Biosimilars: Is the Future Safer, More Cost-Effective, and Efficacious?

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Objectives

• Define biosimilars and explain the difference between biologics and generic drugs

• Review the regulatory process for biosimilars by the FDA

• Discuss the benefits and concerns of implementation of biosimilars into practice

Introduction to Biosimilars

What is a biologic?

• Large, complex proteins that are produced in living systems

• Wide range of products including vaccines, blood and blood components, allergens, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins

• Biologic reactions are variable and yield heterogenous products

What is a biosimilar?

• The FDA defines a biosimilar as:
  • “A biosimilar product is a biological product that is approved based on a showing that it is highly similar to an FDA-approved biological product, known as a reference product, and has no clinically meaningful differences in terms of safety and effectiveness from the reference product.”

Disclosures

• Daniel Wojenski has disclosed that he is on the speaker’s bureau for Sanofi Oncology

All conflicts resolved through peer review
### Biosimilar Medications Approved in the US

<table>
<thead>
<tr>
<th>Biosimilar Product</th>
<th>Date of Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>pegfilgrastim-sndz/Zarxio</td>
<td>March 6, 2015</td>
</tr>
<tr>
<td>infliximab-dyyb/Inflectra</td>
<td>April 5, 2016</td>
</tr>
<tr>
<td>etanercept-szsz/Erelzi</td>
<td>August 30, 2016</td>
</tr>
<tr>
<td>adalimumab-atto/Amjevita</td>
<td>September 23, 2016</td>
</tr>
<tr>
<td>infliximab-dyyb/Renflexis</td>
<td>April 24, 2017</td>
</tr>
</tbody>
</table>

### Cost of Cancer Care

- 18.1 million cancer survivors predicted in 2020
- 30% more than 2010
- $174 billion projected costs for 2020
- $157 billion in 2010
- Biologics accounted for 32% of $9.5 billion Medicare Part B drug spending in 2005 and by 2014 they represented 62% of $18.5 billion

### Oncology Biologic Patent Expiration

- Pegfilgrastim: 2015
- Rituximab: 2016
- Cetuximab: 2017
- Bevacizumab: 2018
- Trastuzumab: 2019

### Biosimilars and Cost Savings

- Biosimilars are expected to decrease costs by ~30%
- One review projected that biosimilars will lead to a $44.2 billion reduction in drug spending over a 10 year span (2014-2024)

### Reimbursement

- Health plans considering placing biosimilars on lower tiers, which could require biosimilar use prior to the reference biologic
- In physician office, fee-for-service payment based on average sale price plus 4.3%
- Medicare Part D likely to cover wholesale acquisition cost plus a surcharge
Regulatory Process for Biosimilar Approval

**Legislation**

- Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments) of 1984
  - Generic medication approval without studies that demonstrate safety and efficacy
- Biologics Price and Competition and Innovation (BPCI) Act of 2009
  - Amendment in the Affordable Care Act
  - Biologic medication can be deemed “biosimilar” if the medication is highly similar to an existing biologic product

**Small Molecules**

- New Drug Application 505(b)(1) or 505(b)(2)
- Full report of safety and efficacy
- Two pathways dependent on right of reference

- Generics
  - Abbreviated new drug application 505(j)
  - Identical to an already approved product
  - No safety or efficacy needed

- Biosimilar
  - Biologics License Application 351(a)
  - Identical to a 351(a) product
  - Full reports of safety and efficacy investigations
  - Applicant has right of reference to essential investigations
  - Demonstration of absence of clinically meaningful difference

- Biologic License Application 351(k)*
  - Highly similar to a 351(a) product

**Regulatory Requirements of Biologic Agents**

- Preclinical Studies
  - Phase I
  - Phase II
  - Phase III
  - Comparative structural and functional analysis
  - Animal Studies to assess toxicity
  - PK, PD, and Immunogenicity
  - Comparative clinical trials

**Biosimilar Drug Approval Process**

**Naming of Biosimilar Medications**

- At time of licensure a suffix is added consisting of four lowercase letters that will serve to distinguish the biosimilar agent

<table>
<thead>
<tr>
<th>Suffixes SHOULD</th>
<th>Suffixes SHOULD NOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Be unique</td>
<td>Be false or misleading</td>
</tr>
<tr>
<td>Be devoid of meaning</td>
<td>Include numerals or symbols</td>
</tr>
<tr>
<td>Be four lowercase letters of which three are distinct</td>
<td>Include abbreviations commonly used in clinical practice</td>
</tr>
<tr>
<td>Be nonproprietary</td>
<td>Contain or suggest any drug substance</td>
</tr>
<tr>
<td>Be attached to the core name with a hyphen</td>
<td>Look similar to or be capable of being mistaken for the name of a currently marketed product</td>
</tr>
<tr>
<td>Be free of legal barriers that would restrict its usage</td>
<td>Be similar to any FDA-assigned non-proprietary name suffix</td>
</tr>
</tbody>
</table>

**Immunogenicity**

- Immune response to biologic medications may affect safety and efficacy of patients
- Immunological based adverse events could include anaphylaxis, cytokine release syndrome, or neutralization of endogenous proteins
- Evaluation includes assays for anti-drug antibody, product specific sampling, comparative immunogenicity studies and postmarketing surveillance

**Notes:**

- FDA. Scientific considerations in demonstrating biosimilarity to a reference product: guidance for industry. 2015.
HERITAGE Study: Trastuzumab Biosimilar (MYL-1041O)

- Study Population
  - ERBB2-positive metastatic breast cancer
  - ECOG PS 0-2
  - Normal LVEF
- Primary Endpoint
  - ORR

**MYL-1041O**

- 8mg/kg loading dose followed by q 3 week
- 3mg/kg biosimilar + taxane (docetaxel 75mg/m2 q 3 wk or paclitaxel 80mg/m2 q wk) (N = 230)

**Trastuzumab**

- 8mg/kg loading dose followed by q 3 week
- 3mg/kg biosimilar + taxane (docetaxel 75mg/m2 q 3 wk or paclitaxel 80mg/m2 q wk) (N = 228)

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HERITAGE Study: Outcomes

- Primary Endpoint (24 week follow-up)
  - Study Arm ORR Confidence Interval
  - MYL-1401O + taxane 69.6% (95% CI, 62.62%‐75.51%)
  - Trastuzumab + taxane 64% (95% CI, 57.81%‐70.26%)

- Secondary Endpoints (48 week follow-up)
  - Study Arm Time to Tumor Progression Progression-Free Survival Overall Survival
  - MYL-1401O + taxane 42.3% 44.3% 89.1%
  - Trastuzumab + taxane 43% 44.7% 85.1%

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HERITAGE Study: Adverse Events

- Adverse Events
  - LVEF
    - Baseline LVEF for the biosimilar arm (64%) and trastuzumab arm (63%) at 24 weeks changed a median of -1% in both groups
  - Neutropenia 27.5% 25.2%
  - Neutropenic Fever 4.5% 4.1%
  - Leukopenia 1.6% 4.9%
  - Pneumonia 1.6% 2%

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HERITAGE Study: PK/PD and Immunogenicity

- PK/PD
  - Cmin, Cmax, AUC were similar in both arms of the study
- Immunogenicity
  - Study Arm Antidrug Antibody Rate Median Titer
  - MYL-1401O + taxane 2.4% 2.5
  - Trastuzumab + taxane 2.8% 2.3

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HERITAGE Study

- MYL-1401O and trastuzumab had similar overall response rates at 24 weeks
- Secondary outcomes supported equivalence
- Adverse events were similar
- Immunogenicity was low
- Long term data needed to evaluate safety and outcomes

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Evaluation of the Data and Implementation in Practice
Interchangeability

- Interchangeability means the biosimilar “can be expected to produce the same clinical result as the reference product in any given patient”
- Risk of switching between products is not greater than using reference product consistently
- FDA guidance varies based on complexity of the biosimilar
- Submission of switching studies between biosimilar and reference product
- No biosimilar in the US has interchangeable status

Illinois State Law

- Pharmacists can substitute biosimilars for biologics and vice versa
  - FDA must designate the biosimilar as interchangeable
  - Physicians may prohibit substitution
  - Prescribers must be notified of substitutions within 5 days
  - Prescribers do not need to be notified if the substitution continues in a refill
  - Patients must be notified of the substitution
  - No requirements for counseling
  - Records of the substitution must be kept for 5 years
  - The state board must maintain a list of interchangeable biologics on their website

Extrapolation of Indications

- FDA may extrapolate to an indication not studied by the biosimilar but has been approved for the reference product
- Biosimilar should demonstrate the same mechanism of action, PK, and biodistribution in the extrapolated indication
  - Varies on complexity of the medication
- Can lead to reduced cost to patients and payers
  - 20% reduction in the price of 5 off-patent pharmaceuticals could result in 9-12 billion savings over 10 years

Tbo-filgrastim post Stem Cell Transplant

- Retrospective chart review of 182 autologous stem cell transplant for multiple myeloma
  - 91 patients received filgrastim post transplant and 91 patients received tbo-filgrastim
  - Safety profiles were similar between agents

Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Tbo-filgrastim</th>
<th>Filgrastim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil engraftment (median days)</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Hospital length of stay (median days)</td>
<td>16</td>
<td>16</td>
</tr>
</tbody>
</table>

Pharmacovigilance

- Monitoring of all biologics following approval is vital
- One example includes increased rates of antibody-mediated pure red cell aplasia (PRCA) observed in Europe between 1998 and 2004 secondary to epoetin manufacturing
- Safety monitoring of biosimilars includes voluntary reporting of adverse events and medication errors to the manufacturer or FDA
Summary

- Biosimilar agents are biologic drugs that are highly similar to an FDA approved biologic agent known as the reference product.
- Application for biosimilar evaluation should be filed under the Biologics License Application 351 (k) and includes information on analytical data, PK/PD, immunogenicity data, and comparative evaluations.
- Biosimilar medications may reduce costs of biologics by ~30%.
- Interchangeability and extrapolation remain points of concern in the United States and require evaluation of the totality of evidence in order to make the decision.

Which of the following questions regarding biosimilars is true?

A. A biosimilar is a biologic product that is highly similar to an FDA approved reference biologic product.
B. Biosimilar legislation stemmed from the Hatch-Waxman Amendment.
C. Manufacturing of a biosimilar is predictable and bioequivalent to the reference biologic product.
D. All of the above.

Which of the following is NOT a requirement for review when evaluating a biosimilar?

A. Analytical Structure Review
B. Switching studies between biosimilar medications and the reference product.
C. Pharmacokinetic and Pharmacodynamic Data
D. Immunogenicity.

How many biosimilars have interchangeable status in the United States?

A. 0
B. 1
C. 3
D. 4.

Which of the following is NOT a rule in Illinois with regards to biosimilar medications?

A. Prescribers must be notified of substitutions within 5 days.
B. Illinois requires FDA interchangeable status in order to substitute a biologic with a biosimilar.
C. Patients must be notified about the substitution and pharmacists must complete a biosimilar counseling checklist with each patient.
D. Records must be maintained for 5 years.

Which of the following are concerns for using biosimilars at this time?

A. Inappropriate extrapolation leading to lack of efficacy.
B. Increased risk of immunogenicity leading to safety concerns.
C. Lack of insurance reimbursement.
D. All of the above.
Bibliography


• National Cancer Institute. https://costprojections.cancer.gov/


