Overcoming Challenges in the Emerging Biosimilar Landscape

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Objectives

• Identify the safety and efficacy of biosimilars in relation to biologics and generic pharmacologics
• Assess the clinical data and evidence for current and emerging biosimilars that demonstrate biosimilarity compared to the branded products
• Evaluate clinical implications of the manufacturing processes used to produce biosimilars in regards to the complexity and regulatory pathways
• Discuss the different therapeutic areas that rely on biologics and how biosimilars can broaden treatment options in relation to safety & effectiveness
• Discuss the potential cost savings associated with current and emerging biosimilars and how this could affect improved access for patients
Complexity of Biologics

Small molecules / Large molecules

ASA (21 atoms)  ACE inhibitor (62 atoms)  Insulin (790 atoms)  Monoclonal Antibody (20,000 atoms)

Deeper Complexity of Biologics
Complex Process

Manufacturing of biological product
(DNA: Deoxyribonucleic acid)

Process of Making Biologics

- Characterization parameters set up for the reference product.

Different process = different product
**The Principle and Main Concern**

- Biosimilars will reduce cost, but...
- There is one critical underlying principle: *Biologics are large, complex glycoprotein molecules that cannot be duplicated*
- There is uncertainty
  - How will uncertainty influence use of biosimilars?

**Questions**

- Will doctors be comfortable prescribing a biosimilar that is not identical to the original drug?
- Will we accept patients being switched from originator to biosimilar without our knowledge?
- Will we be satisfied if biosimilars are tested in patients with rheumatoid arthritis and not psoriasis?
- Will we be comfortable with potential differences in immunogenicity, safety and efficacy?
- Will we be comfortable with the biosimilar using the same generic name that the originator drug uses?
Biologics: Awesome Efficacy

- Patients Achieving PASI-75 at Week 12

Biologics: Awesome Safety

- Severe infection rate per 100 PY (95% CI)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Severe Infection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>UST (N=49)</td>
<td>0.83</td>
</tr>
<tr>
<td>IFX (N=56)</td>
<td>2.49</td>
</tr>
<tr>
<td>ETAN (N=55)</td>
<td>1.47</td>
</tr>
<tr>
<td>ADA (N=102)</td>
<td>1.97</td>
</tr>
<tr>
<td>MTX Non-biologic (N=16)</td>
<td>0.23</td>
</tr>
<tr>
<td>Non-MTX Non-biologic (N=40)</td>
<td>1.05</td>
</tr>
<tr>
<td>All (N=323)</td>
<td>1.45</td>
</tr>
</tbody>
</table>

N = number of serious infections per treatment group

Biologics: Costly

Biosimilars: Standard Perspective
Pure Red Cell Aplasia

• Incidence increased after exposure to a form of erythropoetin
• Occurred after minor changes in production and storage in one brand
  – Glycine and polysorbate 80 as a stabilizer instead of human serum albumin to eliminate the risk of prion transmission
  – Rubber stoppers were used to cap prefilled syringes

Cannot Duplicate the Innovator

• Biologics are large, complex glycoprotein molecules that cannot be duplicated
• The innovator changes from batch-to-batch, too
Variation in Enbrel/Etanercept

Etanercept is Not a Single Entity

Figure 3. Comparison of the different pre- and post-change batches of Enbrel. (a) Relative amounts of basic variants of the pre-change \( (n=6) \) and the post-change \( (n=6) \) batches as measured by CEX. (b) Relative amount of the G2F glycan of the pre-change \( (n=25) \) and the post-change \( (n=9) \) batches. (c) Exemplary CEX chromatograms. (d) Exemplary glycan mapping chromatograms.
Humira/Adalimumab Variation

[Graph showing variation over time with peaks and annotations]

Humira/Adalimumab Variation

[Graph showing variation over time with bars and annotations]
Primary Structure is the Same
FDA: CT-P13 has a matching chromatographic profile (map) to that of US-licensed Remicade and EU-approved Remicade

1: CT-P13, infliximab, biosimilar

2: US-licensed Remicade

3: EU-approved Remicade

Statistical Equivalence in Biological Activity
TNFα Binding Affinity

Drift: The Telephone Game

• Multiple process changes over time
  – Adalimumab 15, etanercept 20, infliximab 35
  – Small variation with each one may not matter much
  – How much effect is there after many changes?

“The” Innovator Drug

• The innovator drug is not one thing
• It varies over time
• No head-to-head clinical trials showing equivalency over time
• But it still seems to do the job, and we are happy with it
Biosimilars: Principled Perspective

Innovator small molecule → Generic Comfortable

Innovator biologic → Biosimilar Comfortable

Regulatory Definitions

• A biosimilar is a biologic medicinal product that contains a version of the active substance of an already authorized original biologic medicinal product (reference medicinal product). A biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biologic activity, safety, and efficacy based on a comprehensive comparability exercise.

• Biosimilarity means “that the biologic product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the biologic product and the reference product in terms of the safety, purity, and potency of the product”
Pathway to Approval

• Analytics
  – Biochemical and structural similarity
  – Extensive studies!

• Function
  – In vitro binding/potency

• Human studies
  – Pharmacokinetics/pharmacodynamics
  – Immunogenicity
  – Clinical trial of safety/efficacy
  – Registry

Biosimilarity

• Numerous pre-clinical studies to show remarkable similarity
• Equivalent functional effects
• Clinical trial
  – Efficacy within an equivalence margin
Pharmacokinetics of Innovator and Biosimilar Adalimumab in Healthy Subjects


Equivalent Efficacy in Rheumatoid Arthritis (RA) and Plaque Psoriasis (PsO)

RA (n = 526 patients)  PsO (n = 350 patients)

Week 24 ACR20 Response  Week 16 PASI Improvement

71%  72%  81%  83%

NOR-SWITCH: Results

ClinicalTrials.gov. NCT02148640.

NOR-SWITCH: Efficacy, Immunogenicity

**PLANETAS (Ankylosing Spondylitis) Extension Study**

54-week Main Study

- CT-P13 (5 mg/kg) N = 125
- Remicade (5 mg/kg) N = 125
- Completed N = 106

Extension Study

- Maintenance CT-P13 (5 mg/kg) N = 88
- Switch CT-P13 (5 mg/kg) N = 86
- Completed N = 81

ASAS20 Response

Week 14 Week 30 Week 54 Week 78 Week 102

- Maintenance
- Switch

0% 20% 40% 60% 80% 100%


**PLANETRA (Rheumatoid Arthritis) Extension Study**

54-week Main Study

- CT-P13 (3 mg/kg) N = 302
- Remicade (3 mg/kg) N = 304
- Completed N = 233

Extension Study

- Maintenance CT-P13 (3 mg/kg) N = 158
- Switch CT-P13 (3 mg/kg) N = 144
- Completed N = 133

ACR20 Response

Week 14 Week 30 Week 54 Week 78 Week 102

- Maintenance
- Switch

0% 20% 40% 60% 80% 100%

Anti-Drug Antibodies (ADA)

**PLANETAS (AS)**

<table>
<thead>
<tr>
<th>Week</th>
<th>Patients Positive for ADAs</th>
</tr>
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<tbody>
<tr>
<td>14</td>
<td>Maintenance 24/28 (86%) Switch 24/27 (89%)</td>
</tr>
<tr>
<td>30</td>
<td>Maintenance 24/28 (86%) Switch 24/27 (89%)</td>
</tr>
<tr>
<td>54</td>
<td>Maintenance 24/28 (86%) Switch 24/27 (89%)</td>
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</tr>
<tr>
<td>102</td>
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**PLANETRA (RA)**

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<tr>
<td>14</td>
<td>Maintenance 73/91 (80%) Switch 74/92 (80%)</td>
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**Extrapolation**

- May only get clinical data from one disease indication
  - Structurally similar
  - Equivalent potency and pharmacokinetics
  - Expect it to work the same
- Clinical trial data in one disease is a bonus!
  - Pick the most sensitive disease
- The variants in the innovator don’t provide even that much evidence
Cost Savings
The European experience with biosimilar epoetin and G-CSF

Price change since introduction in biosimilar accessible market

Germany
France
Italy
Spain
UK

-55%
-39%
-13%
-24%
-18%

Causes of Variation

- Differences in the product
- Differences in the handling of the product
- Differences in patients’ disease
- Differences in patient characteristics
- Differences in adherence

Variation in Adherence


Questions

• Should we be comfortable with a biosimilar that is not identical to the original drug?
• It is acceptable to switch patients from originator to biosimilar without our notification?
• Will we be satisfied if biosimilars are tested in patients with rheumatoid arthritis and not psoriasis?
• Will we be comfortable with potential differences in immunogenicity, safety and efficacy?
• Will we be comfortable with the biosimilar using the same generic name that the originator drug uses?
Should we be comfortable with a biosimilar that is not identical to the original drug?

- We are now
- “The innovator” isn’t what it used to be

Is it acceptable to switch patients from originator to biosimilar without notification?

- We do now
- Patients switch from one batch of innovator to another, and no one cares
Will we be satisfied if biosimilars are tested in patients with rheumatoid arthritis and not psoriasis?

- We are now
- We are satisfied with even less, as new versions of the innovator don’t compare in clinical trials at all

Will we be comfortable with potential differences in immunogenicity, safety and efficacy?

- We are now
- There is uncertainty about changes in the innovator, but we don’t pay it any mind at all
Will we be comfortable with the biosimilar using the same generic name that the originator drug uses?

- We are now
- We don’t require or expect different batches of the innovator to have different names

Conclusions

- Biologics are awesome
- They cannot be duplicated
  - Current innovator products are not the same as the originals
  - We are comfortable with that
- Biosimilars will give us even more data—far more data—to support being comfortable than we have now