Update on Immunoglobulin Use for Primary Immunodeficiency

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Outline of Discussion

• Overview of Primary Immunodeficiency
• Manufacturing and Purification of Immunoglobulin
• Intravenous versus Subcutaneous administration
• Dosing of Immunoglobulin
• Relationship between Dose, Level and Efficacy
• Developments in Immunoglobulin Therapy
Primary Immunodeficiency

- First PID described in 1952 by Colonel Ogden Bruton: a young boy with recurrent respiratory infections who could not make specific antibodies who was successfully treated by immunoglobulin.

- Prevalence of diagnosed PID in US is around 1 out of 2000 patients.

- Incidence of newly diagnosed PID is around 1 out of 10,000 patients.

- There are over 200 characterized PID disease syndromes.
Breakdown of PID Conditions

- Antibody (B cell) deficiencies (65%)
- Combined B and T cell deficiencies (15%)
- Cellular (T cell) deficiencies (5%)
- Phagocytic deficiencies (10%)
- Complement/other innate deficiencies (5%)
Antibody Deficiencies

- Common Variable Immune Deficiency
- Specific Antibody Deficiency
- Agammaglobulinemia
- Hyper-IgM Syndrome
- Transient Hypogammaglobulinemia of Infancy
- IgA Deficiency
Manufacturing of Immunoglobulin

- A commodity, not a drug
- All derived from Plasma donors
  - Direct Plasma donations
  - Collected from Whole Blood donations
- Pooled from 10,000 to 50,000 donor plasmas
- Screening of Donor Plasma
- Undergoes multiple steps of isolation, purification, and viral inactivation
Screening of Plasma Source

- Individual Plasma donations are screened using serology testing for various viral pathogens: HIV, HBV, HCV
- Plasma Pool screenings: Nucleic Acid Testing for various viral pathogens
- Blood Type Antibody Screening (New):
  - Screening of Donors
  - Future Development: Immunoaffinity Chromatography - once implemented will replace donor screening
Steps Involved in Manufacturing

- Takes 9 months from collected plasma to finished product
- Newer Products have introduced 3 rather than 2 viral inactivation steps
  - Low pH Incubation
  - Depth Filtration
  - Nanofiltration
- Multiple Partitioning and Fractionation Steps
  - Cold Ethanol Precipitation
  - Octanoic Acid Fractionation
  - Chromatography
Intravenous Immunoglobulin Therapy

- First introduced in late 1970s-early 1980s - considered a novel route of administration from previous Intramuscular injections
- Exists in a myriad of formulations and concentrations
  - 5%, 6%, and 10%
  - Lyophilized or Liquid Based
- Varying degree of IgA content
- Various Stabilizers
  - Sugars: Maltose, Sucrose
  - Amino Acids: L-Proline, Glycine
Subcutaneous Immunoglobulin Therapy

- Initially first used by Colonel Bruton in the 1950s, but resurfaced again in the 1990s

- Various Concentrations:
  - 10%, 16% and 20%

- Slow release of Immunoglobulin into systemic circulation
Pharmacokinetic Comparisons of IVIG vs. SCIG

Why do we care about Pharmacokinetics

- Serum Peak: often associated with incidence of systemic adverse reactions
- Serum Trough: hypothesized to be associated with Wear-Off effect
- Area Under Curve associated with high peak levels above “physiologic level”: considered wasted IG
- No Peak in SCIG
- SCIG associated with far less systemic adverse effects than IVIG
- SCIG is associated with more local adverse reactions: swelling, injection site pain, redness - **but these reactions are mild and temporary**

Review of Systemic Adverse Reactions of IG Therapy

• Mild
  • Headache
  • Fever
  • Body Aches

• Severe
  • Aseptic Meningitis
  • Hemolytic Anemia
  • Neutropenia
  • Thrombosis
  • Renal Failure
  • Anaphylaxis
Local Adverse Reactions of IG Therapy

- Redness surrounding the site of infusion
- Swelling around the site of the infusion
- Temporary and fades over time often disappearing after a day following therapy
- Quantification not standardized - various studies have measured it in different ways
  - When is it reported? Immediately or several days later
  - Who is reporting? Patient or Provider
- Seen far more frequently in SCIG than IVIG
Relationship Between Dose and Serum Level

- Steady State level of SCIG generally higher than trough level in IVIG

- In one prior study of 65 patients switching from IVIG to SCIG, the mean serum level rose from 786 mg/dL to 1040 mg/dL\(^1\)

- In another study with 16 children who switched, the mean serum level rose from 780 to 920 mg/dL\(^2\)

Dose Conversions from IVIG to SCIG

- US FDA mandated label to state 1: 1.37 conversion from IVIG dose to SCIG dose
- Dose conversion derived from strict comparisons between Area-Under-Curve in Pharmacokinetics
- Dose conversion not based on any clinically meaningful rationale
- European immunologists do not perform dose conversion and most US immunologists do not either
Relationship between Dose, Level and Efficacy

- Meta-Analysis of retrospective data showed that pneumonia incidence was 5 times higher in patients with 500 mg/dL vs. 1000 mg/dL

- Same study showed that for every increase of 100 mg/dL of serum level, there was a 27% reduction in Pneumonia incidence

- Troughs higher than 600 mg/dL may be needed to control chronic lung disease in CVID patients

- Hypogam patients with chronic lung disease may need trough level > 800 mg/dL to achieve adequate control

- One older prospective study showed that dose of 500-600 mg/kg/month achieved better lung function (FEV1) than 200-300 mg/kg/month

2. De Gracia J. Immunoglobulin therapy to control lung damage in patients with common variable immunodeficiency
4. Roifman CM. The Lancet. May 9, 1987: 1075-1077
**Level and Efficacy**

**Figure 1.** IgG trough levels in patients A and B before, during, and after initiating IVIG therapy and associated infection history. *Time at which our practice assumed the care of this patient. S, Acute sinusitis; P, pneumonia; OM, otitis media.

Bonagura et al JACI, 2008
Dose and Trough

Orange et al Clin Immunol, 2010
IgG Level and Pneumonia

Orange et al Clin Immunol, 2010
Infection Rate and IgG Level

• Relationship between Trough and % Patients with zero infections per year
• Blue: XLA and Red: CVID

Lucas et al. JACI, 2010
Inverse Relationship of IgG Level and Infection Rate

Fig. 1 Correlation of annualized rate of infections other than aSBI with steady-state serum IgG level studies listed in Table I. Y-axis is the annual rate of infections other than aSBI, episodes/subject/year. X-axis is mean serum IgG level at steady state, mg/dl

### Comparison of Higher vs. Lower SCIG Dose: US vs. EU

<table>
<thead>
<tr>
<th>Health Outcome</th>
<th>1:1 dose cohort (EU) (N=46)</th>
<th>1.5:1 dose cohort (US) (N=38)</th>
<th>Analysis of differences between cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of serious infections (events/patient/year)</td>
<td>0</td>
<td>0</td>
<td>&lt;0.0001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rate of infections (events/patient/year)</td>
<td>5.18</td>
<td>2.76</td>
<td>&lt;0.0001&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Sensitivity analysis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.16</td>
<td>6.67</td>
<td>&lt;0.0001&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Rate of days of hospitalization due to infection (days/patient/year)</td>
<td>3.48</td>
<td>0.20</td>
<td>&lt;0.0001&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Sensitivity analysis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.95</td>
<td>2.6</td>
<td>0.0003&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Percent of patients hospitalized due to infection</td>
<td>8.7</td>
<td>2.6</td>
<td>0.2423&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sensitivity analysis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.67</td>
<td>6.67</td>
<td>0.3925&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rate of days with antibiotics for treatment or prophylaxis of infection (days/patient/year)</td>
<td>72.75</td>
<td>48.5</td>
<td>&lt;0.0001&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Sensitivity analysis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>66.62</td>
<td>66.62</td>
<td>&lt;0.0001&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Rate of days missed off work/school due to infection (days/patient/year)</td>
<td>8.0</td>
<td>2.06</td>
<td>&lt;0.0001&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Sensitivity analysis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.25</td>
<td>5.25</td>
<td>&lt;0.0001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Percent of patients missing ≥1 day off work/school per year due to infection</td>
<td>43.5</td>
<td>31.6</td>
<td>0.2637&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>Sensitivity analysis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>42.2</td>
<td>0.3179&lt;sup&gt;c&lt;/sup&gt;</td>
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</tbody>
</table>

<sup>a</sup> Sensitivity analysis to account for covariates.

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Patient Experience of IVIG vs. SCIG

• No wear-off effect with SCIG:
  • Seen in IVIG patients
  • Sense of non-specific sensation of “being unwell” during the last week of cycle
  • Increased incidence of infections
  • Seen more often in 4 week IVIG than 3 week IVIG patients

• Quality of Life differences

• Greater Independence with SCIG

• Less Individual Initiative and Responsibility with IVIG
Wear-off Effect of IVIG

Quality of Life Comparisons Between IVIG and SCIG

Comparison of SF-36 QOL between SCIG and IVIG

- 630 American home infusion patients: 103 IVIG and 527 SCIG
- Data collected by phone by set group of surveyors from one home infusion company
- SF-36 collected on average every 6 months (each subject between 1-3 data points)

Geng et al. Abstract at ESID 2016
Longitudinal Comparison in QOL

- Within same cohort of patients, 104 had therapy started after survey program initiation: true comparison between baseline pre-therapy vs. post-therapy.

- Even though both IVIG and SCIG led to improvement in QOL, SCIG led to statistically significant improvement in 8 domains.

Geng et al. Abstract at ESID 2016
Technical Aspects of SCIG

- Starting Dose of 0.4-0.6 g/kg per month divided into 4 weekly doses of 0.1-0.15 g/week

- Specialized Syringe pumps: electronic or wound-up

- Start Slow but can ramp up rate: For 1st infusion, maximum volume = 15 ml per infusion site, maximum rate = 25 ml/hr

- Subsequently may increase to 25 ml/site, 35 ml/hr/site, 50 ml/hr all sites combined
Ancillary Equipment for SCIG

- Needles: 4-12 mm 24-26 gauge
- Needles: 90 degree insertion for leave-in needles and 45 degree insertion for soft cannula needles
- Tubing: can be bifurcated or trifurcated
Initiation of SCIG

- Patients need to be taught
- Initial 4 infusions should be done by an experienced infusion nurse
- Nurse should teach patient, parent or caregiver on how to locate site, insert needle, secure site, set-up pump and discard disposable equipment
- Patients need to be able to perform at least one infusion in front of healthcare professional to demonstrate ability before being allowed to infuse at home independently
- Need to tell patients that it’ll take between an hour to 90 minutes depending on dose and number of sites
- Nurse should call regularly
Start of SCIG for IG Naïve Patients

- No uniform standard method
- Can load with one dose of IVIG and then start SCIG in a week
- Can load with 2 consecutive IVIG doses then start SCIG a few weeks later
- Can start with 5 days of consecutive dose SCIG then switch to weekly
- My approach: Just start with weekly SCIG- will take around 9-12 weeks to reach steady-state (3-4 half-lives of IgG)
Developments in IG Therapy

- Delivery of SCIG: Hyaluronidase Assisted SCIG
- Increased titers of antibodies against respiratory pathogens
- Increased Infusion Parameters
- SCIG for Immunomodulation
- Decrease Hemolysis Risk of IG Therapy
Hyaluronidase Assisted SCIG

• Hyaluronic Acid is a gel like substance under the skin
• Presence of Hyaluronic Acid limits the administration of subcutaneous medication
• Hyaluronic acid is naturally turned over on a daily basis
• Hyaluronidase temporarily breaks-down hyaluronic acid creating the “space” for high volume delivery of medication
Advantages of Hyaluronidase Assisted SCIG

- High Volume infusion of SCIG: 300 to 600 ml of product given over 2 hours in one site
- Given Monthly or every 3 weeks
- Convenience for patients who have difficult venous access but does not wish to have weekly infusions with multiple sites of infusion
- Fewer systemic adverse effects compared to IVIG: lower and delayed serum peak
Concerns Regarding Hyaluronidase Assisted SCIG

- Long term safety of Hyaluronidase given chronically is not well established
  - Skin effects
  - Anti-Hyaluronidase antibodies

- While serum peak is lower than IVIG, still has higher peak than SCIG. Comparison of systemic adverse reaction with SCIG not well studied.

- Pharmacokinetics mirror IVIG more than SCIG: trough similar to IVIG and lower than SCIG

- Technically more challenging for patients:
  - Need to push Hyaluronidase first prior to IG infusion
  - Need for Ramp Up dosing
  - More complex infusion parameters
Summary

- Significant relationship between Dose, Level and Efficacy

- Differences between IVIG vs. SCIG
  - Pharmacokinetics
  - Safety
  - Infusion process
  - Quality of Life

- Individualized Therapy is essential: different products and delivery methods are suitable for different people
Thank you!

Questions?