IVIG in Neurology

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Neuromuscular Diseases in which Immunosuppressive Therapy is Used

- Neuropathies
  - GBS
  - CIDP
  - Multifocal Motor Neuropathy
  - Multifocal Acquired Sensory and Motor (MADSAM) Neuropathy
  - Vasculitis
- Neuromuscular Junction
  - Myasthenia Gravis
  - Lambert-Eaton Syndrome
- Myopathy
  - Polymyositis/Dermatomyositis
  - Duchenne’s Muscular Dystrophy
Immunotherapeutic Options in Neuromuscular Disease

- Corticosteroids
- Azathioprine
- Cyclophosphamide
- Methotrexate
- Mycophenylate
- Cyclosporine

- IVIG
- Plasmapheresis
- Mycophenolate
- Rituximab
- Thymectomy
What is IVIG?

- Intravenous immunoglobulin – IVIG – is a polymeric, highly purified preparation of IgG that is derived from large pools of plasma donors.

- IVIG is used to treat an increasing number of immune mediated neurologic disorders that affect the peripheral nerve, neuromuscular junction, muscle, and CNS, because it has the potential to modulate numerous different effectors of autoimmune disease.
Screening of Plasma for IVIG Production

- Donors are screened
- Plasma is screened for units of HIV, HBV, HCV, and CJD
- Nucleic acid testing is performed on plasma pools for viral genomes
- No incidence of HIV, CJD or HBV
Mechanisms of Action

IVIG has multiple immunomodulatory mechanisms of action relevant to the development of different disorders:

• Inhibits complement activation and MAC formation (Dermatomyositis, MG, CIDP, GBS)
• Down-regulates antibody production (MG, LEMS, anti-MAG and anti-GM1 Ab syndromes)
• Neutralizes pathogenic cytokines (Dermatomyositis, GBS, CIDP, PM)
• Modulates macrophage-mediated phagocytosis through blockade of Fc receptors (Demyelinating dz, DM, PM)
• Modulates T-cell function and antigen recognition (GBS, CIDP, DM, PM)
Neuromuscular Disorders Treated with IVIG

- Acute Inflammatory Demyelinating Polyneuropathies (GBS, Miller Fisher Syndrome)
- Multifocal Motor Neuropathy
- Multifocal Acquired Sensory and Motor Neuropathy
- Chronic Demyelinating Polyneuropathies
- Myasthenia Gravis
- Lambert-Eaton Syndrome
- Dermatomyositis
- Polymyositis
- Stiff-person Syndrome
IVIG Treatment in Neuromuscular Disease

Indications

- **First Line Rx In:**
  - GBS (off label)
  - MMN (FDA approved)
  - CIDP (FDA approved)

- **Second Line Rx In:**
  - CIDP (off label)
  - DM (off label)
  - MG (off label)
Acute Inflammatory Demyelinating Polyneuropathies

(Guillain–Barre Syndrome)
# 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>
<td>--</td>
</tr>
</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>

Practice Parameters: Immunotherapy for GBS
(Quality Standards Subcommittee AAN)

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

GBS in Adults: Conclusions
AAN Therapeutics & Tech Subcommittee. Neurology. 78;1009; 2012.

• Based on 2 Class I studies, IVIG is as efficacious as plasmapheresis for treating GBS in adults. Because plasmapheresis is established as effective GBS treatment, we conclude that IVIG also has established effectiveness.

• Based on one adequately powered Class I study, the combination of plasmapheresis and IVIG is probably not better than either treatment alone.
## PE and IVIG for GBS

<table>
<thead>
<tr>
<th></th>
<th>Plasma Exchange</th>
<th>IVIG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regimen</strong></td>
<td>200-259 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>Rationale</strong></td>
<td>Removal of autoantibodies and other humoral factors</td>
<td>Reduces inflammatory cytokine production and inhibits C’</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>

van der Meche et al. *Current Treatment Options in Neurology*. 2000;2:507-516
# PE vs. IVIG

<table>
<thead>
<tr>
<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>Not as long as track record</td>
</tr>
<tr>
<td>Longer track record</td>
<td>Need sophisticated equipment and PE team</td>
<td>Faster to give full course</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Expense</td>
<td>No sophisticated equipment</td>
<td></td>
<td>Expense</td>
</tr>
<tr>
<td>?Rebound</td>
<td>Less side effects</td>
<td></td>
<td>?Rebound</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Product shortage</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Insurance issues</td>
</tr>
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</table>
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
Chronic Acquired Demyelinating Polyneuropathies (CADP)

- Chronic Acquired Demyelinating PNs
  - Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
  - Multifocal motor neuropathy (MMN)
  - Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM)
- Although CIDP, MMN, and MADSAM are subtypes of CADP, they have differing clinical presentations and distinct treatment responses
CIDP: Clinical Features

- Symmetric proximal and distal weakness
- Generalized areflexia
- Progressive or relapsing course over 8 weeks
- CSF protein typically > 60 mg/dl
- 15% have a monoclonal (IgM or IgG)
- Electrodiagnostic Criteria:
  - NCV <75% LLN in 2 or more nerves
  - DL >130% ULN in 2 or more nerves
  - Unequivocal TD or CB in 1 or more nerves
  - F wave latency >130% ULN in 1 or more nerves
### Randomized Controlled Trials of IGIV in CIDP Before 2008

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Therapy</th>
<th>No. of Pts</th>
<th>Design/Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Doorn et al¹</td>
<td>1990</td>
<td>IGIV</td>
<td>7</td>
<td>Double-blind, placebo-controlled, crossover; single-dose comparison</td>
<td>Improvement in all patients</td>
</tr>
<tr>
<td>Vermeulen et al²</td>
<td>1993</td>
<td>IGIV</td>
<td>28</td>
<td>Double-blind, placebo-controlled, parallel-group comparison of 5 consecutive daily doses</td>
<td>No significant difference between groups</td>
</tr>
<tr>
<td>Hahn et al³</td>
<td>1996</td>
<td>IGIV</td>
<td>30</td>
<td>Double-blind, placebo-controlled, crossover; 4 weeks</td>
<td>Improvement in 63% of patients</td>
</tr>
<tr>
<td>Thompson et al⁴</td>
<td>1996</td>
<td>IGIV</td>
<td>7</td>
<td>Double-blind, placebo-controlled, crossover; 24 weeks (stopped early)</td>
<td>Improvement in 3 of 7 patients</td>
</tr>
<tr>
<td>Mendell et al⁵</td>
<td>2001</td>
<td>IGIV</td>
<td>53</td>
<td>Double-blind, placebo-controlled; 6 weeks</td>
<td>Improvement in 75% of patients</td>
</tr>
<tr>
<td>Hughes et al⁶</td>
<td>2001</td>
<td>IGIV vs prednisolone</td>
<td>32</td>
<td>Double-blind, placebo-controlled, crossover; 6 weeks</td>
<td>Improvement but no significant difference between groups</td>
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<tr>
<td>Dyck et al⁷</td>
<td>1994</td>
<td>IGIV vs plasma exchange</td>
<td>15</td>
<td>Randomized, observer-blinded, crossover; 6 weeks</td>
<td>Improvement but no significant difference between groups</td>
</tr>
</tbody>
</table>

Randomized controlled trial of IVIg in untreated chronic inflammatory demyelinating polyradiculoneuropathy

J.R. Mendell, MD; R.J. Barohn, MD; M.L. Freimer, MD; J.T. Kissel, MD; W. King, RPT; H.N. Nagaraja, PhD; R. Rice, PhD; W.W. Campbell, MD; P.D. Donofrio, MD; C.E. Jackson, MD; R.A. Lewis, MD; M. Shy, MD; D.M. Simpson, MD; G.J. Parry, MD; M.H. Rivner, MD; C.A. Thornton, MD; M.B. Bromberg, MD; R. Tandan, MD; Y. Harati, MD; M.J. Giuliani, MD; and the Working Group on Peripheral Neuropathy*

Article abstract—Objective: To determine the efficacy of IV immunoglobulin (IVIg) given patients with untreated chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Methods: A randomized, double-blind, multicenter, investigator-initiated study compared IVIg (Aventis Behring LLC, King of Prussia, PA) with placebo (5% albumin). On days 1, 2, and 21, IVIg (1 g/kg) or placebo was given. The primary outcome measure was the change in muscle strength from baseline to day 42, using the average muscle score (AMS). Secondary outcome measures included change from baseline AMS at days 10 and 21, the Hughes’ functional disability scale, forced vital capacity (FVC), and nerve conduction studies (NCS) of four motor nerves (median, ulnar, peroneal, and tibial). Results: The patients (n = 33) were randomized. Of these, 30 (14 women, 16 men, aged 54 ± 20 years, range 13 to 82) received IVIg and 23 were given placebo (12 women, 11 men, aged 50 ± 18 years, range 23 to 73). Baseline AMS values of the groups were similar (IVIg 7.06 ± 1.31 versus placebo 7.28 ± 1.18, p = 0.53). There were two dropouts in placebo group and one in the IVIg group. Mean AMS improved at day 42 comparing IVIg with placebo (0.63 versus −0.1, p = 0.006). Improved strength was seen by day 10. The placebo group lost strength over this same interval. In the IVIg, 11 subjects improved by the functional disability scale; none worsened. This differed (p = 0.019) from those in the placebo-treated group (two improved, two got worse, remainder unchanged). Forced vital capacity did not improve with IVIg treatment. IVIg improved ulnar motor distal latency (p = 0.005), tibial distal compound muscle amplitude (p = 0.003), and peroneal nerve conduction velocity (p = 0.03). Conclusions: IVIg improves strength in patients with untreated CIDP by day 10 with continued benefit through day 42; more than one third improve by at least a functional grade on a disability scale. This study provides data supporting IVIg as the initial treatment for CIDP.

NEUROLOGY 2001;56:445–449
IVIG in Untreated CIDP
CIDP-IVIG Study Group
Mendell et al 2001

- 50 patients: 29 IVIG / 21 placebo
- Baseline Average Muscle Score (AMS)
  - IVIG vs. placebo 7.06 vs. 7.28, p=NS
- Delta AMS > IVIG vs. placebo @ day 10, 21, 42 (p<0.05)
- Improvement on Hughes Functional Disability Scale
  - 10 IVIG / 1 placebo
- Conclusion: IVIG is an effective 1st line Rx for CIDP
IVIG in Untreated CIDP
CIDP-IVIG Study Group
Mendell et al 2001

Figure 2. The change in the strength, determined by the average muscle score (AMS), is shown for days 10, 21, and 42. The IV immunoglobulin (IVIg) group improved significantly at each time point (mean ± SE). Over this interval, the IVIg group gradually increased strength, whereas the placebo group lost strength. Black bars = IVIg; gray bars = placebo.

Figure 3. The proportion (± SE) of patients who improved at least one grade by functional disability scale is shown at days 10, 21, 42. This reached significance at day 42 (11 patients versus two, exact p = 0.019). Black bars = IV immunoglobulin; gray bars = placebo.
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*

Summary

Background Short-term studies suggest that intravenous immunoglobulin might reduce disability caused by chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) but long-term effects have not been shown. We aimed to establish whether 10% caprylate-chromatography purified immune globulin intravenous (IGIV-C) has short-term and long-term benefit in patients with CIDP.

Methods 117 patients with CIDP who met specific neurophysiological inflammatory neuropathy cause and treatment (INCAT) criteria participated in a randomised, double-blind, placebo-controlled, response-conditional crossover trial. IGIV-C (Gamunex) or placebo was given every 3 weeks for up to 24 weeks in an initial treatment period, and patients who did not show an improvement in INCAT disability score of 1 point or more received the alternate treatment in a crossover period. The primary outcome was the percentage of patients who had maintained an improvement from baseline in adjusted INCAT disability score of 1 point or more through to week 24. Patients who showed an improvement and completed 24 weeks of treatment were eligible to be randomly re-assigned in a blinded 24-week extension phase. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00220740.

Findings During the first period, 32 of 59 (54%) patients treated with IGIV-C and 12 of 58 (21%) patients who received placebo had an improvement in adjusted INCAT disability score that was maintained through to week 24 (treatment difference 33.5%, 95% CI 15.4–51.7; p=0.0002). Improvements from baseline to endpoint were also recorded for grip strength in the dominant hand (treatment difference 10.9 kPa, 4.6–17.2; p=0.0008) and the non-dominant hand (8.6 kPa, 2.6–14.6; p=0.005). Results were similar during the crossover period. During the extension phase, participants who continued to receive IGIV-C had a longer time to relapse than did patients treated with placebo (p=0.011). The incidence of serious adverse events per infusion was 0.8% (9/1096) with IGIV-C versus 1.9% (11/575) with placebo. The most common adverse events with IGIV-C were headache, pyrexia, and hypertension.

Interpretation This study, the largest reported trial of any CIDP treatment, shows the short-term and long-term efficacy and safety of IGIV-C and supports use of IGIV-C as a therapy for CIDP.
Inflammatory Neuropathy Care and Treatment Score (INCAT)

**INCAT – Upper Extremity**
- Arm Disability Score
  - 0 No upper limb problems
  - 1 Minor symptoms in one or both arms, but not affecting any of the functions (zips and buttons, washing or brushing).
  - 2 Disability in one or both arms affecting any of the above mentioned functions.
  - 3 Disability in one or both arms preventing one or two of the above mentioned functions.
  - 4 Disability in both arms preventing three or all functions.
  - 5 Inability to use either arm for any purposeful movement.

**INCAT – Lower Extremity**
- 0 Walking not affected
- 1 Walking affected but walks independently outdoors
- 2 Usually uses unilateral support to walk outdoors (stick, single crutch, one arm)
- 3 Usually uses bilateral support to walk outdoors (stick, crutches, frame, two arms)
- 4 Usually uses wheelchair to travel outdoors, but able to stand and walk a few steps
- 5 Restricted to wheelchair, unable to stand and walk a few steps with help

INCAT Disability scores and total below:
- Upper Extremity Disability Score = _______ (0-5)
- Lower Extremity Disability Score = _______ (0-5)
- Overall Extremity Disability Score = _______ (Sum of Upper and Lower Disability Scores)

**Responder** = change (decrease) or > 1 point
**Relapse** = increase in score
GAMUNEX-C Significantly Improved CIDP in 24 weeks (Disability Scores, INCAT)

- Primary endpoint: Percentage of adjusted INCAT responders who completed the initial treatment period without crossing over and maintained ≥1 point through week 24.
- * First period nonresponders who crossed over, responded to therapy, and maintained a response to crossover therapy continued on crossover therapy to the end of the 24-week initial treatment period.

Graph showing:
- Percentage of Responders (%)
- Gamunex-C: 47.5 (n=59)
- Placebo: 22.4 (n=58)

$P = 0.006$
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:
  - Mycophenylolate 2-3 gm/d
  - Cyclosporine 3-6 mg/kg/d
  - Cyclophosphamide 1.5-2 mg/kg/d
  - Methotrexate 20 mg/week
Multifocal Motor Neuropathy

• Clinical:
  • Adults, Male > female, initially in nerve distribution
  • Slowly progressive distal weakness of hands > feet
  • No sensory symps/signs & No UMN signs

• Lab:
  • Serum-elevated GM-1 AB in 50-80%
  • EDX-CB or other demyel features
  • CSF – usually normal
  • Sensory nerve Bx – normal or minimally abnl

• Treatment options limited:
  • No response to pred; +/- pheresis
  • IVIG is Rx of choice based on RCT phase III
  • Cyclophosphamide is 2nd line of Rx
  • ? Rituximab monoclonal Ab to CD20 cells
Electrodiagnostic Changes in MMN

Terminal Slowing

Focal Conduction Block
<table>
<thead>
<tr>
<th>Study</th>
<th>Dosing</th>
<th>Duration</th>
<th>Patients</th>
<th>Improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azulay, et al, 1994</td>
<td>0.4 gm/kg/5 days</td>
<td>56 days</td>
<td>12</td>
<td>100%</td>
</tr>
<tr>
<td>Van den Berg, et al, 1995</td>
<td>0.4 gm/kg/5 days</td>
<td>14 days</td>
<td>16</td>
<td>83%</td>
</tr>
<tr>
<td>Federico, et al, 2000</td>
<td>0.4 gm/kg/5 days</td>
<td>28 days</td>
<td>16</td>
<td>67%</td>
</tr>
<tr>
<td>Léger, et al, 2001</td>
<td>0.5 gm/kg/5 days/3 months</td>
<td>120 days</td>
<td>18</td>
<td>78%</td>
</tr>
</tbody>
</table>
10% IVIG in treated MMN

- Blinded cross-over design with stabilization phase before & after blinded phases over 15 months
- 40 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 $\geq 30\%$ 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
Forty-four enrolled cases, 17 sites & 41 completed the study

Accelerated switch to open-label IVIG if grip strength decreased ≥ 50% in the more affected hand or intolerable functional deterioration was objectified

Substantially greater decline from baseline (34%) in the mean grip strength in the more affected hand following placebo administration, as compared to IGIV (p=0.005)

A greater proportion of subjects had a ≥ 30% decline in grip strength of the more affected hand (43% vs. 5%; p<0.001), as well as the less affected hand (31% vs. 0%; p<0.001), PBO vs. IVIG

69% of PBO 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
Comparison of MADSAM Neuropathy and MMN Patients: Clinical and Laboratory Features
Saperstein et al, 1999

<table>
<thead>
<tr>
<th></th>
<th>MADSAM</th>
<th>MMN</th>
</tr>
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<tbody>
<tr>
<td>Gender</td>
<td>10 male, 1 female</td>
<td>12 male, 4 female</td>
</tr>
<tr>
<td>Average age of onset</td>
<td>51.5 years (37-72)</td>
<td>40.5 years (20-64)</td>
</tr>
<tr>
<td>Mean duration of symptoms</td>
<td>5.3 years (1-11)</td>
<td>7.6 years (2-20)</td>
</tr>
<tr>
<td>Initial symptoms in the arms</td>
<td>6 (55%)</td>
<td>12 (75%)</td>
</tr>
<tr>
<td>Abnormal sensory exam</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal SNAPs</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Elevated CSF protein</td>
<td>9/11 (82%)</td>
<td>1/11 (9%)</td>
</tr>
<tr>
<td>Anti-GM1 antibodies</td>
<td>0/11 (0%)</td>
<td>9/16 (56%)</td>
</tr>
<tr>
<td>Response to IVIg therapy</td>
<td>5/9 (56%)</td>
<td>6/9 (67%)</td>
</tr>
<tr>
<td>Response to prednisone therapy</td>
<td>3/6 (50%)</td>
<td>NA</td>
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# IVIG for MADSAM

<table>
<thead>
<tr>
<th></th>
<th>Saperstein et al(^1)</th>
<th>Van den Berg, et al(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Patients</strong></td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td><strong>Duration of Symptoms</strong></td>
<td>5.3</td>
<td>8.8</td>
</tr>
<tr>
<td>(years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Abnormal SNAPs</strong></td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td><strong>Elevated CSF Proteins</strong></td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td><strong>Response to IVIG</strong></td>
<td>56%</td>
<td>100%</td>
</tr>
</tbody>
</table>


IVIG for CADP: Summation

- AAN Therapeutics and Technology Subcommittee: IVIG is effective for long term treatment in CIDP
- IVIG may be effective in some MADSAM patients
- Labeling indication for IVIG in CIDP and MMN
Myasthenia Gravis
• Gajdos et al. assessed efficacy/tolerance of IVIG and PE in acute MG exacerbation

• Randomizing 87 patients to 0.4 gm/kg IVIG daily for either 3 days (N=23) or 5 days (N=23), or PE (N = 41)

• Myasthenic muscular score (MSS) through day 15 as primary end-point. MSS variation was 18 in the PE group and 15.5 in the IVIG group

• Patients’ tolerance of IVIG was superior to PE: side effects occurred in 8 PE patients vs. 1 with IVIG

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’ed

RESULTS: No difference in QMG (1°)

No difference in RS, SFEMG, MG-ADL (2°)

Some PLAC pts improved on SFEMG

Conclusion: underpowered study

Beware of placebo response - Some things we have no control over!
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”
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”

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Mean ± SD change in QMGS for disease severity from baseline to days 14, 21, and 28a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IVlg (n = 41)</td>
</tr>
<tr>
<td>Baseline QMGS</td>
<td>14.2 ± 4</td>
</tr>
<tr>
<td>△ QMGS</td>
<td>Day 0-14c</td>
</tr>
<tr>
<td></td>
<td>Day 0-21</td>
</tr>
<tr>
<td></td>
<td>Day 0-28</td>
</tr>
</tbody>
</table>

Abbreviations: IVlg = IV immunoglobulin; PLEX = plasma exchange; QMGS = Quantitative Myasthenia Gravis Score for disease severity.
a This table demonstrates that the changes of QMGS for disease severity did not differ between the 2 treatment groups for the 28-day study duration.
b p Values are for QMGS differences from baseline with IVlg compared to PLEX.
c Primary efficacy parameter.

Improved: 69% IVIG and 65% PE
Conclusion: IVIG & PE both effective Rx
IVIG for MG: Summation

- IVIG appears to have a role in treatment of MG, when patients are not responding to corticosteroids and other immunosuppressive drugs.
- AAN Tech and Therapeutics: 1 Class I study showed IVIG probably effective in treatment MG
- Evidence insufficient to compare IVIG and plasmapheresis in MG
- Role in crises still unclear
## 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 – 2013

- **1st Line:**
  - Enlon
  - Pyridostigmine
  - Prednisone
  - Thymectomy

- **2nd Line:**
  - Azathioprine
  - Cyclosporine
  - IVIg

- **3rd Line:**
  - Mycophenolate Mofetil
  - Plasmapheresis

- **4th Line:**
  - Methotrexate
  - Rituximab

- **5th Line:**
  - Cyclophosphamide
  - Tacrolimus
Additional Disorders Benefiting From IVIG

- Lambert-Eaton Syndrome

- Dermatomyositis

- Polymyositis

- Stiff-Person Syndrome
## Class of Evidence Supporting Use of IVIG

<table>
<thead>
<tr>
<th>Neuromuscular Disorder</th>
<th>Class of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBS in Adults</td>
<td>I</td>
</tr>
<tr>
<td>GBS in Children</td>
<td>II</td>
</tr>
<tr>
<td>CIDP</td>
<td>I</td>
</tr>
<tr>
<td>Multifocal Motor Neuropathy</td>
<td>I</td>
</tr>
<tr>
<td>Myasthenia Gravis</td>
<td>I</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>I</td>
</tr>
<tr>
<td>Stiff Person Syndrome</td>
<td>I</td>
</tr>
</tbody>
</table>
# Class of Evidence Supporting Use of IVIG

<table>
<thead>
<tr>
<th>Neuromuscular Disorder</th>
<th>Class of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher Syndrome</td>
<td>IV</td>
</tr>
<tr>
<td>Neuropathies Associated with Monoclonal Proteins</td>
<td>IV</td>
</tr>
<tr>
<td>Neuropathies Associated with Cryoglobulinemia</td>
<td>IV</td>
</tr>
<tr>
<td>Idiopathic Neuropathies</td>
<td>IV</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>IV</td>
</tr>
<tr>
<td>Inclusion Body Myositis</td>
<td>None</td>
</tr>
<tr>
<td>Idiopathic Brachial Plexopathy</td>
<td>IV</td>
</tr>
<tr>
<td>Diabetic Lumbosacral Radiculoplexopathy</td>
<td>IV</td>
</tr>
</tbody>
</table>
IVIG for Multiple Sclerosis (MS)

- IVIG reduces relapse rate and gadolinium-enhancing lesions on magnetic resonance imaging in MS patients
- IVIG failed to affect disability in secondary-progressive MS\(^1\)
- IVIG failed to improve stabilized visual and motor deficits in two large trials\(^2, 3\)

Summary of MS: Meta-Analysis

- Sorensen et al. performed a meta-analysis of 4 double-blind trials of IVIG for relapsing-remitting MS
- IVIG produced a significant beneficial effect on the annual relapse rate, proportion of relapse-free patients, change in EDSS scores, and a reduction in the number of patients who deteriorated
- They concluded that IVIG may be a valuable alternative for the treatment of relapsing-remitting MS, and could be considered in patients who do not tolerate or are unwilling to take the approved injectable medications

ABC’s of IVIG
IVIG Dosing Schedule

- IVIG initiated at 0.01 ml/kg/min (40cc/hr), increased to 0.02 ml/kg/min after 15 to 30 minutes, if tolerated.
- If no adverse events after 30 minutes, infusion rate gradually increased to a max rate of 0.06 ml/kg/min (200cc/hr and 350cc/hr).
- The average, well tolerated, maintenance rate of IVIG is 0.03 ml/kg/min to 0.06 ml/kg/min.
- 80 kg at 0.06 = 288ml/hr
- 95 kg at 0.06 = 345 ml/hr
- Average time for 1gm/kg IVIG infusion: 3 hours
- Liquid product 10% solution
- Crystaline product 6 gm or 12 gm bottles
- Reconstitute w/D5W to 6.0% - 15.0%
IVIG RX in Neuromuscular Disease

Dosing

- Induction Dose: 2 gm/kg
  - Either: 0.4 gm/kg x 5 days
  - or 0.6-0.7 gm/kg x 3 days

- Maintenance Dose (For Chronic Diseases)
  - 0.4 to 1.0 gm/kg every 3-4 weeks
  - But may need infusion q 2 weeks or only q 8 weeks
IVIG Rx in Chronic Neuromuscular Diseases

• For chronic disease usually determine effectiveness in 2-3 months
• Usually Rx lasts at least 6-12 months
• Reassess for continued use every 6 months
• Eventually either in time between infusions (6-8-12 wks) then discontinue or decrease number of grams per infusion
Contraindications for IVIG

- Known allergy to blood products, especially anaphylactic reaction after exposure to human immunoglobulin
- IgA Deficiency
- Severe renal dysfunction
- Severe congestive heart failure
Monitoring of Patients Receiving IVIG

- Patients receiving IVIG should be closely monitored during the first 5 minutes of administration, and also every time the infusion rate is increased.
- Transfusion reactions generally occur 30 to 60 minutes after administration is initiated, and each time the infusion rate is increased.
- The patient’s vital signs and symptoms of adverse effects should be continually monitored throughout the administration of IVIG.
Adverse Effects

• The majority of adverse effects from IVIG are infusion rate-related and usually mitigated by reducing the infusion rate or by interruption of the infusion until symptoms subside.

• Premedication with acetaminophen (1000mg) and/or diphenhydramine (50mg) may be useful for mitigating infusion-related adverse effects.

• Rarely use methylprednisolone 100mg pre infusion.
IVIG: Toxicity

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

- Anaphylaxis - rare; most cases reported in setting of IgA deficiency
- Hepatitis
- Neurotropenia
- Hives
- Red, macular palm/sole/trunk with desquamation of skin on palms/soles
- Renal insufficiency
- Thrombosis: PE/CVA – Very Rare!
IVIG-induced Rash
IVIG Cost

• Wholesale Price:
  • 40-100 per gram
• Cost to Consumer May 2x
• Ex: $100/gm
  • Induction 70 kg at 2 gm/kg
    • 140 gm = $14,000
  • Maintenance at 0.4 gm/kg
    • 28 gm = $2,800/mo
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: 1.5
- 1gm/kg dose of 80gm/4 weeks
  \[= 120gm\]
- Weekly give approx 30 gm
  or 15 gm per infusion twice a week
- 20% solution = 75ml
- Use 2 pumps each w/ 2 ports
- 18-20cc per port
- Can infuse approx 20 cc/hr/per port
## 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>

SCIG in CIDP

- Vivaglobin® 160 mg/ml & portable programmable pump
- Gradual build-up
- Case 1: IVIG dependent 0.4 gm/kg/month (60 gm)
  - Weekly SCIG dose 16 g in 100 ml infused over 10 hours divided into 5 equal doses of 3.2 g over 3 days
- Case 2 responded to IVIG induction 40 g x 5 d
  - Weekly SCIG dose 6.4 g in 40 ml divided into 2 equal doses of 3.2 g in 1 day

Lee et al. MN 2008 Mar;37(3):406-9
## SCIG in MMN: Published/Presented Reports

<table>
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<tr>
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<th>Study type, duration</th>
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<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koller, 2006</td>
<td>Case report</td>
<td>Previous IVIG</td>
<td>2</td>
<td>SCIG well tolerated in 1 pt, disease stable; generalized exanthema in 1 pt, relationship to SCIG unknown, treatment terminated</td>
</tr>
<tr>
<td>Harbo, 2009</td>
<td>Randomized, single-blinded cross-over, SCIG 84 d</td>
<td>IVIG responders</td>
<td>9</td>
<td>Muscle strength and nerve conduction similar between SCIG and placebo; SCIG well tolerated</td>
</tr>
<tr>
<td>Eftimov, 2009</td>
<td>Prospective, open-label, 6 months</td>
<td>IVIG responders, stable disease</td>
<td>10</td>
<td>Low dose, 4/5 pts deteriorated; 1:1 dose, 4/5 disease stable; SCIG generally well tolerated</td>
</tr>
<tr>
<td>Dacci, 2010</td>
<td>Case report (part of a CSL clinical study)</td>
<td>IVIG responder</td>
<td>1</td>
<td>Muscle strength stabilized after prelim SCIG dose adjustment; SCIG well tolerated</td>
</tr>
<tr>
<td>Harbo, 2010</td>
<td>Follow up from 2009 study, 2 years</td>
<td>SCIG pts</td>
<td>6</td>
<td>Strength remained stable; small dose increase in 4 pts; SCIG well tolerated</td>
</tr>
<tr>
<td>Misbah, 2011</td>
<td>Prospective, open-label, 6 months</td>
<td>IVIG responders, stable disease</td>
<td>8</td>
<td>1 pt deteriorated and withdrew; 7 pts strength stable; SCIG well tolerated</td>
</tr>
</tbody>
</table>

Case Report #1

- 45 y/o WM presents with progressive R>L distal arm weakness over the past 2 years
- No associated neck pain or sensory changes.
- Normal laboratory workup including CSF analysis and MRI of cervical spine.
- NCS show normal SNAPs. Right median and ulnar CMAPs show prolonged distal latencies with proximal conduction block.
Case Report #1

- TRY Steroids?
- TRY IVIG?
- TRY Plasmapheresis?
Case Report #2

• 25 y/o WF with a history of generalized antibody-positive MG presents with worsening dysphagia, proximal weakness, diplopia, and ptosis
• Medications include Mestinon 60mg TID and Cellcept 1 g BID
• Pregnancy test is positive
Case Report #2

- TRY Steroids?
- TRY IVIG?
- TRY Plasmapheresis?
Case Report #3

- 25 y/o homosexual male presents with a 3 month history of progressive, symmetric, proximal and distal weakness with diffuse areflexia
- CSF shows a protein of 150 mg/dL and 60 WBC
- CMAPs show prolonged distal latencies with slowed CVs and conduction block
- SNAPs show prolonged peak latencies with decreased amplitudes
Case Report #3

- TRY Steroids?
- TRY IVIG?
- TRY Plasmapheresis?