Individualizing Immune Globulin Therapy

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About Me

• 18 Years of Experience in Home Infusion

• Co-Founder & CEO for CSI Pharmacy

• IgNS Committee Member

• Therapure Biopharma Advisory board member

• BoD for MG Hope Foundation
Objectives / Goals

• What is Immune Globulin Therapy? IVIG versus SCIG

• How can IG Therapy be individualized?
  - Brand Selection
  - Hydration & Infusion Rate
  - Adverse Reactions (Prevention versus Treatment).

• Complaints we have heard about home infusion.
What is IVIG

• Immune Globulins = Antibodies (IgA, IgD, IgE, IgG, & IgM)

• Intravenous Immune Globulins (IVIG)
  - 10 brands of IVIG, 3 brands of SCIG in the U.S.
  - manufactured from plasma pools (1,000 to 60,000 donors)
  - primary component is IgG
  - brands generally considered equally effective, however have different tolerability profiles.
Plasma Products

- Plasma (55% of Blood Volume)
  - Water 91.5%
  - Proteins (7%)
    - Albumin (54%)
    - Ig (38%)
    - Misc (7%)
  - Factors, et.al. (1%)
    - FII
    - FV
    - FX
    - FIX
    - FVII
    - FXI
    - FXII
    - FXIII
    - VWF
    - ATIII
    - Prot C
    - Prot S
    - Plasmin
    - Plasmin-inhibitor
Antibody Function

Fight off harmful substances in the body.

Recognize antigens on the surface of pathogens and toxins.

Facilitate the neutralization, destruction, and elimination of pathogens and toxins.
Autoimmune Disorders

- Autoantibodies incorrectly label a healthy normal part of the body as harmful.

- IG Therapy (IVIG or SCIG) decreases the production of these autoantibodies.
<table>
<thead>
<tr>
<th>Product</th>
<th>Route</th>
<th>Manufacturer</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carimune NF 3%,</td>
<td>IV</td>
<td>CSL Behring</td>
<td>• Primary humoral immunodeficiency</td>
</tr>
<tr>
<td>6%, 9%, 12%</td>
<td></td>
<td></td>
<td>• Immune thrombocytopenic purpura</td>
</tr>
<tr>
<td>(once reconstituted)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cuvitru 20%</td>
<td>SC</td>
<td>Shire</td>
<td>• Primary humoral immunodeficiency</td>
</tr>
<tr>
<td>Flebogamma DIF 5%, 10%</td>
<td>IV</td>
<td>Instituto Grifols, SA</td>
<td>• Primary humoral immunodeficiency</td>
</tr>
<tr>
<td>Gammagard Liquid 10%</td>
<td>IV/SC</td>
<td>Shire</td>
<td>• Primary humoral immunodeficiency (IV/SC)</td>
</tr>
<tr>
<td>Gammagard S/D 5%,</td>
<td>IV</td>
<td>Shire</td>
<td>• Primary humoral immunodeficiency</td>
</tr>
<tr>
<td>10% (once reconstituted)</td>
<td></td>
<td></td>
<td>• B-cell chronic lymphocytic leukemia</td>
</tr>
<tr>
<td>Gammaked 10%</td>
<td>IV/SC</td>
<td>Kedrin Biopharma</td>
<td>• Primary humoral immunodeficiency (IV/SC)</td>
</tr>
<tr>
<td>Gammaplex 5%, 10%</td>
<td>IV</td>
<td>Bio Products Laboratory</td>
<td>• Primary humoral immunodeficiency</td>
</tr>
<tr>
<td>Gamunex-C 10%</td>
<td>IV/SC</td>
<td>Instituto Grifols, SA</td>
<td>• Primary humoral immunodeficiency (IV/SC)</td>
</tr>
<tr>
<td>Hizentra 20%</td>
<td>SC</td>
<td>CSL Behring</td>
<td>• Primary humoral immunodeficiency</td>
</tr>
<tr>
<td>HyQvia 10%</td>
<td>SC</td>
<td>Shire</td>
<td>• Primary humoral immunodeficiency</td>
</tr>
<tr>
<td>Octagam 5%, 10%</td>
<td>IV</td>
<td>Octapharma Pharmazeutika</td>
<td>• Primary humoral immunodeficiency (5%)</td>
</tr>
<tr>
<td>Privigen 10%</td>
<td>IV</td>
<td>CSL Behring</td>
<td>• Primary humoral immunodeficiency</td>
</tr>
</tbody>
</table>

**July 2017** - Octapharma granted orphan drug status for the use of Octagam 10% in dermatomyositis

**Aug 2018** – FDA approves Octapharma’s new IVIG product … Panzyga 10%

**PHASE III Trial** – proDERM Study in DM by Octapharma.

2gm/kg IVIG Q 4 weeks in refractory DM.
Individualized Therapy

- Prevention of adverse effects
  - Product Selection.
  - Hydration & Pre-medications
  - Taper up rate slowly.
- Treatment of adverse effects
- Customize future Infusions
General Statements on Product Differences

• IG Manufacturers have tweaked their formulations over the past decades in an effort to improve their product’s safety.

• The primary component of Ig products is immunoglobulin G (IgG). Brands of Ig can differ in IgG monomer, dimer, and aggregate concentrations, IgA and IgM content, stabilizers, additives, and levels of impurities.

• These differences result in different side-effect profiles.

• **By appropriate product-selection & utilization, the rate of adverse drug reactions and adverse events can be reduced!**
<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Carimune NF</th>
<th>Flebogamma DIF</th>
<th>Gammagard Liquid</th>
<th>Gammagard S/D IgA &lt;1 μg/mL in a 5% solution</th>
<th>Gammaplex</th>
<th>Gamunex-C Gammaked</th>
<th>Octagam</th>
<th>Privigen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Form</strong></td>
<td>Lyophilized</td>
<td>Liquid</td>
<td>Liquid</td>
<td>Lyophilized</td>
<td>Liquid</td>
<td>Liquid</td>
<td>Liquid</td>
<td>Liquid</td>
</tr>
<tr>
<td><strong>Shelf-Life/Storage Requirement</strong></td>
<td>24 months RT</td>
<td>24 months RT</td>
<td>36 months REF 24 months RT</td>
<td>24 months RT</td>
<td>36 months RT</td>
<td>24 months RT 6 months RT</td>
<td>24 months RT (5%) 24 months REF (10%)</td>
<td>36 Months RT</td>
</tr>
<tr>
<td><strong>Concentration</strong></td>
<td>3-12%</td>
<td>5%, 10%</td>
<td>10%</td>
<td>5%, 10%</td>
<td>10%</td>
<td>5%, 10%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td><strong>Stabilizer</strong></td>
<td>Sucrose</td>
<td>Sorbitol</td>
<td>Glycine</td>
<td>Glucose, Glycine</td>
<td>Sorbitol, Glycine, Polysorbate 80 (5%) Glycine, Polysorbate 80 (10%)</td>
<td>Glycine Maltose</td>
<td>Proline</td>
<td></td>
</tr>
<tr>
<td><strong>Sodium Content mEq/L</strong></td>
<td>20 mg/gm Ig 154 (NS as diluent)</td>
<td>&lt;3.2</td>
<td>No added sodium</td>
<td>146 @5% 292 @10%</td>
<td>30-50 (5%) ≤5 (10%)</td>
<td>&lt;7</td>
<td>≤30</td>
<td>Trace Amounts</td>
</tr>
<tr>
<td><strong>Osmolality (mOsm/kg)</strong></td>
<td>192-1074 (3-12%) 384 (6% SWFI)</td>
<td>240-370</td>
<td>240-300</td>
<td>636 (5%) 1250 (10%)</td>
<td>Not &lt;230, typically 420-600 (5%) Not &lt;240, typically 280 (10%)</td>
<td>258</td>
<td>310-380</td>
<td>320</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>6.4-6.8</td>
<td>5.0-6.0</td>
<td>4.6-5.1</td>
<td>6.8±0.4</td>
<td>4.8-5.1 (5%) 4.9-5.2 (10%)</td>
<td>4.0-4.5</td>
<td>5.1-6.0 (5%) 4.5-5.0 (10%)</td>
<td>4.8</td>
</tr>
<tr>
<td><strong>IgA Content (µg/ml)</strong></td>
<td>1000-2000 (6%)</td>
<td>Average: &lt;3 (Specification value: &lt;50 [5%), &lt;100 [10%])</td>
<td>37</td>
<td>≤1 @5% ≤2 @10%</td>
<td>&lt;10 (5%) &lt;20 (10%)</td>
<td>46</td>
<td>&lt;100 (5%) Ave 106 (10%)</td>
<td>≤25</td>
</tr>
<tr>
<td><strong>anti-A/anti-B titers</strong></td>
<td>Very Low</td>
<td>Unknown</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>High</td>
<td>Low</td>
</tr>
</tbody>
</table>

*Will be lower
## Risk Factors Affecting Tolerability

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Volume Load</th>
<th>Sugar Content</th>
<th>Sodium Content</th>
<th>Osmolality</th>
<th>pH</th>
<th>IgA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Impairment</td>
<td>●</td>
<td></td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal Dysfunction</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-IgA Antibodies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Thromboembolic Risk</td>
<td>●</td>
<td></td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Geriatrics</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonates/Pediatrics</td>
<td>●</td>
<td></td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

# IVIG & SCIG Dosing in DM & PM

| **IVIG dose in dermatomyositis & polymyositis** | 2gm/Kg in divided doses over 2 to 5 days.  
Typically dosed once month and then according to patient response* |
|---|---|
| **SCIG dose in Dermatomyositis & Polymyositis** | Varies greatly, and not well defined in the literature. In our experience;  
2gm/Kg per month divided into once weekly or twice weekly doses. |

• IgNS Immunoglobulin Therapy Standards of Practice  
AANEM Consensus, IVIG 2009
Dosing Frequency

**IVIG** typically dosed every 2 to 4 weeks.

**SCIG** typically dose once or twice weekly.
Prevention of Adverse Reactions

• Product Selection based on risk factors
• Pre-medicate with Tylenol & Benadryl
• Adequate Hydration
• Slow Infusion rate
IVIG Infusion Reactions

1) Aseptic Meningitis (Severe Post Infusion Headache)
2) Headaches during infusion or Hypertension/Hypotension
3) Flu-Like Symptoms
4) Dermatological
5) Anaphylactic reactions
6) Rigors
7) Severe Back and/or Leg pain
8) Thromboembolic events
9) Hemolytic Anemia
Anaphylactic Reaction

• True anaphylactic reactions to Ig therapy are extremely rare, but should be prepared for.
• Patient will experience severe hypotension and difficulty breathing.
• Stop Infusion, administer EPI & IV Benadryl, call emergency services
• IgA deficient patients may be at higher risk – choose low IgA product or switch to SCIG
Aseptic Meningitis (severe post-infusion headache)

• Severe HA after infusion, lasting for hours to days.
• Ig Induced inflammation of the spinal cord.
• Risk factors – high dose, rapid infusion, dehydration, history of migraine.
• Future infusions – Aggressive Hydration, slow infusion rate, Switch Brands, Ideal candidates for SCIG
Headache during the Infusion and/or Hypertension / Hypotension

- May be due to low levels of impurities or high concentration of Ig proteins.
- Slowing the infusion rate often rapidly reverses these side effects (establish max rate).
- Pretreatment with APAP, Benadryl, and Hydration
- Future infusions – If necessary, may switch brands or try SCIG
Flush-Like Symptoms

- Can be mild to moderate occurring hours to days after the infusion.
- Slowing the infusion rate and add pre and post-infusion hydration.
- Pretreatment with APAP & Solu-Medrol 1mg/Kg (max 125mg) IV push over at least 5 minutes.
- Switch Brands or try SCIG (very low incidence).
Dermatological (Rash or Hives)

- Likely allergic reaction to a component in the IVIG solution.
- Usually can be treated with single dose of antihistamine or glucocorticoid.
- Future Infusions – pre-medicate with antihistamine, switch IVIG brands, if necessary try SCIG.
Other Adverse Effects

**Thromboembolism**
- Increased plasma viscosity, Factor Xia

**Acute Renal Failure**
- Most associated with sucrose-containing Ig

**Hemolytic Anemia**
- Select Brand with low anti-ABO titers
- Separate Doses
- Switch to SCIG
Subcutaneous Immune Globulins (SCIG)

• Hizentra 20%
• HyQvia 10%
• Cuvitru 20%

• Gammagard Liquid, Gamunex-C & Gammaked may be administered IV or SC
<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Cuvitru</th>
<th>Gammagard Liquid</th>
<th>Gamunex-C / Gammaked</th>
<th>Hizentra</th>
<th>HyQvia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Form</strong></td>
<td>Liquid</td>
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<td>Liquid</td>
</tr>
<tr>
<td><strong>Shelf-Life/Storage Requirement</strong></td>
<td>36 months REF 12 months RT</td>
<td>36 months REF 24 months RT</td>
<td>36 months REF 6 months RT</td>
<td>30 months RT</td>
<td>36 months REF 3 months RT</td>
</tr>
<tr>
<td><strong>Concentrations</strong></td>
<td>20%</td>
<td>10%</td>
<td>10%</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Sugar Content (mg/ml)</strong></td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>Sodium Content (as Sodium Chloride) mEq/L</strong></td>
<td>None</td>
<td>No added sodium</td>
<td>Trace Amounts</td>
<td>≤10</td>
<td>No added sodium</td>
</tr>
<tr>
<td><strong>Osmolarity/Osmolality (mOsm/kg)</strong></td>
<td>280-292</td>
<td>240-300</td>
<td>258</td>
<td>380</td>
<td>240-300</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>4.6-5.1</td>
<td>4.6-5.1</td>
<td>4.6-5.3</td>
<td>4.6-5.2</td>
<td>4.6-5.1</td>
</tr>
<tr>
<td><strong>IgA Content (µg/mL)</strong></td>
<td>(Ave) 80</td>
<td>37</td>
<td>46</td>
<td>≤50</td>
<td>37</td>
</tr>
<tr>
<td><strong>anti-A/anti-B titers</strong></td>
<td>Unknown</td>
<td>Moderate</td>
<td>High</td>
<td>Unknown</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
SCIG Possible Advantages

• Subcutaneous weekly infusions keep IgG levels at a steady state – consistent
• No pre-meds required
• Side effects are mainly – localized*
• Autonomy and independence
• NO VENOUS ACCESS
Complaints with Home IVIG / Unacceptable Practices

- Pharmacy sent me a bill for my IVIG/SCIG because it wasn’t covered by my insurance.
- I was told Medicare doesn’t cover my IVIG unless I go to an infusion suite.
- Nurse starts infusion leaves patient and comes back at end of infusion.
- Nurse will only infuse IVIG but not saline/hydration.
- Nurse will stay for maximum of 4 hours because insurance will only cover that many hours.
Complaints with Home IVIG / Unacceptable Practices

• Nurse trains patient on how to infuse through port. Patients believe if they have serious adverse reaction they can administer an epi pen and call 911.

• Nurse tells patient that they have to infuse fast because they are required to see a certain number of patients a day.

• Patients having increased side effects...aseptic meningitis which can be due to fast rate of infusion.
Complaints with Home IVIG / Unacceptable Practices

• Lack of follow-up by nurse or home infusion company regarding reactions.

• Lack of training on administering IgG.

• Lack of hygiene (washing hands)
Q & A

james@csipharmacy.com

Toll Free: 1-844-680=2944
Treatment of Infusion reactions

- Slow Infusion Rate
- Administer IV Fluids
- Solu-Medrol 1mg/Kg (max 125mg) IV push over at least 5 minutes. May add as a premedication for future infusions.
- Consider a brand change
- Inability to tolerate IVIG, consider switching to SCIG