Primary Antibody Deficiencies: More than just a B cell Problem

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Agenda:
From ImmunoDEFiciency to ImmuKNOWledge

• How to evaluate the immune system?
• Primary antibody deficiencies: where is the defect?
• Whole exome sequencing: new diagnosis and disease phenotypes
• Immunoglobulin replacement: what’s new?
Agenda:
From ImmunoDEFiciency to ImmuKNOWledge

• How to evaluate the immune system?
Immune System Evaluation: Count Immune Cells
Immune System Evaluation: Assess Immune Cells Performance
Immune System Evaluation: B cells make Antibodies

T cell-independent
B cell activation

Pneumovax

IgM secretion

B cell

MHC-II
Immune System Evaluation: B cells make Antibodies

Pneumovax

T cell-independent
B cell activation

IgM secretion

B cell

T cell-dependent
B cell activation

IgG secretion

B cell

Antigen uptake

Tetanus
Hib or Diptheria

Julien et al., Biomolecules, 2012
Immune System Evaluation: T cells Proliferate and Differentiate
Immune System Evaluation: Immune cells Communicate via Signaling Responses

Puri et al., Front. Immunol, 2013
Agenda:
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Circle of Immune Life
B cell Development in Bone Marrow

Agammaglobulinemia
- No B cells
- No Immunoglobulins

Durandy et al., *Nature Reviews*, 2013
Circle of Immune Life

- Bone marrow (primary lymphoid structure)
- Undifferentiated (immature) lymphocyte
- Thymus gland (primary lymphoid structure)
- Mature B cell
- Blood vessel
- Tonsils
- Adenoids
- Lymph node
- Spleen
- Secondary lymphoid structures
B cell Migration: Actin Cytoskeleton

Wiskott Aldrich Syndrome (WAS)
- Low B (and T) cell counts
- Defect in B and T cell migration → poor B and T cell responses
- Autoimmunity, eczema, thrombocytopenia
Circle of Immune Life
B cell Survival: Proliferation Signals

CVID
Common: 1:25,000
Variable: autoimmunity, granulomas, inflammatory bowel disease
ImmunoDeficiency: recurrent sinopulmonary infections

- Normal total number of B cells
- Decreased memory B cells
- Low Immunoglobulins

Durandy et al., Nature Reviews, 2013
B cell Activation: Interaction with T cell Help

Durandy et al., *Nature Reviews*, 2013
**B Activation: Interaction with T cell Help**

**CVID**

**Hyper IgM**
- Normal number of B cells
- No B cell activation → cannot switch isotype → High IgM but no other immunoglobulins
Antibody Class Switch Recombination

Durandy et al., *Nature Reviews*, 2013
Antibody Class Switch Recombination
Antibody Class Switch Recombination

Switch recombination

Heavy chain genes in IgE-expressing cell

AID = Activation Induced cytidine Deaminase

Hyper IgM
The tip of the Iceberg

- **Unknown Genetic Basis**
- **Selective IgA Deficiency**
- **CVID**
- **Selective Polysaccharide Deficiency (SPAD)**
- **IgG Subclass Deficiency**
- **Transient Hypogammaglobulinemia of Infancy**
- **Hypogammaglobulinemia, unspecified**
To make matters more complicated ...

- Some mutations result in a protein with REDUCED activity level (hypomorphic mutations) → milder phenotype → hypomorphic Btk mutations with low circulating B cell numbers and residual immunoglobulins

- Some mutations are present in patients with disease and WITHOUT disease → gene variants that predispose to disease rather than causative → TACI mutations

- People with the same mutation can have different DEGREE of SYMPTOMATOLOGY → incomplete penetrance → BAFF receptor deficient patients
Agenda: From ImmunoDEFiciency to ImmuKNOWledge

- How to evaluate the immune system?
- Primary antibody deficiencies: where is the defect?
- Whole exome sequencing: new genes for a known disease, new phenotypes for a known gene
- Immunoglobulin replacement: what’s new?
Whole Exome Sequencing: How does this Work?
Whole Exome Sequencing: How does this Work?

- Exome sequencing cases
- Coding variants
- Exome sequencing controls
- Excluding common variants
- Candidate genes
- Genetic variation databases

Biesecker et al., *Nature Genetics*, 2010
Whole Exome Sequencing: How does this Work?

Proof candidate gene is disease causative

Biesecker et al., *Nature Genetics*, 2010
Whole Exome Sequencing: How does this Work?

- Shot gun approach: usually after exhausting conventional tests, high index of clinical suspicion
- Data interpretation: reading a book of 30 million letters (10 copies of “War and Peace”) → 2-3 months for results
- Expense and insurance coverage: getting better

Biesecker et al., *Nature Genetics*, 2010
Whole Exome Sequencing: Medical Genomics a Reality?
Whole Exome Sequencing: New Genes for Known Disease

NF-κB2 mutation in patients with CVID
Recurrent sinopulmonary infections
Autoimmunity
Adrenal Insufficiency

Chen et al., AJHG, 2013
Whole Exome Sequencing: New Phenotypes for Known Genes

Loss-of-Function STAT1 Mutation: Susceptibility to mycobacterial disease

Chapman et al., Nature Reviews Genetics, 2012
Whole Exome Sequencing: New Phenotypes for Known Genes

Gain-of-Function STAT1 Mutation: Chronic Mucocutaneous Candidiasis and Autoimmunity

And many other phenotypes coming

- Histoplasmosis
- Liver disease

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Immunoglobulin Replacement: Purification Process

Plasma

Ethyl alcohol 8%  
Temperature -3°C  
Protein 5.1%

pH 7.2  
*γ/2 0.14

 Supernatant I

Ethyl alcohol 25%  
Temperature -5°C  
Protein 3.0%

 Fraction I  
(Fibrinogen)

 Supernatant II+III

Ethyl alcohol 18%  
Temperature -5°C  
Protein 1.6%

 Fraction II+III  
(Immunoglobulins)

 Supernatant IV

 Fraction IV  
(α-globulins, α1AT)

 Supernatant V

 Fraction V

Waste

 Albumin

 Fraction II + III

Reconstitution of Fraction II + III

1st addition of caprylate

Cloth filtration

2nd addition of caprylate

Caprylate incubation

Depth filtration

Column chromatography

Final formulation

Low pH incubation in FC

Buchacher et al., Biotech Journal, 2006
# Immunoglobulin Replacement: Products on the Market

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>IgG conc.</th>
<th>IgA conc. (µg/mL)</th>
<th>Excipients</th>
<th>Osmolality (mOsm/kg)</th>
<th>Viral safety</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Products intended for intravenous use (liquid preparations)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flebogamma® DIF</td>
<td>Grifols</td>
<td>5%</td>
<td>&lt;50</td>
<td>50 mg/mL D-sorbitol</td>
<td>240–370 Chromatography ↓ pH/↑ temp treatment, S/D, NF</td>
</tr>
<tr>
<td>Gammagard Liq.</td>
<td>Baxter</td>
<td>10%</td>
<td>37</td>
<td>250 mM glycine</td>
<td>240–300 Chromatography ↓ pH/↑ temp treatment, S/D, NF</td>
</tr>
<tr>
<td>Gamunex®</td>
<td>Talecris</td>
<td>10%</td>
<td>46</td>
<td>200 mM glycine</td>
<td>258 Chromatography ↓ pH incubation</td>
</tr>
<tr>
<td>Octagam®</td>
<td>Octapharma</td>
<td>5%</td>
<td>&lt;100</td>
<td>10% maltose</td>
<td>310–380 Chromatography S/D</td>
</tr>
<tr>
<td>Privigen®</td>
<td>CSL-Behring</td>
<td>10%</td>
<td>&lt;25</td>
<td>250 mM L-proline</td>
<td>320 Chromatography ↓ pH incubation, NF</td>
</tr>
<tr>
<td><strong>Products intended for subcutaneous use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vivaglobin®</td>
<td>CSL-Behring</td>
<td>16%</td>
<td>&lt;1700</td>
<td>3 mg/mL NaCl</td>
<td>445 Chromatography ↑ Temp treatment</td>
</tr>
<tr>
<td><strong>Products intended for intramuscular use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GamaSTAN®</td>
<td>Talecris</td>
<td>16%</td>
<td>NL</td>
<td>300 mM glycine</td>
<td>NL S/D</td>
</tr>
</tbody>
</table>
## Immunoglobulin Replacement: IV vs SubQ

<table>
<thead>
<tr>
<th></th>
<th>SC Ig</th>
<th>IV Ig</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacokinetics</strong></td>
<td>Consistent serum IgG levels</td>
<td>Wide difference in serum IgG level between peak and trough</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>Two prospective trials demonstrate noninferiority compared to IV Ig</td>
<td>Long clinical experience demonstrating efficacy</td>
</tr>
<tr>
<td><strong>Systemic side effects</strong></td>
<td>Infrequent</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Infusion site reactions</strong></td>
<td>Common</td>
<td>Infrequent</td>
</tr>
<tr>
<td><strong>Factors contributing to total cost</strong></td>
<td>Self administered at home. US trials of vivaglobin suggested using higher dose (1.37x) than IV Ig</td>
<td>Typically administered in an infusion center with nursing support.</td>
</tr>
<tr>
<td><strong>Patient satisfaction</strong></td>
<td>Offers flexibility of infusion frequency, site, etc. Multiple studies confirm enhanced quality of life in PIDD patients.</td>
<td>Often a better option for patients who have difficulty with needles and/or self-injection. Preferable in patients who have difficulty with compliance.</td>
</tr>
</tbody>
</table>
Recombinant Human
Hyalouronidase Facilitated SubQ Infusion of Immunoglobulin

Hyaluronidase temporarily breaks down hyaluronan to open access to lymphatic can capillary vessels
Recombinant Human Hyaluronidase Facilitated SubQ Infusion of Immunoglobulin

Hyaluronidase temporarily breaks down hyaluronan to open access to lymphatic capillary vessels

Open access to subQ space → allow injected Ig to be absorbed quickly

Hyaluronan rebuilds naturally and the barrier is completely restored within 48hrs
Hyqvia: Gammagard Liq 10% + rHuPH20

Stable serum IgG levels

Wasserman et al., JACI, 2012
## Hyqvia: Duration of Infusion and Side Effects

### TABLE V. Duration of infusions

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Age group</th>
<th>No. of subjects</th>
<th>Duration of infusion (h)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>IGIV</td>
<td>Subjects aged 2 to &lt;12 y</td>
<td>14</td>
<td>1.40</td>
<td>2.49</td>
<td></td>
<td>5.03</td>
</tr>
<tr>
<td></td>
<td>Subjects aged ≥12 y</td>
<td>73</td>
<td>0.92</td>
<td>2.33</td>
<td></td>
<td>6.33</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>87</td>
<td>0.92</td>
<td>2.33</td>
<td></td>
<td>6.33</td>
</tr>
<tr>
<td>IGHy</td>
<td>Subjects aged 2 to &lt;12 y</td>
<td>11</td>
<td>1.15</td>
<td>1.73</td>
<td></td>
<td>3.28</td>
</tr>
<tr>
<td></td>
<td>Subjects aged ≥12 y</td>
<td>70</td>
<td>0.83</td>
<td>2.13</td>
<td></td>
<td>4.68</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>81</td>
<td>0.83</td>
<td>2.08</td>
<td></td>
<td>4.68</td>
</tr>
</tbody>
</table>

### Adverse events

<table>
<thead>
<tr>
<th>Adverse event†</th>
<th>Percentage of subjects (N = 81)</th>
<th>Rate of adverse events per infusion† (N = 1129)§</th>
<th>Percentage of subjects (n = 87)</th>
<th>Rate of adverse events per infusion (N = 365)§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local adverse events</td>
<td>51.9</td>
<td>0.199</td>
<td>4.6</td>
<td>0.011</td>
</tr>
<tr>
<td>Headache</td>
<td>19.8</td>
<td>0.031</td>
<td>25.3</td>
<td>0.112</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8.6</td>
<td>0.012</td>
<td>9.2</td>
<td>0.027</td>
</tr>
<tr>
<td>Nausea</td>
<td>7.4</td>
<td>0.010</td>
<td>11.6%</td>
<td>0.027</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>7.4</td>
<td>0.009</td>
<td>5.7</td>
<td>0.016</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7.4</td>
<td>0.008</td>
<td>5.7</td>
<td>0.016</td>
</tr>
<tr>
<td>Chills</td>
<td>1.2</td>
<td>0.003</td>
<td>8.0</td>
<td>0.025</td>
</tr>
</tbody>
</table>
Hyqvia: What are the Drawbacks?

• New product: no long term data
• Development of interfering/inhibitory antibodies against hyaluronidase
• PH20 associated with sperm maturation and fertilization process → auto antibodies against PH20 could affect fertility → data in guinea pigs but no other in vivo animal models, no human data
• PH20 expression in CNS → new suggestive data, unknown significance
THANK YOU!
KEEP CALM AND ASK QUESTIONS