Monoclonal antibody biosimilars: robustness of products vs clinical experience

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The structure of monoclonal antibodies is highly complex

Monoclonal antibodies: Multifunctional molecules

**Fab region**
Selected for optimum target-mediated effects (light chain and heavy chain variable binding domains)

**Fc region**
- Different isotypes with different effector functions
- Contains 2 glycosylation sites (1 in each of the 2 chains)

All parts contribute to the efficacy and safety in a cooperative way

(9600)² ≈ 10⁸ potential variants

Adapted from: Steven Kozlowski; FDA
Antibodies have different modes of actions

- Activation of Effector Mechanisms
- Antibody-dependent cellular Cytotoxicity (ADCC)
- Complement Activation (CDC)
- Targeting of Toxins
- Blocking Ligand Binding
- Induction of Apoptosis
- Inhibition of Signal Transduction or Receptor Activation
  - Inhibition of Ligand Binding
  - Induction of Receptor Internalization
  - Inhibition of Receptor Dimerization
  - Inhibition of Receptor Shedding

Both amino acid sequence and glycosylation pattern of C2 fragment influence FcR binding and ADCC activity.

The presence or absence of one fucose residue can affect the biological activity (killing of target cells via ADCC).

Even very small differences in fucosylation may have significant effects on in vitro ADCC.

Small Glycosylation Differences May Have Significant Effects on Immune Effector Functions

Modified from Hasmann M, et al. (2009)
Antibodies have different modes of actions

Anti-ROR1 MAb (Kancera) - intervened in the non-canonical Wnt signaling pathway

Antibodies have different modes of actions

- Inhibition of Signal Transduction or Receptor Activation
  - Inhibition of Ligand Binding (e.g., neutralization)
  - Induction of Receptor Internalization (e.g., FcγR)
  - Inhibition of Receptor Dimerization
  - Inhibition of Receptor Shedding

- Complement Activation (CDC)

- Targeting of Toxins
  - (e.g., monoclonal antibodies)

- Induction of Apoptosis
  - (e.g., rituximab, cetuximab, trastuzumab)

- Activation of T-Cells

- Activation of Effector Mechanisms

- Antibody-dependent cellular Cytotoxicity (ADCC)


Principles of biosimilarity

Stepwise approach

Entire biosimilar process is built on a solid foundation of extensive analytical characterization which is robustly assessed.

Principles of biosimilar comparability exercise are based on the evaluation of the impact of changes in the manufacturing process (ICH Q5E).

Typical physiochemical biosimilarity exercise

**Primary Structure**
- Peptide map
- Amino acid sequence
- Total mass analysis
- Disulfide bonds
- Free sulfhydryls

**Higher Order Structure**
- FTIR
- Far UV
- Near UV
- DSC

**Purity**
- SE-HPLC
- CE-SDS
- SDS-PAGE
- AUC
- MALS
- Deamidation
- Oxidation

**Potency**
- Binding affinity (ELISA/SPR)
- Cell based assay
- Apoptosis
- ADCC
- C1q binding
- CDC
- FcyRI binding
- FcyRII binding
- FcyRIII binding
- FcRn binding

**Glycosylation**
- N-linked glycans
- Oligosaccharide profile
- Monosaccharide analysis
- Sialic acid analysis

**Charge variants**
- Cation exchange HPLC
- Ion exchange HPLC

Comparability of pharmaceutical quality determining functional characteristics

- **N- Glycosylation**
  - Amounts of nonfucosylated oligosaccharides
  - Portion of G2 glycan
  - Content of high mannose oligosaccharides

- **Aggregate Levels**
  - PK profile (clearance)
  - Immunogenicity

- **Similarity of functional aspects deduced from comparability of corresponding quality attributes**

Bernd Liedert, CDMA


A higher level of resolution – ADCC
Antibody-Dependent Cell-Mediated Cytotoxicity as exemplified by anti-CD20 MAb

- Mediated by effector cells including NK cells, granulocytes and macrophages: Interactions with CD16 (FcγRIII), CD32 (FcγRII), CD64 (FcγRI)
- CD16 has an allelic variation
- CD16 homozygous for valine at 158 (VV) has a higher affinity for Rituximab (IgG1) than does CD16 with phenylalanine at that position (VF or FF)

- In FL (monotherapy) and DLBCL (CHOP combi) patients carrying the VV genotype have a better clinical response than patients that are VF or FF

But: Predictivity of CD16 polymorphisms not clear for CLL: reduced expression of CD20 on the neoplastic CLL cells?
FL treated with Rituximab plus CHOP: Negative impact of chemo on NK activity?

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Clinical efficacy in oncology – Monoclonal antibodies

Compared with growth factors, mAbs are more complex

- Similarities and comparability to the innovator biologicals will be more difficult to assess

Which endpoints should be evaluated for mAbs?

<table>
<thead>
<tr>
<th>Clinical endpoints</th>
<th>mAbs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR according to guideline.</td>
<td></td>
</tr>
<tr>
<td>PFS more reliable.</td>
<td></td>
</tr>
</tbody>
</table>

- Which patient population?
  - The most sensitive (efficacy, safety, immunogenicity)

ESA, erythropoiesis-stimulating agent; ANC: absolute neutrophil count; Hb, haemoglobin

Phase I/IIb Trial Comparing Herceptin and its Biosimilar CT-P6 in MBC: Results

- Multicenter trial: Korea, Russia, Ukraine, Latvia, Serbia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment</th>
<th>N</th>
<th>Geometric mean</th>
<th>% CV</th>
<th>Ratio (%)</th>
<th>90% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC\textsubscript{ss} (μg/h/mL)</td>
<td>CT-P6</td>
<td>48</td>
<td>32,000</td>
<td>43.5</td>
<td>104.57</td>
<td>93.64, 116.78</td>
<td>.5029</td>
</tr>
<tr>
<td></td>
<td>Herceptin</td>
<td>49</td>
<td>30,600</td>
<td>30.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(C\text{\textsubscript{t}}\text{\textsubscript{r}}\text{\textsubscript{ough ss}}) (μg/mL)</td>
<td>CT-P6</td>
<td>51</td>
<td>19.5</td>
<td>37.0</td>
<td>101.35</td>
<td>87.94, 116.82</td>
<td>.8754</td>
</tr>
<tr>
<td></td>
<td>Herceptin</td>
<td>49</td>
<td>19.2</td>
<td>39.6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusions of the study:
- CT-P6 demonstrated equivalent PK profile to Herceptin
- CT-P6 well tolerated with a comparable safety profile to Herceptin
- (infusion-related reaction, cardiotoxicity, and infection)


Biosimilar monoclonal antibodies in oncology

Randomized first line study in metastatic breast cancer combining trastuzumab biosimilar (CT-P6) and paclitaxel

<table>
<thead>
<tr>
<th>MAb</th>
<th>No. of patients</th>
<th>ORR</th>
<th>TTR (months)</th>
<th>TTP (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innovator trastuzumab</td>
<td>231</td>
<td>62%</td>
<td>1.38</td>
<td>12.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NS</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Biosimilar trastuzumab</td>
<td>244</td>
<td>57%</td>
<td>1.38</td>
<td>11.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NS</td>
<td></td>
<td>NS</td>
</tr>
</tbody>
</table>

Kaplan Meier plots of time to progression in the responder group of trastuzumab/paclitaxel compared to CT-P4 paclitaxel

Key principles for extrapolation of indications (I)

- Clinical experience with the reference product
- Mechanism(s) of action/active site(s) of the active substance in each indication (including its degree of certainty)
- The degree to which the functional moieties of the molecule can be analytically characterized and compared
- Differences in the safety/immunogenicity profile between the therapeutic indications
- Acceptable clinical safety profile must have been established for the biosimilar
Key principles for extrapolation of indications (II)

- Increased immunogenicity of the biosimilar must have been reasonably excluded

- Extrapolation of immunogenicity is only possible from high to low risk patient populations and clinical settings (e.g., from SC to IV route of administration or from immunocompetent to immunocompromised patients, but normally not vice versa)

- Additional tests or studies may be needed to further support extrapolation, e.g. relevant pharmacodynamic parameters and/or specific functional assays reflecting the pharmacological action(s) of the molecule; **clinical studies using outcome endpoints are usually less sensitive to detect potential differences between the biosimilar and the reference product**

- **TOTALITY OF THE EVIDENCE OF BIOSIMILARITY DERIVED FROM THE COMPARABILITY EXERCISE**

Weise M et al, Blood online October 8, 2014: doi10.1182/blood-2014-06-583617

Acceptability of biosimilar infliximab by gastroenterologists

**6. Conclusion**

The overall position of ECCO is that the use of most biosimilars in patients with IBD will require testing in this particular patient population, with comparison to the appropriate innovator product. Although wider access to appropriate use of biological therapy in IBD and potential direct cost savings are important, rigorous testing is necessary in patients with IBD to ensure that appropriate efficacy and safety standards are met. Final clinical decisions should always be made on an individual basis, taking into account both circumstances of the individual patient and prescribing physician.
Comments on Extrapolation of Biosimilars

- Epoetin has a simple mechanism of action. Tested in a sensitive population. Extrapolation to oncology/hematology accepted.
- Monoclonal antibodies complex MOA. Intensive debate among rheumatologists and oncologists/hematologists. Infliximab approved for all indications in Europe, Korea, Japan but not for IBD in Canada. What will happen with rituximab and trastuzumab is unclear.

Biosimilar Filgrastim Market Penetration

Average up-take in Europe 2013, 90%. (Igregatovic. www.datamonitorhealthcare.com)
Executive summary of monoclonal antibody biosimilars for health care providers

- The mode of action of monoclonal antibodies is multifactorial depending on the antibody and indication. The contribution of each function to the totality of the effect of a monoclonal antibody is not fully established.

- The monoclonal antibody product is pre-clinically highly well characterized using the latest advances in biotechnology.

- A rigorous approval process has been applied.

- Limited clinical information at approval with regard to clinical efficacy, immunogenicity and extrapolated indications.