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Oncologist perspective
Antibody biosimilars in oncology: an analytical to clinical perspective

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15 November 2016
Retos en el desarrollo de biosimilares en oncología: una perspectiva clínica

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SEOM Position on Biosimilar Antibodies

Unlike support therapy biosimilars such as erythropoietin and colony stimulating factors, which have easy to measure efficacy surrogate markers (haemoglobin concentrations, leukocyte levels), the development of antibody biosimilars poses significant challenges. This is due to the structural complexity of antibodies, their role in the treatment of a wide range of tumours, the limited correlation between efficacy surrogate markers and clinical benefits, and the heterogeneity of their mechanisms of action.
Trastuzumab mechanisms of action are complex and their relative role in clinical activity largely uncharacterised.


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Trastuzumab improves the prognostic outcomes associated with HER2: clinical practice data

Following the addition of trastuzumab, HER2-positive disease no longer dictates the probability of survival


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Adjuvant trastuzumab reduces the risk of relapse by 50%
Biosimilar manufacturers have limited knowledge of the reference product

**Known**
- DNA sequence

**Unknown**
- Cell line
- Growth media
- Method of cell expansion
- Bioreactor conditions
- Protein recovery conditions
- Purification conditions
- Formulation methods
- Reagents
- Reference standards

**Analytical characterisation**
- Compare structure and function to the reference product

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1. Roger SD. Nephrology (Carlton) 2006;11:341–346;
Monoclonal antibodies (mAbs) are heterogeneous, complex proteins and sensitive to manufacturing conditions

- Manufacturing processes affect post-translational modifications
  - Cell type and culture conditions
  - Purification
  - Raw materials
- Post-translational modifications can affect
  - Mechanism of action
  - Bioavailability, clearance
  - Immunogenicity
  - Effector functions
  - Binding

Analytical foundation of mAb biosimilars

Critical quality attributes (CQAs)

- Biological activity
- Pharmacokinetics
- Immunogenicity
Glycosylation differences may lead to differences in biological function

Antibodies are subject to post-translational modification, including glycosylation

<table>
<thead>
<tr>
<th>Modifications</th>
<th>Biological effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyro-E</td>
<td>50% loss of circulating protein</td>
</tr>
<tr>
<td>Pyro-Glu (2)</td>
<td>Affects CDC and ADCC</td>
</tr>
<tr>
<td>Deamidation (3 x 2)</td>
<td>Enhanced ADCC</td>
</tr>
<tr>
<td>Methionine oxidation (2 x 2)</td>
<td>Enhanced CDC</td>
</tr>
<tr>
<td>Glycation (2 x 2)</td>
<td>Increase in clearance</td>
</tr>
<tr>
<td>High mannose, G0, G1, G1, G2 (5)</td>
<td>Increase in clearance; decrease in CDC</td>
</tr>
<tr>
<td>Sialylation (5)</td>
<td></td>
</tr>
<tr>
<td>C-term Lys (2)</td>
<td></td>
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</tbody>
</table>

Examples of changes in Fc glycans
- 20% loss of total sialic acid content
- Differential glycosylation
- Fucose deficiency
- Increase in terminal galactosylation
- Increase in mannose
- Increase in terminal GlcNAc

Modifications may result in approximately $10^8$ potential variants


CDC, complement dependent cytotoxicity; GlcNAc, N-acetylglucosamine
Biosimilar mAbs: key clinical aspects

Facts
Similar, but not identical, particularly glycosylation (immune response)
Complex mechanisms of action and insufficiently characterised

Challenges
Clinical trial: sensitive population and endpoint?
Extrapolation?
Interchangeability?
SEOM Position on Biosimilar Antibodies

SEOM’s position on the possibility of extrapolating from a specific trial with a homogeneous population with a clinical endpoint capable of detecting differences in activity (defined as a sensitive endpoint), to other indications in which the drug’s mechanisms of action, the disease biology, and the treatment objectives (for example, prolonging survival in metastatic disease in one indication and avoiding relapses or increasing the cure rate in early stage disease, in another one) can be different, is that it should be done only on a case-by-case basis and when the mechanism of action is clear.
SEOM Position on Biosimilar Antibodies

SEOM’s position is that since the biosimilar and the reference biologic are different drugs, *interchangeability should not be automatic at the time of dispensation and it can only be acceptable in certain cases, with clinical justification, if conducted by the prescribing physician*, who is also accountable for the treatment before the patient. The situation would be different if there were specific clinical studies proving the safety of interchangeability at an individual level, as regulated by the FDA. However, viability of these clinical trials is difficult.
SEOM Position on Biosimilar Antibodies

SEOM agrees with the need to **prescribe by brand name** and, furthermore, requires that before introducing a biosimilar in a hospital, **adequate circuits** are established for prescription, dispensation, administration and registration using the brand name. **Pharmacovigilance** of biosimilars is regulated as obligatory at a European level to rule out differences with the original biologic in relation to efficacy or toxicity among the real population.