<td>290</td>
<td>371</td>
<td>281</td>
</tr>
<tr>
<td>Unable to walk after 48 days</td>
<td>19</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td>Deaths</td>
<td>5</td>
<td>6</td>
<td>8</td>
</tr>
</tbody>
</table>

AAN PRACTICE PARAMETERS: IMMUNOTHERAPY FOR GBS
(Quality Standards Subcommittee AAN)

- Treatment with plasma exchange (PE) or IVIG hastens recovery from GBS
- PE is recommended in non-ambulant adult pts within 4 weeks of onset symps
- IVIG is recommended for non-ambulant adult pts within 2 or possibly 4 weeks of onset of symps
- PE and IVIG are treatment options for children with severe GBS
- Corticosteroids are not recommended for the management of GBS

# PE and IVIG for GBS

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Plasma Exchange</th>
<th>IVIG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rationale</strong></td>
<td>200-250 ml/kg plasma x 4 sessions over 7-14 days</td>
<td>0.4 g/Kg IV x 5 days</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>Limited availability; requires an experienced team</td>
<td>Allergy, headache, transient LFT, meningitis</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Coagulopathy, thrombocytopenia, hemodynamic instability, poor venous access</td>
<td>Prior allergy, antibodies to IgA, poor renal function</td>
</tr>
</tbody>
</table>

**Rationale**: Removal of autoantibodies and other humoral factors

- Reduces inflammatory cytokine production and inhibits C’

**Disadvantages**: Limited availability; requires an experienced team

**Contraindications**

- Coagulopathy, thrombocytopenia, hemodynamic instability, poor venous access
- Prior allergy, antibodies to IgA, poor renal function

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van der Meche et al. *Current Treatment Options in Neurology*. 2000;2:507-516
GBS: TREATMENT CAVEATS

• After PE or IVIG, Be Patient, 
  Don’t Expect Dramatic Results

• No Reason to Use Both PLEX and IVIG

• No Reason to Use Steroids
CIDP: PLASMAPHERESIS

• Each PLEX reduces IgG by 45%; 3-5 PLEX removes 90%

• 2 RCTs demonstrated transient NDS & NCS improvement:
  – Sham-controlled, 33% response at 3 weeks
  – Cross-over with 5-week washout, 80% response at 4 weeks

• AAN: 2011 – Level of evidence: Class 1
  – Rec: Level A

• Efficacy equivalent to that of IVIG

• Risks of central venous catheter placement

• Hypotension, cardiac arrhythmia, vasovagal

• Allergy to albumin

• Hypocalcemia, anemia, thrombocytopenia

• Citrate toxicity (use heparin)

Hahn AF et al Brain 1996:1055-66
Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial

Richard A C Hughes, Peter Donofrio, Vera Bril, Marinos C Dalakas, Chunqin Deng, Kim Hanna, Hans-Peter Hartung, Norman Latov, Ingemar S J Merkies, Pieter A van Doorn, on behalf of the ICE Study Group

GAMUNEX-C Significantly Improved CIDP in 24 weeks (Disability Scores, INCAT)

Led to FDA appeal & labeling indication
CIDP RX RECOMMENDATIONS

• 1st Line:
  – IVIG 2 gm/kg, then 0.4 to 1 gm/kg/q 3-4 weeks  OR
  – Pred 100 mg/d x 2 wks, then 100 mg qod

• 2nd Line (Relapse or Non-Responder):
  – IVIG or Pred if not 1st line
  – PE 5-10x over 1-6 wks
  – AZA 2-3 mg/kg/d

• 3rd Line:
  – Mycophenylate 2-3 gm/d
  – Cyclosporine 3-6 mg/kg/d
  – Cyclophosphamide 1.5-2 mg/kg/d
  – Methotrexate 20 mg/week
  – Rituximab 2gm (1gm 14 day apart). Repeat 6 mo.
Pts stabilized on IVIG then randomized to IVIG or placebo
41 subjects: 5 phases / subject, each phase for 3 months
Primary endpoint measures:
- Grip strength* (DynEX)
- Upper arm section of Guy’s Neurological Disability Scale
Secondary endpoint measures:
- % of subjects with ≥ 30% grip strength decline*
- # & % of subjects with decline in less affected hand
- # of subjects with accelerated switch
- Patient disability assessment
- Overall Disability Sum Score
- Timed Peg Board Test
- Patient VAS assessment

*In the more affected hand
10% IVIG IN TREATED MMN


- 44 pts (17 sites) & 41 completed the study
- Greater decline from baseline (34%) in mean grip strength in more affected hand following placebo, as compared to IGIV (p=0.005)
- A greater proportion of subjects on IVIG had a ≥ 30% decline in grip strength of the more affected hand (43% vs. 5%; p<0.001), & less affected hand (31% vs. 0%; p<0.001), PBO vs. IVIG
- 69% of PLAC required accelerated switch compared to only 1 (2.4%) on blinded IVIG
- IVIG was demonstrated to be safe, well-tolerated and an effective treatment for MMN in this phase III study
- FDA-approval and labeling indication
SHORT REPORT

ABSTRACT: We initiated a randomized, double-blinded, placebo-controlled trial of intravenous immunoglobulin (IVIG) treatment in myasthenia gravis (MG). Patients received IVIG 2 gm/kg at induction and 1 gm/kg after 3 weeks vs. 5% albumin placebo. The primary efficacy measurement was the change in the quantitative MG Score (QMG) at day 42. Fifteen patients were enrolled (6 to IVIG; 9 to placebo) before the study was terminated because of insufficient IVIG inventories. At day 42, there was no significant difference in primary or secondary outcome measurements between the two groups. In a subsequent 6-week open-label study of IVIG, positive trends were observed.


RANDOMIZED, CONTROLLED TRIAL OF INTRAVENOUS IMMUNOGLOBULIN IN MYASTHENIA GRAVIS

GIL I. WOLFE, MD,1 RICHARD J. BAROHN, MD,1 BARBARA M. FOSTER, PhD,2 CARLAYNE E. JACKSON, MD,3 JOHN T. KISSEL, MD,4 JOHN W. DAY, MD, PhD,5 CHARLES A. THORNTON, MD,6 SHARON P. NATIONS, MD,1 WILSON W. BRYAN, MD,1 ANTHONY A. AMATO, MD,7 MIRIAM L. FREIMER, MD,4 GARETH J. PARRY, MD,5 and JERRY R. MENDELL, MD,4 for The Myasthenia Gravis–IVIG Study Group*

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Accepted 20 May 2002

Make lemonade out of lemons – publish neg data
Randomized, controlled trial of intravenous immunoglobulin in myasthenia gravis

Goal: new MG and IS Dep – 2 studies
100 pts (50 each study)
IVIg 2 gm/kg & 1 gm/kg 3 wks vs. PLAC
Reality – IVIg ‘shortage’
Entered 15 pts – then study DC’d
RESULTS: No diff in QMG (1°)
No diff in RS, SFEMG, MG-ADL (2°)
Some PLAC pts improved on SFEMG
Concl: Underpowered study
Beware of placebo response
Some things we have no control over!
Make lemonade out of lemons – publish neg data
IV IMMUNOGLOBULIN IN PATIENTS WITH MYASTHENIA GRAVIS

Zinman, Eduardo, Bril  Neurology 2007; 68:837-881

• 51 pts IVIG vs. placebo
• QMG: Sig diff at day 14 (p=0.047)
• Persisted at day 28
• Change in
  – IVIG: -2.54
  – PLAC: -0.89
• Post intervention status at day 14
  – IVIG imp 25%
  – Plac imp 6%
• RNS/SFEMG-no sig diff
• Meriggioli editorial:
  – Getting enough “bang for the buck”
• Note: GRIFOLS labeling indication trials for MG in progress
COMPARISON OF IVIG & PLEX IN MG
Barth, et al Neurology 2011;76

- 84 pts to IVIG PE 1g/kg/d x 2 days
  - Or PE x 5
- QMG > 10.5 and “worsening”

Improved: 69% IVIG and 65% PE
Conclusion: IVIG & PE both effective Rx
INDICATIONS FOR PLASMAPHERESIS IN MG

• Crisis
• Pre-surgery
• Worsening while adjusting meds
• Chronic Rx
### Evidence-based guideline update: Plasmapheresis in neurologic disorders

Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology

#### Table 1: Summary of evidence

<table>
<thead>
<tr>
<th>Disease</th>
<th>Conclusion</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute inflammatory demyelinating polyneuropathy/Guillain-Barré syndrome</td>
<td>Established effective</td>
<td>Class I</td>
</tr>
<tr>
<td>Chronic inflammatory demyelinating polyneuropathy, short-term treatment</td>
<td>Established effective</td>
<td>Class I</td>
</tr>
<tr>
<td>Polyneuropathy with monoclonal gammopathies of undetermined significance</td>
<td>Probably effective</td>
<td>Class I</td>
</tr>
<tr>
<td>Immunoglobulin A/immunoglobulin G</td>
<td>Probably effective</td>
<td>Class I</td>
</tr>
<tr>
<td>Immunoglobulin M</td>
<td>Probably ineffective</td>
<td>Class I</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>Insufficient evidence</td>
<td>Class III</td>
</tr>
<tr>
<td>Preoperative preparation</td>
<td>Insufficient evidence</td>
<td>Class III</td>
</tr>
<tr>
<td>Crisis</td>
<td>Insufficient evidence</td>
<td>Class III</td>
</tr>
<tr>
<td>Fulminant demyelinating CNS disease</td>
<td>Possibly effective</td>
<td>Class II</td>
</tr>
<tr>
<td>Chronic or secondary progressive multiple sclerosis</td>
<td>Established ineffective</td>
<td>Class I</td>
</tr>
<tr>
<td>Relapses in multiple sclerosis</td>
<td>Probably effective</td>
<td>Class I</td>
</tr>
<tr>
<td>Sydenham chorea</td>
<td>Insufficient evidence</td>
<td>Class III</td>
</tr>
<tr>
<td>Acute obsessive-compulsive disorder and tics in PANDAS</td>
<td>Insufficient evidence</td>
<td>Class III</td>
</tr>
</tbody>
</table>

Abbreviation: PANDAS = pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection.

---

**Neurology 2011**

Pheresis for MG: Recommendations

Level U (Unknown)
IVIG: TOXICITY

• Headaches, usually infusion related (20-30%)
• Chills/fever
• Diaphoresis/flushing
• Hypotension
• Tachycardia/shortness of breath
• Nausea/vomiting
• Backaches/myalgias
• Flushing
IVIG: TOXICITY

- Anaphylaxis – rare (IgA deficiency)
- Hepatitis
- Neutropenia
- Hives
- Renal insufficiency
- Thrombosis: PE/CVA – Rare!
- Red, macular palm/sole/trunk with desquamation of skin on palms/soles
IVIG-INDUCED RASH
PLASMAPHERESIS Rx

LIMITATIONS

• Trained technician
• Equipment
• IV Access - Often Requires Large Double-Lumen Catheter
• Complications: Pneumothorax, Hypotension, Sepsis, Pulmonary Embolism
• Expensive
• Benefit Lasts Several Weeks
PLASMAPHERESIS: THE PROBLEM OF ACCESS

• Periph IV hard to access
• Chron IJ line – 1 mo to 12 mo infection
• Ports
  – We tried Vortex Dx
  – Can’t take pressure
• AV fistulas
  – Clot
  – Cosmetic
A-V FISTULAS FOR PHERESIS
HOW MUCH TO REMOVE?

• GBS:
  – 200-250 cc/kg total; 70 kg = approx 15,000 cc. Approx 4-6 exchanges of 2-4 liters over 5-14 days

• CIDP:
  – 2 times/wk for 3-6 wks (per Dyck), or as in GBS

• MG:
  – Usually as in GBS, but no exact science for number of exchanges or amount required. Often depends on how patient tolerates and responds to PE
<table>
<thead>
<tr>
<th></th>
<th>Pro-PE</th>
<th>Con-PE</th>
<th>Pro-IVIG</th>
<th>Con-IVIG</th>
</tr>
</thead>
<tbody>
<tr>
<td>It works</td>
<td>Morbidity</td>
<td>Easy to give</td>
<td>Makes less sense</td>
<td></td>
</tr>
<tr>
<td>It makes sense</td>
<td>Central line</td>
<td>Faster to give full course</td>
<td>Not as long as track record</td>
<td></td>
</tr>
<tr>
<td>Longer track record</td>
<td>Need sophisticated equipment and PE team</td>
<td>No sophisticated equipment</td>
<td>May not work</td>
<td></td>
</tr>
<tr>
<td>? Works faster</td>
<td>Expense</td>
<td>? Less side effects</td>
<td>Anaphylaxis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Expense</td>
<td>Insurance issues</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal insuff</td>
<td>Product shortage</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Insurance issues</td>
<td></td>
</tr>
</tbody>
</table>
WHAT IS SUBCUTANEOUS IG (SCIG)?

• Infusion of IgG into subcutaneous tissue, usually using an infusion pump or syringe driver
• Weekly dose usually ≈ ¼ monthly IVIG dose
• Typically self-administered at home
• Flexible schedule and regimens available
• Patient can be ambulatory during administration
• Once pt is trained and demonstrates competence, routine nursing intervention not necessary
CONVERSION FROM IVIG TO SCIG

• Rec is 1: 1.3
• 1gm/kg dose of 80gm/4weeks
  = 110gm
• Weekly give approx. 28 gm
  or 14 gm per infusion twice a week
• 20% solution =70 ml
• Use 2 pumps each w/ 2 ports
• 18 cc per port
• Can infuse approx. 15 cc/hr/per site; ramp up over 3 weeks / 6 injections to maximum of 25 cc/hr/site
## SCIG IN CIDP: PUBLISHED/PRESENTED REPORTS

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study type, duration</th>
<th>Study pop.</th>
<th>N</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koller, 2006</td>
<td>Case report</td>
<td>Previous IVIG, methylprednisolone, mycophenolate mofetil</td>
<td>1</td>
<td>Improved INCAT disability and MRC sum score with no relapses; SCIG well tolerated</td>
</tr>
<tr>
<td>Lee, 2008</td>
<td>Case report</td>
<td>IVIG responders</td>
<td>2</td>
<td>Pts remained clinically stable; SCIG well tolerated</td>
</tr>
<tr>
<td>Magy, 2009 (PNS)</td>
<td>Prospective, open label, 36 wks</td>
<td>IVIG responders</td>
<td>16</td>
<td>2 pts relapsed, 1 pt had slight sensory deterioration, 13 pts remained stable</td>
</tr>
<tr>
<td>Cocito, 2011</td>
<td>Prospective, 6 mo</td>
<td>IVIG responders, clinically stable</td>
<td>5</td>
<td>Pts remained clinically stable; SCIG well tolerated</td>
</tr>
<tr>
<td>Jakobsen, 2012 (AAN)</td>
<td>Prospective, placebo-controlled, 12 wks</td>
<td>IVIG responders, switched to SCIG or placebo</td>
<td>30</td>
<td>Muscle strength, disability, walking distance improved with SCIG vs placebo; local side effects only</td>
</tr>
<tr>
<td>Bayas, 2012</td>
<td>Case report</td>
<td>Lewis-Sumner syndrome, IVIG responders</td>
<td>2</td>
<td>Pts remained clinically stable with dosing adjustments; SCIG well tolerated</td>
</tr>
</tbody>
</table>

OPEN LABEL STUDY OF SUBCUTANEOUS IMMUNOGLOBULIN (SCIG) IN MYASTHENIA GRAVIS

• M Dimachkie PI
• Funded by CSL Bering
• Phase 2 multi-center study
• 25 participants in the IVlg screening phase (ISP)

| Screening visit [Week -10] | IVlg Screening phase [Week -9, -5, -1] | Baseline Visit [Week 0] | Experimental Treatment Phase [Week 0.1 – 12] | End of Study visit & follow-up calls [Week 13, 14, 16] |

• **Primary outcome:** % subjects ETP experiencing ≤ 3 points increase in QMG from Week 0 to Week 12

• **Secondary Outcomes:**
  – MG-ADL, MG-QOL-15, MGC & Treatment Satisfaction Questionnaire (TSQM)
RITUXIMAB

• Monoclonal Ab to B-cell surface membrane marker CD20
• Designed for Rx B-cell lymphoma
RANDOMIZED, PLACEBO-PHASE TRIAL OF RITUXIMAB IN THE TREATMENT OF REFRACTORY ADULT & JUVENILE DERMATOMYOSITIS

• NIH funded
• Rituximab – B cell depleting agent
• 195 pts (76 PM, 76 DM, 48 JDM)
• Refractory to PRED and other oral IS
• 2 groups:
  – RITUX early – RITUX wks 0/1; PLAC wks 8/9
  – RITUX late – PLAC wks 0/1; RITUX wks 8/9
• Primary endpoint: time to DOI
  • DOI = >20% improv in 3/6 core measures & no >2 CSMS worsening by >25%
• Secondary
  • time to 20% imp MMT
    • % DOI week 8
RANDOMIZED, PLACEBO-PHASE TRIAL OF RITUXIMAB IN THE TREATMENT OF REFRACTORY ADULT & JUVENILE DERMATOMYOSITIS (CONT.)

• Dose – adults 1.5 gm/m²; child 575 mg/m²
• Core set measures – MMT; patient & MD VAS; HAQ; CK; extraneuromuscular disease/activity score
• Results: DOI time: 20.0 wks early group; 20.2 wks late group
• Time to 20% imp MMT: no diff
• % meeting DOI @ 8 wks: Ritux 15%; Plac 20.6%
• AE inf reactions – Ritux 15%; Plac 5.3%
• Lessons: Trial design – overestimated how fast Ritux worked
  – Placebo effect – underestimated
  – ? instruments
RITUXIMAB

• Our current dose: 1 gm IV and repeat in 15 days
• Reports of (+) effect in MG (including MuSK), CIDP, MMN, DADS, DM, PM
• NIH trial (Oddis et al) in DM/PM was negative!
• Ongoing NIH trial in ACH-Receptor AG⁺ MG
RITUXIMAB FOR ACHR-AB POSITIVE MYASTHENIA GRAVIS

- Rituximab depletes B-cells that make antibodies
- Study PI – R. Nowack (Yale)
- CoPIs – J. Goldstein, M. Dimachkie, R. Barohn
- Funded by NeuroNext/NIH
- 50 pts; 1:1 randomization
- Enrolling since mid 2014 – now fully enrolled
- Last patient finishes April 2017
- Rituximab dose for trial: 375 mg/m² IV weekly x 4  Repeat in 6 months
RANDOMIZED BLINDED TRIAL OF THYMECTOMY FOR MG

- Newsom-Davis, Wolfe, Cutter, Kaminski, Jaretski
- Randomized/controlled NIH trial
- REQ – gen, AChR Ab+
- All pts go on prednisone
- All get transternal thymectomy
- Blinded evaluations
- OUTCOME: Pred dose and QMG at 3 yrs
- QUESTION: Do THY pts do better than pred alone?
- Difficult/slow enrollment but enrollment complete (# 126 patients)
  - Most subjects outside USA
Randomized Trial of Thymectomy in Myasthenia Gravis


ABSTRACT

BACKGROUND
Thymectomy has been a mainstay in the treatment of myasthenia gravis, but there is no conclusive evidence of its benefit. We conducted a multicenter, randomized trial comparing thymectomy plus prednisone with prednisone alone.

METHODS
We compared extended transthoracic thymectomy plus alternate-day prednisone with alternate-day prednisone alone. Patients 18 to 85 years of age who had generalized nonthymomatomatous myasthenia gravis with a disease duration of less than 5 years were included if they had Myasthenia Gravis Foundation of America clinical class II to IV disease (on a scale from I to V, with higher classes indicating more severe disease) and elevated circulating concentrations of acetylcholine-receptor antibody. The primary outcomes were the time-weighted average Quantitative Myasthenia Gravis score (on a scale from 0 to 30), with higher scores indicating more severe disease over a 3-year period, as assessed by means of blinded rating, and the time-weighted average required dose of prednisone over a 3-year period.

RESULTS
A total of 126 patients underwent randomization between 2006 and 2012 at 36 sites. Patients who underwent thymectomy had a lower time-weighted average Quantitative Myasthenia Gravis score over a 3-year period than those who received prednisone alone (6.15 vs. 8.39, P=0.001); patients in the thymectomy group also had a lower average requirement for alternate-day prednisone (44 mg vs. 60 mg, P=0.001). Fewer patients in the thymectomy group than in the prednisone-only group required immunosuppression with azathioprine (12% vs. 48%, P<0.001) or were hospitalized for exacerbations (9% vs. 57%, P<0.001). The number of patients with treatment-associated complications did not differ significantly between groups (P=0.73), but patients in the thymectomy group had fewer treatment-associated symptoms related to immunosuppressive medications (P<0.001) and lower distress levels related to symptoms (P=0.003).

CONCLUSIONS
Thymectomy improved clinical outcomes over a 3-year period in patients with nonthymomatous myasthenia gravis. (Funded by the National Institute of Neurological Disorders and Stroke and others; MGTX ClinicalTrials.gov number, NCT00294658.)

The authors’ full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Wolfe at the Department of Neurology, University at Buffalo Jacobs School of Medicine and Biomedical Sciences, State University of New York, 100 High St., Buffalo, NY 14203, or at gwolfe@buffalo.edu.

* A complete list of the members of the Thymectomy Trial in Non-Thymomatomatous Myasthenia Gravis Patients Receiving Prednisone Therapy (MGTX) Study Group is provided in the Supplementary Appendix, available at NEJM.org.
WOLFE ET AL. THYMECTOMY IN MG  

QMG Score (Mean±SE) by Treatment Group

• QMG difference: 2.85 pts (99.5% CI 0.47-5.22; p<0.001)

Time-Weighted Average AD Prednisone Dose (Mean±SE) by Treatment Group

• Prednisone dose difference: 44 mg vs 60 mg (95% CI 7-25 mg; p<0.001)
THYMECTOMY FOR MG SUMMARY

• Now a Controlled Trial Exists! Positive study!
• But Response May Not be Immediate
  — Measured in Months to Years
• No Guarantee of Improvement
• Numerous Procedures
• Thymoma is an absolute indication
• Not rec for:
  — Ocular
  — Very young children
  — Greater than 60, or, ? > 70, or ? > 80
    • (Depends on how old the Rx Neurologist is)
# THYMECTOMY PROCEDURES

<table>
<thead>
<tr>
<th>Type</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sternal splitting</td>
<td>Early 1900s</td>
</tr>
<tr>
<td>Maximally invasive</td>
<td>1980s</td>
</tr>
<tr>
<td>Transcervical</td>
<td>1988</td>
</tr>
<tr>
<td>Video-assisted thoracoscopic surgery</td>
<td>Late 1990s</td>
</tr>
<tr>
<td>Robotics (DaVinci)</td>
<td>Early 2000s</td>
</tr>
</tbody>
</table>
MYASTHENIA GRAVIS

My Rx Recommendations - prior to 2007

• 1st Line: Tensilon
  Mestinon
  Prednisone
  Thymectomy

• 2nd Line: Azathioprine
  Mycophenolate Mofetil
  Cyclosporine

• 3rd Line: IVIg
  Plasmapheresis

My Rx Recommendations – 2016

• 1st Line: Enlon
  Pyridostigmine
  Prednisone
  Thymectomy!

• 2nd Line: Azathioprine
  Cyclosporine
  IVIg

• 3rd Line: Plasmapheresis
  Tacrolimus

• 4th Line: Rituximab
  Mycophenolate Mofetil
  Methotrexate

• ? 5th Line: ? Cyclophosphamide
RANDOMIZED, PILOT TRIAL OF ETANERCEPT IN DERMATOMYOSITIS
Muscle Study Group (Amato, et al)
Neurology 2011

• Etanercept = tumor necrosis factor α inhibitor
• NIH funded 16 subjects: 11 ETAN/5 PLAC
  – ETAN 50 mg subQ weekly x 52 weeks
• All on PRED at least 2 mo
• After ETAN vs. PLAC, PRED taper
• Results: All 5 PLAC relapsed (med 148 days)
  – 5/11 ETAN tapered off PRED
  – 6/11 ETAN failures (med 358 days)
RANDOMIZED, PILOT TRIAL OF ETANERCEPT IN DERMATOMYOSITIS
Muscle Study Group (Amato, et al)
Neurology 2011

• Avg PRED dose after week 24:
  – PLAC – 29.2 mg/day
  – ETAN – 1.2 mg/day

• Other outcome measures: no diff
  – MMT, MVIC, IMACS, MITAX, MYOACT, HAQ, SF36, INQOL, CK

• No AE/SAE diffs

• Conc: ETAN may have steroid sparing in DM
  – Needs further study

• Lessons: PRED taper & dose good for endpoint
  – Small, underpowered trial can be positive – if lucky!
OLD DRUG REVISITED
ADRENOCORTICOTROPHIC HORMONE GEL: ACTHAR

• ACTH – binds to melanocortin receptors
  – Direct and indirect IS effects

• 80 units SQ 2x/week

• Levine et al, 2012
  – 5 refractory DM (3)/PM (2) pts responded
  – 3 Rx 12 weeks; 2 Rx > 12 weeks

• FDA approved (!) for:
  – PM/DM
  – RA/Psoriatic arthritis
  – SLE
  – Ankylosing spondylitis

• Company: Mallinckrodt
NEW / NOVEL DRUG

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE II STUDY OF ECULIZUMAB IN PATIENTS WITH REFRACTORY GENERALIZED MYASTHENIA GRAVIS

JAMES F. HOWARD, Jr., MD,1 RICHARD J. BAROHN, MD,2 GARY R. CUTTER, PhD,3 MIRIAM FREIMER, MD,4 VERN C. JUEL, MD,5 TAHAZEA MOZAFIAR, MD,6 MICHELLE L. MELLION, MD,7 MICHAEL G. BENATAR, MD, PhD,8 MARIA ELENA FARRUGIA, DPhii, MD,9 JING JING WANG, MD, MS,10 SUNEIL S. MALHOTRA, PhD,10 JOHN T. KISSEL, MD,4 and the MG Study Group

Muscle Nerve 2013;48:76-84

• 14 MG pts – 4 mo RTC crossover

• Results:
  - 86% on eculuz met QMG DOI (3 pt imp) (57% placebo)
  - QMG score sig less after eculuz (p < 0.0001)
  - MGADL: eculizumab 9/13 imp 2 pts placebo 3/13

• Plan – phase 3 study just completed
ECULIZUMAB PHASE 3 TRIAL RESULTS

MG-ADL and QMG Worst-Rank ANCOVA

Change From Baseline Total Score at Week 26, As Analyzed by Worst-Rank ANCOVA

Primary Endpoint
MG-ADL, p=0.0698

First Secondary Endpoint
QMG, p=0.0129

• 3 of 4 prospectively defined sensitivity analyses to validate the primary endpoint of MG-ADL achieved p-value < 0.05
• For QMG, 4 of 4 prospectively defined sensitivity analyses achieved p-value < 0.05
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Now also Pots & Pans, RRMSF
Thank you