IVIG or Plasmapheresis for Neuromuscular Disease: Pros and Cons

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Texas Neurological Society
February 28, 2014

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)
10 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/Apheresis

- PE removes autoantibodies, immune complexes, complement & cytokines
- Boosts T-cell suppressor function
- Plasma exchange volume is 250 cc/kg
- Risks of central venous catheter placement
- Hypotension, cardiac arrhythmia, vasovagal
- Allergy to albumin
- Hypocalcemia, anemia, thrombocytopenia
- The first treatment shown to be effective in GBS based on randomized controlled trials within 2-4 weeks of onset
Acute Inflammatory Demyelinating Polyneuropathies

(Guillain–Barre Syndrome)

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

Appropriate Number of Plasma Exchanges in GBS

French Coop Group
Ann Neurol 1997; 41:298

- Each Exchange: 1.5 Plasma Volume
- Mild GBS (91): 2 exchanges better than none
  4 exchanges no better than 2
- Moderate GBS (390): 4 exchanges better than 2
- Severe GBS (81): 6 exchanges no better than 4
- Rec:
  - Mild GBS – 2 exchanges
  - Mod/Sev GBS – 4 exchanges
### 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 Control</td>
<td></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

PE & IVIG in GBS
AAN Practice Parameters 2003

- PLEX
  - First effective therapy
  - Nonambulant patients within 4 wks of onset (Level A)
  - Ambulant patients within 2 wks of onset (Level B)
- IVIG:
  - Nonambulant patients within 2 weeks (level A)
  - Nonambulant patients within 4 weeks of onset (Level B)
- PLEX & IVIG: treatment options for children with severe GBS
- Corticosteroids NOT recommended in GBS (level A)


Immunotherapy for GBS: A Systematic Review

- 4 PE trials (585):
  - cases improved by 0.89 more grades at 4 weeks as compared to placebo
- 4 IVIG trials (536):
  - cases improvement similar to PE at 4 weeks
- 1 PE followed by IVIG (148): no additional benefit
- 6 corticosteroids trials (587): Less/no improvement compared to no treatment

Hughes RA et al. Brain. 2007;130:2245-2257

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>Regimen</th>
<th>Plasma Exchange</th>
<th>IVIG</th>
</tr>
</thead>
<tbody>
<tr>
<td>200-259 ml/kg plasma x 4 sessions over 7-14 days</td>
<td>6-4 g/Kg IV x 5 days</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rationale</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Removal of autoantibodies and other humoral factors</td>
<td>Reduces inflammatory cytokine production and inhibits C'</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disadvantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited availability, requires an experienced team</td>
<td>Allergy, headache, transient LFT, meningitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<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*

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**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

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**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
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
- 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)

Dyck PJ et al. NEJM. 1986:461-5
Hahn AF et al Brain 1996:1055-6

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 al</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 al</td>
<td>1993</td>
<td>IGIV</td>
<td>28</td>
<td>Double-blind, placebo-controlled, parallel group; 5 consecutive daily doses</td>
<td>No significant difference between groups</td>
</tr>
<tr>
<td>Hahn et al</td>
<td>1996</td>
<td>IGIV</td>
<td>10</td>
<td>Double-blind, placebo-controlled, crossover; 4 weeks</td>
<td>Improvement in 70% of patients</td>
</tr>
<tr>
<td>Thompson et al</td>
<td>1996</td>
<td>IGIV</td>
<td>1</td>
<td>Double-blind, placebo-controlled, crossover; 24 weeks</td>
<td>Improvement in 6 of 7 patients</td>
</tr>
<tr>
<td>Meldrum et al</td>
<td>1997</td>
<td>IGIV</td>
<td>12</td>
<td>Double-blind, placebo-controlled, crossover; 6 weeks</td>
<td>Improvement in 70% of patients</td>
</tr>
<tr>
<td>Hughes et al</td>
<td>1998</td>
<td>IGIV vs. prednisone</td>
<td>15</td>
<td>Double-blind, placebo-controlled, crossover; 6 weeks</td>
<td>Improvement but no significant difference between groups</td>
</tr>
<tr>
<td>Dyck et al</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>

Reference Year Therapy No. of Pts Design/Duration Results
van Doorn et al 1990 IGIV 7 Double-blind, placebo-controlled, crossover; single-dose comparison Improvement in all patients
Vermeulen et al 1993 IGIV 28 Double-blind, placebo-controlled, parallel group; 5 consecutive daily doses No significant difference between groups
Hahn et al 1996 IGIV 10 Double-blind, placebo-controlled, crossover; 4 weeks Improvement in 70% of patients
Thompson et al 1996 IGIV 1 Double-blind, placebo-controlled, crossover; 24 weeks Improvement in 6 of 7 patients
Meldrum et al 1997 IGIV 12 Double-blind, placebo-controlled, crossover; 6 weeks Improvement in 70% of patients
Hughes et al 1998 IGIV vs. prednisone 15 Double-blind, placebo-controlled, crossover; 6 weeks Improvement but no significant difference between groups
Dyck et al 1994 IGIV vs. plasma exchange 15 Randomized, observer-blinded, crossover; 6 weeks Improvement but no significant difference between groups

Lancet Neurol 2008;7:136-144

Dr. Intravenous immune globulin (10% caprylyletherochromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial

Inflammatory Neuropathy Care and Treatment Score (INCAT)

INCAT – Upper Extremity
- 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) of ≥ 1 point
Relapse = increase in score

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

- **1st Line:**
  - IVIG 2 gm/kg, then 0.4 to 1 gm/kg/q 3-4 weeks
  - 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

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

IVIG for MMN: Double-Blind, Placebo-Controlled Trials

<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 ≥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
Preliminary Data 2012 AAN meeting

- 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

Myasthenia Gravis
Plasmapheresis vs. IVIG for MG

Gajdos et al, Ann Neurol 1997

- 87 pts with MG exacerbation
- Randomized: 3 PLEX vs. 3 or 5 IVIG 0.4 gm/kg
- Endpoint – Myasthenic muscular score day 15
- Results – Equal improvements with both Rx:
  - PLEX + 18 pts
  - IVIG + 15.5 points
  - p = 0.65
- Fewer side effects with IVIG (1) vs. PLEX (8)

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"

Evidence-based guideline update: Plasmapheresis in neurologic disorders
Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology

Neurology 2011

Phereses for MG: Recommendations Level U (Unknown)
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 Mean ± SD change in QMG for disease severity from baseline to days 4, 8, 16, and 22</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Baseline QMG</td>
</tr>
<tr>
<td>ITIG x 2 days</td>
</tr>
<tr>
<td>ITIG x 5 days</td>
</tr>
</tbody>
</table>

Improve: 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 (Neurology 2012)
- Evidence insufficient to compare IVIG and plasmapheresis in MG
- Role in crises still unclear

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 for MG:
  - Crises
  - pre-thymectomy
  - severe MG (not in crises) when initiating or increasing oral immunosuppressive drugs
  - chronic treatment monthly
### Indications for Plasmapheresis in MG

- Crisis
- Pre-surgery
- Worsening while adjusting meds
- Chronic Rx

### Myasthenia Gravis

<table>
<thead>
<tr>
<th>My Rx Recommendations - prior to 2007</th>
<th>My Rx Recommendations – 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Line: Tensilon Mestinon Prednisone Thymectomy</td>
<td>1st Line: Enlon Pyridostigmine Prednisone Thymectomy</td>
</tr>
<tr>
<td>2nd Line: Azathioprine Mycophenolate Mofetil Cyclosporine</td>
<td>2nd Line: Azathioprine Cyclosporine IVIg</td>
</tr>
<tr>
<td>3rd Line: IVIg Plasmapheresis</td>
<td>3rd Line: Mycophenolate Mofetil Plasmapheresis</td>
</tr>
<tr>
<td></td>
<td>4th Line: Methotrexate Rituximab</td>
</tr>
<tr>
<td></td>
<td>5th Line: Cyclophosphamide Tacrolimus</td>
</tr>
</tbody>
</table>

### 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>

**Neurology 2012;78:1009**

### 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>

**Neurology 2012;78:1009**

### 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
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.

**Adverse Effects**

**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
- Neutropenia
- 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

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
Chronic Outpatient Plasma Exchange
Ahmed, Dimachkie, Barohn et al 2009

- 12 patients (10 MG, 1 LEMS, 1 CIDP)
- 13 double-lumen tunneled internal jugular catheters
- Mean retention time: 2 months
- Complications: infection (38%) and clotting (31%)%

- 9 AV fistulas placed
- Average time to mature: 6-8 weeks
- Mean retention time: 6 months (still working in 6 patients)
- Complications: thrombosis 3 (33%), 1 while taking ASA
- Adverse effects during outpatient PLEX (n=91)
  - Transient dizziness (6%) with resumption of PLEX after fluid bolus in most
  - Nausea (1%)

Plasma Exchange vs. IVIG: Pros & Cons

Pro-PLEX: Pro-IVIG:
- It makes sense
- It works
- Longer track record
- Works faster
- Easy to give
- Faster to give full course
- No sophisticated equipment needed

Con-PLEX: Con-IVIG:
- Central line
- Morbidity
- Need sophisticated equipment and PLEX team
- Expense
- Makes less sense
- Not as long a track record
- Renal insufficiency
- Anaphylaxis
- Expense
- Unavailability
- Works slower
- May not work
- If fails – PLEX out!

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>Expense</td>
<td></td>
</tr>
<tr>
<td>Rebound</td>
<td>Less side effects</td>
<td>Rebound</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Product shortage</td>
<td></td>
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<tr>
<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: 1.5
- 1gm/kg dose of 80gm/4weeks = 120gm
- Weekly give aprox 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 aprox 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 INCA T disability and MRC sum score with no relapses; SCIG well tolerated</td>
</tr>
<tr>
<td>Lee, 2006</td>
<td>Case report</td>
<td>IVIG responders</td>
<td>2</td>
<td>Pre-remained clinically stable; SCIG well tolerated</td>
</tr>
<tr>
<td>Magy, 2009</td>
<td>Prospective, open-labeled, 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>Pre-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-Summer syndrome, IVIG responders</td>
<td>2</td>
<td>Pre-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

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 60 mg 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?
Case Study

Lab
- CSF:
  - Prot 28 mg/dl
    2 Weeks Later: 203 mg/dl
- NCS: F Waves Unobtainable
  Minimal LE CV Slowing

Case Study

Course
- PE 200 ml/kg Begun Hosp Day 1
- Subclav IV – Pneumothorax / Chest Tube
- On Vent Hosp Day 4
- Extubated Hosp Day 9
- Discharged Hosp Day 20
- At 2 Week F/U: No Bulbar Symps
  Minimal Face / Arm Weakness