Historical changes in Ig therapy
‘Improving Treatment Options & Quality of Life along the way’

Castlegar Recreation Complex
Castlegar, B.C
September 30th, 2011

Ayman Kafal, Medical Liaison
Medical Affairs
CSL Behring Canada
AGENDA

1. Evolution of Ig therapy (IVIg vs. SCIg)
   
   1. Intravenous Immunoglobulin
      ➢ Privigen (10% liquid solution)
   
   2. Subcutaneous Immunoglobulins
      ➢ Vivaglobin (16% liquid solution)
      ➢ Hizentra (20% liquid solution)
What is Immune Globulin (Human)?

- Made from pooled plasma – 8000-10,000 Donors
- All use cold ethanol fractionation
- Content >95% IgG, IgA and other constituents vary in different products
- Stabilizers, chemical treatments and forms vary per manufacturer
- All use multiple safety steps beginning with donor selection, screening, specific viral inactivation/removal steps in manufacturing process
- Immune Replacement dosing 400-800 mg/kg every 3-4 weeks
- Immunomodulation 1-2 grams/kg
Landmarks in the History of Ig Therapy

1952  
Bruton treats first patient diagnosed with agammaglobulinemia with SC injections of immune serum globulin (ISG)\(^1\)

1953  
Janeway and Gitlin prefer IM injections, and this becomes standard of care in US\(^2\)-\(^4\)

1955  
Berger introduces battery-powered pumps to slowly administer IM ISG by SC route\(^5\)

1960  
Renewed interest in SCIg as alternative to IV therapy, especially for home use\(^6\)

1970  
Berger introduces battery-powered pumps to slowly administer IM ISG by SC route\(^5\)

1980  

1990  
Vivaglobin in CDN

2000  
Vivaglobin in USA.

2016/2017

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Immune Replacement Therapy

IVIg vs. SCIlg
Choice of Ig Treatment

IVIg features

- Large volumes
- Less frequent dosing

SClG features

- Venous access not required
- Gradual absorption reduces systemic adverse events
- Consistent IgG serum levels maintained with weekly infusions
- Facilitates self-infusion in home setting, allowing patients to actively participate in therapy with physician oversight
PIDD Treatment National Consensus, 2010

Canadian Blood Services and Canada's National Advisory Committee on Blood and Blood Products

The Use of Immunoglobulin Therapy for Patients With Primary Immune Deficiency: An Evidence-Based Practice Guideline

N. Shehata, V. Palda, T. Bowen, E. Haddad, T.B. Issekutz, B. Mazer, R. Schellenberg, R. Warrington, D. Easton, D. Anderson, and H. Hume, Transfusion Medicine, January 2010
Efficacy and Administration

• With respect to clinical efficacy and adverse events, there is insufficient evidence to recommend one formulation of Ig over another for currently available products.

• With respect to clinical efficacy for reducing infections, IVIG and SCIG preparations should be considered equivalent.

• When deciding on route of administration, patient preference should be taken into account.
Privigen™ – the new breed of IVIG

Simple Yet Sophisticated
Privigen™: The Recipe we were looking for

- What was working
  - 10% Liquid Formulations
  - Large Donor pools with highly concentrated IgG

- What we were looking for
  - Stable at room temperature for entire shelf life
    - The right stabilizer
    - Low Dimers
    - The right pH
  - Lower IgA content
L-Proline: Amphiphilic Structure and Dimer Formation

L-proline shields hydrophobic domains of the IgG molecules and thus interferes with IgG Dimer formation.

Privigen™: The Recipe we were looking for

• What was working we kept!
  • 10% Liquid Formulations
  • Large Donor pools with highly concentrated IgG

• What we were looking for we found!
  • Stable at room temperature for entire shelf life

• The Novel stabilizer: L-Proline
  • Proline inhibits IgG dimer formation (improved tolerability)
  • L-proline is superior to glycine in preventing aggregation and fragmentation of IgG, as well as yellowish discoloration during storage*

• Low Dimers
• The right pH:
• Lower IgA content

*Bolli R, Woodtli K, Hoefferer L, Lerch P. L-proline – a superior stabilizer for liquid immunoglobulin formulations. Presented at the American College of Allergy, Asthma and Immunology, Dallas, Texas, USA, November 8-14, 2007, Abstract P205.
† Cramer M et al. Stability over 36 months of a new liquid 10% polyclonal immunoglobulin product (IgPro 10, PrivigenTM) stabilized with L-proline. Vox Sanguinis 2008:
‡ Spycher MO et al Well-tolerated liquid intravenous immunoglobulin G preparations (IVIGs) have a low immunoglobulin G dimer (IgG-dimer) content. J autoimmun 1999; 96(Suppl. 1):96.
Simple yet Sophisticated

Simple

- Ready-to-use 10% liquid IVIg
- Latex-free
- Storage at room temperature for the entire shelf-life*
- No refrigeration required*
- Always ready for immediate infusion

* Privigen™ may also be stored refrigerated (Data on file: CSL Behring)
Simple yet Sophisticated

Sophisticated

- First and only Proline stabilized liquid IG therapy
- Low dimers/aggregates/fragments
- Lowest IgA content
Subcutaneous Immunoglobulins
What Is Subcutaneous Ig?

- Infusion of IgG into subcutaneous tissue using an infusion pump or syringe driver
- Weekly dose ~ ¼ monthly IVIg dose
- Typically self-administered

Patient can be ambulatory during administration

Once independent nursing may not be needed
**Infusion site(s)**

- Select an appropriate injection site(s).

- The following areas are recommended for subcutaneous injection:
  - Abdomen
  - Thighs
  - Upper arms
  - Hip
SClG Weekly Dosing Results
In More Even Levels of Plasma IgG
SCIG - IgG levels

- Steady Ig Level
- Avoids high peaks
- Prevent low through
- Represent serum Ig profile seen in normal individual
# Comparison of IVIg and SCIg

<table>
<thead>
<tr>
<th></th>
<th>IVIg</th>
<th>SCIg</th>
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<tbody>
<tr>
<td><strong>Monthly Dose (mg/kg by weight)</strong></td>
<td>400-800</td>
<td>400-800</td>
</tr>
<tr>
<td><strong>Infusions Per Month</strong></td>
<td>≈1</td>
<td>≈ 4</td>
</tr>
<tr>
<td><strong>Clinical efficacy</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Steady Ig Plasma Levels</strong></td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td><strong>Quick Increase of IgG Plasma Levels</strong></td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td><strong>Tolerability</strong></td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td><strong>Patient Satisfaction</strong></td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td><strong>Systemic Site effects</strong></td>
<td>+</td>
<td>−</td>
</tr>
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Skoda-Smith, Subcutaneous immunoglobulin replacement therapy in the treatment of patients with primary immunodeficiency disease. 2009

IVIG Candidates

Medical considerations
- I have another medical condition that requires me to receive IVIG.
- I have persistent severe local reactions after SCIG injection.
- I have constant energy levels throughout the month (I do not get tired between IVIG infusions).
- I feel well and satisfied with my IVIG.

Lifestyle considerations
- I enjoy taking the time to go to the hospital for my infusions every 3-4 weeks.
- My infusion clinic is close to my home and very convenient for me.
- I feel I need a healthcare professional to manage my infusions.
- I feel unsafe treating myself.
- I do not have a clean/appropriate space to conduct my therapy at home.
SCIG Candidates

Medical considerations
□ I have side effects after IVIG or I need to take other medication before I get IVIG.
□ IVIG affects my ability to perform daily activities.
□ I feel fatigued in the days before I get my IVIG infusion.
□ I have small, hard to find veins and require many needle sticks to administer my IVIG.

Lifestyle considerations
□ I wish to schedule my therapy around my life and not my life around my therapy.
□ My IVIG Infusions interfere with my family demands / work / school / business travel / vacation plans.
□ I cannot afford the time / money to go to the hospital every 3-4 weeks.
□ I would like to be mobile during my infusions.
□ My infusion clinic is far away from home.
□ I want to improve my quality of life and take charge of my infusions.
Vivaglobin™
16% liquid solution

Product Features
Product Description

- Sterile ready-to-use liquid
  - 16% (160 mg/mL) protein solution

- At least 96% IgG
  - IgA content ≤1%

- Excipients include:
  - 2.25% Glycine, USP
  - 0.3% Sodium Chloride, USP
  - Water for Injection, USP

- No preservatives or stabilizing sugars
- Store in the refrigerator at 2 - 8°C (36 months) or 5 months at room temperature
Injection Site Reaction (ISR) symptoms

Generally Mild - Moderate
- Redness
- Swelling
- Discomfort
- Itching

This is a normal reaction
- should diminish over 24 – 48 hrs
Hizentra™  
20% liquid solution  

Product Features
Hizentra™ SCIG, 20%

1. Showed protection against infection by maintaining steady state Ig levels (aSBI=0.0)

2. Is the first and only 20% Subcutaneous Immune Globulin

3. Is efficient
   - Shorter infusion time (due to lower volume and faster infusion speed)
   - Fewer infusion sites (due to higher concentration)

4. Convenient
   - Requires no refrigeration
   - Portable administration
   - Switching with Privigen

5. Showed good tolerability
   - Generally well tolerated systemically
   - Comparable local tolerability to Vivaglobin®

Available in:
- 5mL vial (1g)
- 10mL vial (2g)
- 20mL vial (4g)
Indications & Contraindications

**Indications**

- Hizentra™ is indicated for the treatment of patients:
  - With primary immune deficiency (PID), and,
  - Secondary immune deficiency (SID) who require immune globulin replacement therapy.

**Contraindications**

- Hizentra™ is contraindicated in patients:
  - With history of anaphylactic or severe systemic reaction to human normal immunoglobulin or to components of Hizentra™.
  - With hyperprolinemia (contains the stabilizer L-proline)
Benefits of L-Proline

L-proline was chosen as the stabilizer because:

• It reduced dimer formation / fragmentation / coloration \(^1,2\)
• Enables room temperature storage (2-25 °C)
• Product can still be refrigerated
• Switching between IVIG (Privigen®) & SCIG (Hizentra™)


Benefits of 20%

• Reduced infusion volume
• Reduced infusion time
• Fewer infusion sites
• Fewer infusion days
• Reduced ancillary cost
• Lower storage volume
Injection-Site Reactions Over Time

Mild reactions

15 minutes prior to end of infusion
End of infusion
8 hours post infusion
24 hours post infusion

Moderate reactions

Source CSL Behring
### Characteristics of SCig Products \(^1,^2\)

<table>
<thead>
<tr>
<th></th>
<th>Vivaglobin® *</th>
<th>Hizentra™</th>
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<tbody>
<tr>
<td><strong>Concentration</strong></td>
<td>16%</td>
<td>20%</td>
</tr>
<tr>
<td><strong>Stabilizer</strong></td>
<td>Glycine</td>
<td>Proline</td>
</tr>
<tr>
<td><strong>Max infusion rate per site</strong></td>
<td>20 mL/hr</td>
<td>34 mL/hr(^†)</td>
</tr>
<tr>
<td><strong>Max volume per site</strong></td>
<td>15 mL</td>
<td>25 mL</td>
</tr>
<tr>
<td><strong>Storage</strong></td>
<td>Refrigeration (5 months room temp)</td>
<td>Room temperature storage (refrigeration possible)</td>
</tr>
<tr>
<td><strong>IgA content</strong></td>
<td>(\leq 1700) mcg/mL</td>
<td>8 mcg/mL (av) (^**)</td>
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</tbody>
</table>

*Vivaglobin, Immune Globulin Subcutaneous (Human)*

\(^**\) Average of 38 batches

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1. Vivaglobin, Canadian Product Monograph, 22 Nov. 2010
2. Hizentra™, Canadian Product Monograph, July 2011