Quality and Clinical Safety of Immunoglobulin Therapies (Regulator’s Perspective)

DISCLAIMER
Any opinions/recommendations presented here are my own and do not necessarily reflect those of any official body.
Effects

Side-effects

$10^8$ different specificities
$\times 10^{3-4}$ roots
Biasing a hidden variable $x$ can influence the outcomes of multiple studies, leading to biased conclusions and flawed insights.
Guidance for Quality

Biological reference standards

ICH GLs: viral safety, impurities, comparability

Monographs:
- 0918 for IVIG
- 2788 for SCIG
- 0338 for IMIG

IG batch testing in OMCL

2002/98/EC ("Blood Directive"): standards of quality and safety for the collection, testing, processing, storage and distribution of blood + blood products

GL on plasma derived medical products EMA/CHMP/BWP/706271/2010

OMCL = Official Medicines Control Laboratory

ICH = International Committee for Harmonization

GL = Guideline
Guidance for Clinic

Pre-authorisation:
IVIG GL
(EMA/CHMP/BPWP/94033/2007 rev.2)
Ongoing revision

SCIg/IMIg GL
(CHMP/BPWP/410415/2011 rev. 1)

Post-marketing:
Pharmacovigilance Risk Assessment Committee (PRAC)

Product specific Summary of Product Characteristics (SPC)
+ CoreSPC (IVIG + SCIG)

(CHA/CHMP/BPWP/94038/2007 rev. 4)
(EMA/CHMP/BPWP/143744/2011 rev. 1)
Pre-authorisation:
- Adverse events (AEs):
  - AEs and serious adverse events (SAEs) from all subjects throughout all studies
  - Short term tolerance
  - Infusion rates
  - Children and adolescents vs. adults

- Separate safety evaluation of excipients

- Comprehensive risk management plan (RMP) including post-marketing safety data collection in children

→ Adverse drug reactions (ADRs = related AEs) are listed in the SPC/PIL
Causes of Side-effects

- **Product related**
  - Pathogens
  - Impurities
  - Excipients

- **Administration related**
  - 1st administration or Ig switch
  - Infusion rate
  - Administration route

- **Patient related**
  - Underlying disease
  - Co-morbidities
  - Concomitant medication
  - Age, gender, genetics
Impurities

- Contaminants: (viruses, bioburden)
  - donor screening, plasma pool testing, validated virus removal
- Process related impurities: (caprylic acid, S/D related substances, ethanol,...)
  - are removed by the end of the process
- Product related impurities:
  - can be only controlled if known
    - IgG antibodies: Anti A / Anti B haemagglutinins, anti D
    - Polymers
    - IgA content
    - FXIa or other pro-coagulant proteins

What is the impact of impurities not detected?

Basic research ↔ Product specific research
Types of Side-effects

- Thromboembolic events (TEE)
- Haemolysis
- Hypersensitivity, anaphylactoid reactions
- Aseptic meningitis syndrome (AMS)

Can we map 🌿🌿🌿🌿🌿 to 🌿🌿🌿🌿🌿?

- Side-effects/warnings for excipients
Thromboembolic events (TEE)

8/2010
1. Cerebellar infarction
2. Multiple cerebral infarctions, splenic and hepatic infarctions
3. Multiple cerebral infarctions
4. Multiple emboli

<table>
<thead>
<tr>
<th>Period</th>
<th>TEE / 1000 kg Ig</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVIG Octagam</td>
<td>8/2010</td>
</tr>
<tr>
<td>2008</td>
<td>1.8</td>
</tr>
<tr>
<td>2006</td>
<td>0.3</td>
</tr>
<tr>
<td>3 other IVIGs</td>
<td>2006 - 2011</td>
</tr>
<tr>
<td></td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>

Withdrawal of all batches and Marketing Authorisation

1000 kg = 33.333 single administration IVIG
Coagulation cascade

Contact activation (intrinsic) pathway

- Damaged surface
  - XII
  - Xlla
  - XI
  - Xlla
  - IXa
  - VIIIa
  - Fibrinogen (I)
  - Protein C
  - Active Protein C
  - Protein S
  - Protein C + Thrombomodulin

Tissue factor (extrinsic) pathway

- Trauma
  - Tissue factor
  - TFPI
  - VIIIa
  - VII
  - Prothrombin (II)
  - Thrombin (IIa)
  - Cross-linked fibrin clot
  - Fibrin (Ia)
  - Fibrin (Ia)

Common pathway

- Anithrombin
Expected presence of FXIa in the final product

Wessler stasis test in rabbits

- Octagam with low TGA response
- Non implicated Octagam spiked with FXIa
- 10% Maltose + 1% BSA + FXIa
- Octagam with lower TGA response
- Octagam with high TGA response

Safety range

Release limit

TEE batches

Römisch et al 2011 webmedcentral
TEE lessons learned

- **Change of Eur. Pharm. Monographs for IVIGs and SCIGs**
  - *Product does not exhibit thrombogenic activity*

- **All** manufacturers submitted variations that demonstrated compliance with this monograph

- Development of FXIa reference preparation (NIBCS) which is now WHO Reference Reagent

- **Strengthened warning statement in IVIG and SCIG core SPC**
  Patient with risk factors → minimum rate of infusion and dose practicable
Steps reducing pro-coagulant activity

**Plasma**
- **Fractionation:** Kistler-Nitschmann or Cohn-Oncley, *caprylate precipitation, PEG precipitation*
- **Adsorption of FXI**
- **Virus inactivation:** Solvent/Detergent, *caprylate treatment, low pH*, nanometer filtration, *high temperature*
- **Purification:** Reverse phase chromatography, *cation exchange* or anion exchange, castor oil extraction

**IVIG/SCIG**
- **Stabilisation/formulation:** Different sugars or amino acids
## Blood and antibodies

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group AB</th>
<th>Group O</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Red blood cell type</strong></td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
<tr>
<td><strong>Antibodies in Plasma</strong></td>
<td>Anti-B</td>
<td>Anti-A</td>
<td>None</td>
<td>Anti-B and Anti-A</td>
</tr>
<tr>
<td><strong>Antigens in Red Blood Cell</strong></td>
<td><img src="image5.png" alt="Image" /> A antigen</td>
<td><img src="image6.png" alt="Image" /> B antigen</td>
<td><img src="image7.png" alt="Image" /> A and B antigens</td>
<td>None</td>
</tr>
</tbody>
</table>
Haemolysis

Hemolytic anemia
• Haemoglobin ↓ >1 g/dL
  (severe >2 g/dL)
• ↑ bilirubin
• ↑ reticulocyte count

EudraVigilance database 2008 – 2013; 7 IVIGs*

- 466 cases: 93 mild to moderate, 373 severe (thereof 80% blood group A)

*Bellac et al. Transfusion July 2015
Antibodies against A and B antigens co-purified with other Igs

Blood group distribution of donors and their anti-A and anti-B titers

European Pharmacopeia: anti A/B titers of ≤1:64 and < limit reference preparation

High cumulative IVIG doses (>2 g/kg) with anti-A/anti-B titers ≥1:32

Is the current limit in the Ph. Eur. still adequate?

- This limit was defined at a time when much lower cumulative IgG doses were administered than are currently used in immunomodulatory indications
Haemolysis lessons learned

- **Product**
  - Use of low titre plasma
  - Reduction of anti-A and anti-B haemagglutinins through immunoaffinity chromatography (introduced in two products)

- **Strengthened warning statement in IVIG coreSPC**
  - Patients with non-0 blood group
  - Underlying inflammatory state
  - High cumulative doses
HS describes a pathological immune response to repeated exposure to an antigen.

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>Product-related</strong></td>
<td></td>
<td><strong>Patient-related</strong></td>
</tr>
<tr>
<td>Aggregated IgG activates...</td>
<td>complement system</td>
<td></td>
</tr>
<tr>
<td>IgA content</td>
<td>IgA deficient patient + IgG antibodies to IgA (contraindication in the coreSPC)</td>
<td></td>
</tr>
<tr>
<td>(max: 4800µg/ml, min: 25 µg/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naturally occurring anti-neutrophil cytoplasmic antibodies (ANCA)</td>
<td>dependent on autoimmune condition of patient (neutrophil priming e.g. by TNFα)</td>
<td></td>
</tr>
<tr>
<td>Dimers</td>
<td>(+) immunomodulatory effects</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(-) TNF alpha within first hours of infusion</td>
<td></td>
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</tbody>
</table>
Aseptic meningitis syndrome (AMS)

- ASM is rare
- ASM usually begins within 2 days following Ig with headache, neck stiffness, drowsiness, fever, photophobia, nausea, and vomiting
- Cerebrospinal fluid (CSF) shows increase in neutrophils, ↑protein, negative bacterial cultures
- AMS occurs more frequently with high-dose (2 g/kg) Ig

**Product-related (?)**
- activation of TNF-α-primed neutrophils by ANCA's in IVIG might contribute to aseptic meningitis (Jarius et al.)
  Further investigation needed

- More frequent in patients with a history of migraine

Excipients

Excipients are important for structural integrity + stability of IG

Glycine

L-proline

Sucrose
Reports of renal dysfunction and acute renal failure

Glucose
Should be taken into account in the case of diabetes

Maltose
Interference of maltose in blood glucose assays \( \rightarrow \) falsely elevated glucose readings \( \rightarrow \) inappropriate administration of insulin, \( \rightarrow \) life-threatening hypoglycaemia and death. True hypoglycaemia may go untreated, if hypoglycaemic state is masked by falsely elevated glucose readings

Fructose/sorbitol
Patients with hereditary fructose intolerance (HFI) should not take this medicine. In babies and young children HFI may not yet be diagnosed and may be fatal
Safety Summary

- Thorough research by industry into any planned production changes
- Company ↔ agency interaction
- Agency ↔ agency interaction

- Report cases to EudraVigilance databank
- Report side-effects directly to national authority

- Continuous updating of guidance on Quality and Clinic/ EU Monographs
Reporting side-effects

Basic research

Improvement of analytical methods

Biochemical root cause analysis

Improvement of the manufacturing process
## Monograph requirements

<table>
<thead>
<tr>
<th>Tests</th>
<th>IVIG</th>
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<tbody>
<tr>
<td>**Appearance *</td>
<td>Clear or slightly opalescent and colorless or pale yellow</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>4.0 – 7.4</td>
</tr>
<tr>
<td><strong>Osmolality</strong></td>
<td>Min 240 mosmol/kg</td>
</tr>
<tr>
<td>**Protein content *</td>
<td>≥ 30g/l</td>
</tr>
<tr>
<td>**Protein composition *</td>
<td>≥ 95% immunoglobulin G</td>
</tr>
</tbody>
</table>
| **Molecular size distribution *           | Mono/Dimer: ≥90%  
|                                          | Polymer: ≤3%                                                         |
| **Antibody to HBsAg**                     | ≥ 0,5 IU/g IgG                                                       |
| **Anti-Complementary Activity**           | ≤ 1 CH<sub>50</sub>/mg IgG (Hemolytic complement)                    |
| **Pre-Kallikrein Activity (PKA)**         | ≤ 35 IU/ml                                                           |
| **Anti-A/B haemagglutinins *              | ≤ 1/64                                                               |
| **Anti D antibodies *                     | ≤ Biological reference preparation (BRP)                             |
| **Pyrogen or Bacterial endotoxin**        | 0,5g/Kg rabbit  
|                                          | 50g/l: 0,5 IU/ml or 100g/l: 1.0 IU/ml                               |
| **Sterility**                             | sterile                                                              |
| **IgA**                                   | Content ≤ Label                                                      |