Safety concerns with early clinical development of biologicals and biosimilars: clinical relevance of anti-drug antibodies

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Topics

• What makes therapeutic proteins different and what are the safety issues
• Immunogenicity and its clinical significance
• Other safety issues of biologics/biosimilars
• The PK studies in volunteers in biosimilar development
Shifting paradigms: biopharmaceuticals versus low molecular weight drugs

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To celebrate and commemorate Prof. Dr. H.E. Junginger’s 60th birthday

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Differences between classical drugs and biopharmaceuticals

- Relative simple
- Species independent
- Non-immunogenic
- Single molecule
- Metabolized
- Short acting
- Frequent dosing
- Toxic
- Specific mechanism
- Linear dose-response
- Oral
- Generic

- Large complex
- Species specific
- Immunogenic
- Heterogeneous
- Degraded
- Long acting
- Intermittent dosing
- Exaggerated pharmacodynamics
- Pleiotropic effects
- Bell shaped dose response
- Parenteral routes
- Biosimilar
Main safety issues of biologics

- Pharmacodynamic effects
- Immunogenicity
- Skin reactions
Immunogenicity of therapeutic proteins as key issue
History of the medical use proteins

- Proteins of animal origin (e.g. equine antisera, porcine/bovine insulin): foreign proteins

- Human derived proteins (e.g. growth hormone, factor VIII): no immune tolerance

- Recombinant human proteins (e.g. insulin, interferons, GM-CSF): ??
**Conclusion 1**: Nearly all biopharmaceuticals induce antibodies

**Conclusion 2**: There are two mechanisms

- Reaction to neo-antigens (foreign proteins)
- Breakdown of immune tolerance
Types of immune reaction against biopharmaceuticals

*Breaking of self-tolerance*

<table>
<thead>
<tr>
<th>Type of product</th>
<th>Human homologues</th>
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<tbody>
<tr>
<td>Characteristics of antibody production</td>
<td>Slow, after long treatment, binding antibodies, disappear after treatment</td>
</tr>
<tr>
<td>Cause</td>
<td>Mainly impurities and aggregates</td>
</tr>
</tbody>
</table>
Factors influencing immunogenicity

• Main primary factors
  – Level and type of aggregation (“breaking” of tolerance)
  – Level of non-human characteristics (classical immune activation)

• Modulating factors
  – Formulation
  – Route of administration
  – Dose and length of treatment
  – Concomitant therapy
  – Patient characteristics
    • Disease
    • Genetic background
  – Unknown factors

<table>
<thead>
<tr>
<th>Year of introduction</th>
<th>Product</th>
<th>Details</th>
<th>Incidence of Immunogenicity(^1)</th>
<th>Immunogenicity related adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1922</td>
<td>Crystallized bovine and porcine insulins from pancreas extraction.</td>
<td></td>
<td>&gt;95%</td>
<td>Frequent anaphylaxis, local and system hypersensitivity, insulin resistance</td>
</tr>
<tr>
<td>1940ties</td>
<td>NPH (neutral protamine Hagedorn) and lente insulins</td>
<td>Intermediate-acting insulins. Suspension of insulin in combination with protamine (NPH) and zinc</td>
<td>Higher immunogenicity when compared to pure insulins</td>
<td>Comparable to common insulin preparations</td>
</tr>
<tr>
<td>1970ties</td>
<td>Purified monocomponent bovine and porcine insulins</td>
<td>Purified by gel filtration chromatography and ion exchange chromatography,</td>
<td>~60%</td>
<td>Drastic reduction of anaphylaxis, local and system hypersensitivity and skin reactions. Clinical resistance rare.</td>
</tr>
<tr>
<td>1980ties</td>
<td>Semisynthetic conversion of porcine insulin</td>
<td></td>
<td>~40%</td>
<td>Rare and comparable with purified monocomponent animal insulins</td>
</tr>
<tr>
<td>1980ties</td>
<td>r-DNA derived human insulin</td>
<td></td>
<td>~40%</td>
<td>Rare and comparable with semi-synthetic insulins</td>
</tr>
<tr>
<td>1990ties</td>
<td>Insulin analogues</td>
<td></td>
<td>~40%</td>
<td>Rare and comparable with unmodified human insulins</td>
</tr>
</tbody>
</table>
Consequences of antibodies

• Loss of efficacy
  – Interferon alpha 2
  – Interferon beta
  – TNF-inhibitors
  – Algasidase-beta
  – Many others

• Cross neutralization of endogenous factors
  – EPO
  – MGDF

• Anaphylactoid reactions, serum sickness
  – Monoclonal antibodies
Sustained Disease Activity and Remission in Patients With and Without Anti-Adalimumab Antibodies

Bartelds, G. M. et al. JAMA 2011;305:1460-1468

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Pure red cell aplasia associated with EPO treatment

Immunogenicity became an important issue in therapeutic protein development
PRCA cases reported by the FDA and Johnson & Johnson

Bone Marrow Smear

Normal Bone Marrow  PRCA Bone Marrow
What caused Eprex associated PRCA?

A case study showing the importance of product formulation
Recent concern over use of HSA in Europe because of potential transmission of infectious viruses or BSE prions

In 1998, HSA was replaced with polysorbate 80 in prefilled syringes of Eprex® distributed ex-US
What caused Eprex associated PRCA?

- Formation of micelles associated with Epo (Hermeling et al, 2003): unlikely
- Silicon droplets in the prefilled syringes: very unlikely
- Leachates from rubber stoppers: unlikely
- Mishandling: most likely
Arguments in favor of the mishandling/aggregate explanation

- **Epidemiological data**
  - Relation with self injection
  - Low incidence
- **Other immunogenicity problems with epoetins**
  - Epo-associated PRCA in Thailand
  - PRCA/NAB associated with Tungsten induced aggregation
- **Immunogenicity of other products**
  - Interferons
  - GM-CSF
  - Insulin
Can you predict immunogenicity?
The question should be can you predict levels of immunogenicity.
Prediction of immunogenicity?

- PHYSICAL CHEMICAL CHARACTERIZATION
- EPITOPE ANALYSIS (IN SILICO/IN VITRO)
- REACTION WITH PATIENT SERA
- ANIMAL EXPERIMENTS
  - Conventional animals (relative immunogenicity?)
  - Non-human primates
  - Immune tolerant transgenic mice

CAN YOU PREDICT SIMILARITY IN IMMUNOGENICITY BETWEEN BIOSIMILAR AND REFERENCE PRODUCT?

• Intrinsic immunogenicity will not differ

• Difference in immunogenicity will be related to difference in quality

• So similarity in immunogenicity is predictable
Other safety aspects of biologics/biosimilars

• Pharmacodynamic effects, so potency related

• Animal studies not suitable because of species specificity and immunogenicity

• Adverse effects highly predictable, so who needs animal studies
Safety concerns concerning biologics and biosimilars

Is there a difference in safety concerns between biologics and biosimilars?
Specific safety issues for biosimilars?

- The first generation of original reference products are biosimilars of natural regulating proteins: insulins, interferons, G-CSF, GM-CSF, erythropoetin, etc.
- Only one difference seen between a biosimilar and reference product (in potency!)
- No biosimilar specific safety issue identified yet
Haemoglobin levels vs epoetin dose

[Graph showing haemoglobin levels vs epoetin dose over weeks of treatment with randomization and cross-over points marked.]
# Potency of different epoetins

<table>
<thead>
<tr>
<th></th>
<th>Described Potency (IU/ml)</th>
<th>Measured Potency (IU/ml)</th>
</tr>
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<tbody>
<tr>
<td>Eprex</td>
<td>10.000</td>
<td>12.884</td>
</tr>
<tr>
<td>Binocrit</td>
<td>10.000</td>
<td>11.404</td>
</tr>
<tr>
<td>Retacrit</td>
<td>10.000</td>
<td>11.016</td>
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</tbody>
</table>

What is needed for a biosimilar

• Candidate should be indistinguishable from the reference product concerning physical chemical characteristics and invitro biological activity

• Potency of the biosimilar should be the same as the original
The use of PK studies in the biosimilar exercise
The current approach for developing a biosimilar

Proving “highly similar” to reference product often requires multiple iterations of process change and physicochemical characterization

Clinical Trials

PK/PD

Preclinical

Biological characterization

Physicochemical characterization

Design specification

Validation

Analytics

Process development

Develop a highly similar product

Confirm Biosimilarity

McCamish. MAbs. 2011;3(2):209-17
Biosimilar terminology

• Totality of evidence
• Different levels of similarity
• Interchangeable and non-interchangeable biosimilars
Aspects of PK studies in biosimilar development

• Do we need them?
• Sensitivity to show differences?
• Dose?
• Redundancy of bridging between US and EU products
• Immunogenicity and parallel design
Changing regulatory environment

- Investors urge big pharma to stop denigrate biosimilars
- Nature Biotech: request for separate INN names for biosimilars is marketing driven
- WHO: affordability as major consideration for new biosimilar regulations
- Colombia: biologics decree allowing the use of published data for biosimilars
- EMA/CHMP: move to (in vitro) PD markers to show clinical equivalence
Sept 18 2014: President of Colombia signs new Decree for biologics
Different stages of development

- Establishing biosimilarity
  - Reverse engineering
  - Identification
  - Similarity exercise
- Confirming biosimilarity
  - Preclinical stage
  - PK/PD
  - Clinical studies

Based on the principle: level of similarity in physical-chemical and biological characteristics determines the design of the clinical studies.
The first article describing the issues when patents of biologics will expire

‘Biogenerics’: the off-patent biotech products

Huub Schellekens and Jean-Charles Ryff

The first patents of biopharmaceuticals derived from recombinant DNA will expire shortly, which raises the possibility of marketing generic products (‘biogenerics’) with limited documentation, similar to that which occurs with conventional pharmaceuticals. We propose the term off-patent biotechnological products (OPBPs) as an alternative to biogenerics when describing such products. It is questionable whether the majority of OPBPs can be classified as similar to the innovator products, considering the size and complexity of the molecules and the many factors that influence biological activity. There are three classes of OPBPs, each of which needs to meet different regulatory demands when seeking marketing authorization.

Biopharmaceuticals

Most biopharmaceuticals are large, complex molecules that, for several reasons, are heterogeneous. Some heterogeneity is caused by the combination of vector and host cell used to produce the biopharmaceutical, and includes clipping (premature termination of translation) and differences in the sites and amount of glycosylation [1,2]. Protein modification might occur during production, depending on the fermentation and cell culture conditions [3]. The extraction and purification procedures can also add to the heterogeneity, as can process-related impurities and the introduction of contaminants that might appear in the final product [4–6]. Lastly, formulation and storage conditions might alter the biological properties and, thus, the response, as a result of physicochemical or physical...
Big Investors ask Drug Maker Boards not to Denigrate Biosimilars

By Ed Silverman

A group of 19 institutional investors is asking the boards of more than two dozen drug makers and biotechs to agree to various business principles in hopes of supporting use of biosimilar medicines. As you may know, these are designed to emulate brand-name biologics and are forecast to save the U.S. economy valuable health care dollars once they become available.

The investors believe that recent actions taken by some companies could stymie the acceptance of these medicines, which would forestall any projected savings. They also worry that shareholder interests could be harmed if drug makers and biotechs pursue certain policies that are perceived as undermining medical innovation and corporate transparency.

Read More »
Beware of marketing!

The INN crowd

Moves to give biosimilars nonproprietary names different from brand products are more than a wrangle about words—they could mean biosimilars arrive stillborn to the market.

In recent months, a tussle has emerged between industry trade groups representing brand manufacturers and those representing generics on how biosimilars should be named. Specifically, innovator companies are pressing for the World Health Organization (WHO) to give biosimilars International Nonproprietary Names (INNs) that are different from their brand counterparts. Changing INNs in such a manner goes against several decades of naming convention in the industry, and will likely compromise the ability of biosimilars to succeed in the marketplace.

The WHO established the INN system in 1953 to ensure the "clearing the INN due to small differences between an original biologic and that same biologic produced using a slightly different process runs counter to years of naming practice for brand products (a fact that seems to have been conveniently forgotten by innovator companies). Every now and then, drugmakers of an original biologic make changes to the way they manufacture their product. Such changes can be as trivial as changing their supplier of culture materials or as fundamental as changing the cell line or manufacturing site. When this happens the product may change (a process termed 'drift' in the industry) and regul
Item 9.5 of the agenda

Title: Access to biotherapeutic products including similar biotherapeutic products and ensuring their quality, safety and efficacy

The Sixty-seventh World Health Assembly,

PP1 Recalling the WHO Constitution, which affirms that the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition,

PP2 Noting with particular concern that for millions of people, the right to the enjoyment of the highest attainable standard of physical and mental health, including access to medicines, remains a distant goal, that especially for children and those living in poverty, the likelihood of achieving this goal is becoming increasingly remote, that millions of people are driven below the poverty line each year because of catastrophic out-of-pocket payments for health care, and that excessive out-of-pocket payments can discourage the impoverished from seeking or continuing

PP3 Recalling resolution WHA55.14 on ensuring accessibility of essential medicines, which recognizes “the responsibility of Member States to support solid scientific evidence, excluding any biased information or external pressures that may be detrimental to public health”;
The first biosimilar monoclonal antibody in the EU

Extrapolation between different indications completely on in vitro PD data

International non-proprietary name: Infliximab
Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues

Draft