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Unwanted immunogenicity of biotherapeutic products including biosimilars

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Unwanted Immunogenicity of Biotherapeutic Products including Biosimilars

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Unwanted Immunogenicity

- Biological products (including biosimilars) can induce antibodies with different characteristics:
  - Non-neutralizing (binding) antibodies against active (and/or inactive) product-related substance(s).
  - Binding antibodies against contaminants.
  - Neutralising antibodies.
  - Mixtures of the above.

- But antibodies are not necessarily induced by biologicals/biosimilars. Incidence varies.
Potential Clinical Consequences of immunogenicity

• Can range from benign, non-significant to serious life-threatening depending on the therapeutic
• Consequences on efficacy- reduction of the clinical response to the biotherapeutic
• Consequences on safety- safety issues can occur even when there is no loss of efficacy
  
  Acute consequences
  - Infusion reactions, anaphylactic reactions
  
  Non-acute consequences
  - Delayed-type hypersensitivity/immune complexes
  - Cross-reactivity with an endogenous counterpart
Factors Influencing Unwanted Immunogenicity

Product and Patient related
- Molecular structure, novel epitopes, glycosylation, degradation, oxidation, deamidation
- Product impurities
- Formulation
- Aggregation
- Protein – biological properties e.g., immunostimulant
- Dose, route, frequency of administration and duration of therapy
- Immune status, age, genetic profile, disease, treatment
- Previous exposure
Antibodies and Adverse Effects

Eprex: Formulation change (1999)
Cause: Leachates from uncoated stoppers (adjuvant).
Formulation/Containers: risk factors

- MAb against EGFR – colorectal cancer, squamous cell carcinoma of head and neck
- 25/76 patients experienced hypersensitivity
- 17 had pre-existing IgE antibodies against gal-α-1, 3 gal present on Mab (expressed in murine myeloma cells)
- Cases clustered in different US states; IgE antibodies potentially due to tick bites etc

PRCA cases in Thailand, Korea - many marketed products

Cetuximab-Induced Anaphylaxis and IgE Specific for Galactose-α-1,3-Galactose

Cross-reactivity with endogenous protein
Clinical Impact

- Efficacy – impaired clinical response
- Safety – Infusion reactions, hypersensitivity reactions, serum sickness
  – Cross-reactivity with an endogenous counterpart

"significant neurological abnormalities … after… six infusions of natalizumab, …. extremely high titers of antibodies against the drug."
"death..from 'rebound neuroinflammation as a result of the development of natalizumab anti-drug antibodies."
‘Biosimilar’ EPO is Immunogenic?

Under the generic drug paradigm of the Thai Food and Drug Administration, 14 biosimilar r-HuEpos were licensed by 1 January 2009. These products came from various countries such as Argentina, China, South Korea, and India.

The number of cases using ‘biosimilar’ r-HuEpos have increased enormously because of their more affordable prices. With their usage, adverse effects of the less than identical therapeutic agents have started to increase.

Many clinicians in Thailand were starting to see an increase in PRCA cases which raised an important issue whether the immunogenicity of biosimilar therapeutic agents were indeed equivalent to the innovative r-HuEpo.

Recombinant human erythropoietin (r-HuEpo) has been used for the treatment of renal anemia. With the loss of its patent protection, there has been an upsurge of more affordable biosimilar agents, increasing patient access to treatment for these conditions. The complexity of the manufacturing process for these recombinant proteins, however, can result in altered properties that may significantly affect patient safety. As it is not known whether various r-HuEpo products can be safely interchanged, we studied 30 patients with chronic kidney disease treated by subcutaneous injection with biosimilar r-HuEpo and who developed a sudden loss of efficacy. Sera from 23 of these patients were positive for r-HuEpo-neutralizing antibodies, and their bone marrow biopsies indicated pure red-cell aplasia, indicating the loss of erythroblasts. Sera and bone marrow biopsies from the remaining seven patients were negative for anti-r-HuEpo antibodies and red-cell aplasia, respectively. The cause for r-HuEpo hypersensitivity was occult gastrointestinal bleeding. Thus, subcutaneous injection of biosimilar r-HuEpo can cause adverse immunological effects. A large, long-term, pharmacovigilance study is necessary to monitor and ensure patient safety for these agents.

Editor’s note: A biosimilar is a term applied to subsequent versions of biopharmaceutical products that have been approved by the regulatory authorities of a given country. The pathway for approval is thus specific for that country, and because of regulatory differences, the biosimilar classification may not apply to other countries.

Worldwide consensus - A biosimilar is a biotherapeutic accepted by a regulatory pathway which requires biological and clinical comparison with the original licensed product. The ‘biosimilars’ described in this paper are NOT real biosimilars.
Unwanted Immunogenicity - The Most Challenging Issues

• It is impossible to predict
  - the incidence of unwanted immunogenicity
  - the characteristics of the immune response
  - the clinical consequences & significance of such immunogenicity

• THE ABOVE NEED TO BE ASSESSED IN APPROPRIATE STUDIES

• These immunogenicity studies are normally carried out as part of clinical trials.
Unwanted Immunogenicity

Current Position

Testing for unwanted immunogenicity is integral to product development (clinical & post-marketing phase) for ensuring:

– The clinical safety of a biotherapeutic
– Product Comparability
– When a Biosimilar product is developed
COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON IMMUNOGENICITY ASSESSMENT OF BIOTECHNOLOGY-DERIVED THERAPEUTIC PROTEINS

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
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<tr>
<td>DRAFT AGREED BY BMWP</td>
<td>July 2006</td>
</tr>
<tr>
<td>ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION</td>
<td>January 2007</td>
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<td>END OF CONSULTATION (DEADLINE FOR COMMENTS)</td>
<td>July 2007</td>
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<tr>
<td>AGREED BY BMWP</td>
<td>October 2007</td>
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<tr>
<td>ADOPTION BY CHMP</td>
<td>December 2007</td>
</tr>
<tr>
<td>DATE FOR COMING INTO EFFECT</td>
<td>April 2008</td>
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KEYWORDS

Immunogenicity, unwanted immune response, biotechnology derived proteins, immunogenicity risk factors, assays, clinical efficacy and safety, risk management
24 May 2012
EMA/CHMP/BMWP/86289/2010
Committee for Medicinal Products for Human Use (CHMP)


Draft agreed by Similar Biological Medicinal Products Working Party | October 2010
Adoption by CHMP for release for consultation | November 2010
End of consultation (deadline for comments) | May 2011
Final agreed by BMWP | March 2012
Adoption by CHMP | 24 May 2012
Date for coming into effect | 1 December 2012

Disclaimer: This guideline is intended as an addendum to Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins EMEA/CHMP/BMWP/14327/2006 and should be read in conjunction.

Keywords | Immunogenicity, monoclonal antibodies, similar biological medicinal products, clinical use, assay strategy.
Comparability studies are needed to generate evidence substantiating the similar nature, in terms of quality, safety and efficacy, of the new similar biological medicinal product and the chosen reference medicinal product authorised in the Community.
Comparative Immunogenicity for Biosimilar Development

- Compares immunogenicity of different products; Studies need to be designed to demonstrate whether the immunogenicity of the products is the same or significantly different.
- This will affect the design of the studies & their interpretation.
- For this, a homogeneous and clinically relevant patient population should be selected. Head-to-Head studies needed. Same assays & sampling strategy should be used.
- The consequences of immunogenicity also must be compared.
- Post-approval assessment may be necessary, usually as part of pharmacovigilance surveillance.
## Antibody Frequency for Biosimilar (presubmission studies)

<table>
<thead>
<tr>
<th>Biosimilar</th>
<th>Ab frequency</th>
<th>Reference</th>
<th>Ab frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omnitrope (SC)</td>
<td>0/51 (0.0%)</td>
<td>Genotropin</td>
<td>1/44 (2.3%)</td>
</tr>
<tr>
<td>Valtropin (SC)</td>
<td>3/98 (3.4%)</td>
<td>Humatrope</td>
<td>1/49 (2.0%)</td>
</tr>
<tr>
<td>Binocrit (IV)</td>
<td>2/314 (0.6%)</td>
<td>Erypo</td>
<td>3/164 (1.8%)</td>
</tr>
<tr>
<td>Silapo (IV)</td>
<td>0/305 (0.0%)</td>
<td>Erypo</td>
<td>0/304 (0.0%)</td>
</tr>
<tr>
<td>Silapo (SC)</td>
<td>0/323 (0.0%)</td>
<td>Erypo</td>
<td>0/230 (0.0%)</td>
</tr>
<tr>
<td>Ratiograstim (SC)</td>
<td>7/356 (2.0%)</td>
<td>Neupogen</td>
<td>2/134 (1.5%)</td>
</tr>
<tr>
<td>Zarzio (IV / SC)</td>
<td>0%</td>
<td>Neupogen</td>
<td>0%</td>
</tr>
<tr>
<td>(Phase 1, crossover)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivestim</td>
<td>3/183 (1.6%)</td>
<td>Neupogen</td>
<td>0/95 (0.0%)</td>
</tr>
<tr>
<td>Bemfola</td>
<td>0/249 (0%)</td>
<td>Gonal-f</td>
<td>0/123 (0%)</td>
</tr>
<tr>
<td>Insulin Marvel §</td>
<td>T1DM: 25/114 (21.9%)</td>
<td>Humulin</td>
<td>T1DM: 16/114 (14.0%)</td>
</tr>
<tr>
<td></td>
<td>T2DM: 14/131 (10.7%)</td>
<td></td>
<td>T2DM: 17/136 (12.5%)</td>
</tr>
<tr>
<td>Remsima - AS</td>
<td>37.5%</td>
<td>Remicade</td>
<td>36.1%</td>
</tr>
<tr>
<td>- RA</td>
<td>55.6%</td>
<td></td>
<td>54.3%</td>
</tr>
</tbody>
</table>

Data from EPARs at [www.ema.europa.eu](http://www.ema.europa.eu)

$ Application withdrawn. Table courtesy of Martina Weise
Antibodies and Adverse Effects - EPO

Binocrit approved - 2007
Following rigorous physico-chemical, biological characterisation & clinical trial data
Brockmeyer & Seidl (2009) Biologicals

Safety Study for Binocrit (Biosimilar EPO) Suspended
− No increased immunogenicity from IV use in patients with renal anaemia or SC use in cancer patients (both licensed).
− Postmarketing SC trial in previously untreated renal anaemia patients: two cases of neutralising Ab development. Cause linked to syringe plungers?

Problems in Thailand:
>60 PRCA cases identified in Thailand. 16 EPO (or more) products marketed. Link to product(s)?
Biosimilars as Biologicals

- As is clear from the EMA definition, Biosimilars are Biologicals. They differ from innovator Biologicals in the regulatory process used for their approval.

- As Biosimilars are 'scientifically' Biologicals they should be regarded as such when immunogenicity is being considered.

- There is no reason to treat approved Biosimilars any differently from all Biologicals (including innovator products) from the immunogenicity perspective.
Unwanted Immunogenicity; what types of Products are affected?

- Unwanted immunogenicity is a potential problem for ALL biologicals.
- The clinical implications of unwanted immunogenicity are also potential problems for ALL biologicals.
- This applies to innovator biologicals, biosimilars and non-innovator biologicals.
- It is NOT a specific problem for biosimilars.
- So far, the incidence of unwanted immunogenicity for innovator products and biosimilars is very similar.
- There may be increased immunogenicity problems for some non-innovator biologicals (as used in developing countries), but these products are NOT biosimilars.
Conclusions

- Immunogenicity issues occur all along the life cycle of a product and particularly when:
  - a new therapeutic protein is developed and used for various clinical indications
  - a change is introduced e.g. process, formulation, storage conditions etc
  - a biosimilar product is proposed

- Assessment requires
  - an optimal antibody testing strategy
  - validated methodologies and reference standards
Acknowledgements

Meenu Wadhwa

Colleagues of the BMWP
Antibodies and Adverse Effects; Classic Examples-

MGDF administered to patients caused thrombocytopenia.
- Cancer patients 4/650;
- Healthy patients 13/325

Pure red-cell aplasia (PRCA) and anti-EPO antibodies in patients treated with EPO (EPREX)

- Pre 1998 – 2/3 cases
- 2002 - 13 cases in chronic renal failure patients, rapid development of severe transfusion dependence within months of therapy, resistant to other EPO products
- 1998 to June’05 – 260+ cases worldwide (probably an underestimate).

Cause(s) ?

Product development terminated

Unwanted Immunogenicity

- **Proteins**
  - Neutralise biological effects and compromise further therapy (factor VIII, IFNα2a, GM-CSF)
- **Patients**
  - Alter PK/PD
- **Non immunogenic** (G-CSF, IFN-γ)
- **Immunogenic** (induce antibodies)
  - Cross-react with native protein and induce adverse symptoms (Epo, MGDF)
  - No effect (growth hormone, insulin)
<table>
<thead>
<tr>
<th>Product Name</th>
<th>Protein</th>
<th>Indication</th>
<th>% Patients with Immune Response</th>
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<tbody>
<tr>
<td>Intron A</td>
<td>IFN-α2a</td>
<td>Hepatitis C</td>
<td>7</td>
</tr>
<tr>
<td>Roferon</td>
<td>IFN-α2a</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Pegasys</td>
<td>IFN-α2a</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>PegIntron</td>
<td>IFN-α2a</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Betaferon</td>
<td>IFN-β</td>
<td>Multiple Sclerosis</td>
<td>25 – 45</td>
</tr>
<tr>
<td>Avonex</td>
<td>IFN-β</td>
<td></td>
<td>2 – 6</td>
</tr>
<tr>
<td>Rebif</td>
<td>IFN-β</td>
<td></td>
<td>12 – 28</td>
</tr>
<tr>
<td>Eprex, Procrit</td>
<td>Epo</td>
<td>Anemia</td>
<td>Rare</td>
</tr>
<tr>
<td>Neorecormon, Aranesp</td>
<td>Epo</td>
<td>Anemia</td>
<td>Rare</td>
</tr>
<tr>
<td>Neupogen, Nivestim</td>
<td>G-CSF</td>
<td>Myeloregeneration, neutropenia</td>
<td>0-1.5</td>
</tr>
<tr>
<td>Neupogen, Nivestim</td>
<td>G-CSF</td>
<td>Myeloregeneration, neutropenia</td>
<td>1.6</td>
</tr>
<tr>
<td>Leukine, Leucomax</td>
<td>GM-CSF</td>
<td>Myeloregeneration, immunostimulation</td>
<td>2 – 95</td>
</tr>
<tr>
<td>Proleukin</td>
<td>IL-2</td>
<td>Oncology</td>
<td>47–74</td>
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<tr>
<td>Rituximab</td>
<td>Anti-CD20</td>
<td>NHL, SLE</td>
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<tr>
<td>Rituximab</td>
<td>Anti-CD20</td>
<td>NHL, SLE</td>
<td>65</td>
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<tr>
<td>Humira</td>
<td>Fully human anti-TNFα</td>
<td>RA</td>
<td>12 -28</td>
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<tr>
<td>Remicade</td>
<td>Chimaeric anti-TNFα</td>
<td>Crohn’s, RA</td>
<td>61</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>12</td>
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</tbody>
</table>
Biosimilars: Unwanted Immunogenicity

Quote from EMEA BMWP chairmen:

‘Unwanted Immunogenicity is the biggest challenge for the approval of Biosimilars’
Correlation of Antibody Induction with Reduced Clinical Efficacy

In some cases development of (neutralizing) antibodies in patients clearly can reduce the clinical response to the product.

Examples of this are Remicade (anti-TNF alpha), Tysabri (anti-alpha 4 integrin), Humira (anti-TNF alpha).

In other cases there is less clear correlation e.g. Rituximab (anti-CD20).

This makes interpretation and particularly prediction of the clinical effects of antibody development difficult, and generalizations concerning this dangerous.