Disclosures

• None
Learning Objectives

- Clarify the definition of Biosimilars
- Appreciate the changing landscape that led to the emergence of Biosimilars
- Understand the abbreviated FDA approval pathway for Biosimilars
- Appreciate the rationale for extrapolation of indications and understand the concept of interchangeability
- Consider clinical scenarios where Biosimilars can be safely utilized

What Are Biosimilars?

- The World Health Organization defines a biosimilar as a “product that is similar in terms of quality, safety and efficacy to an already licensed reference product”

- Biosimilars are not “generic” biologic drugs

Biosimilars Key Issues

- A biosimilars has the same amino acid sequence as the originator but they are not identical.
- These are complex substances synthesized in cells and are 1000 times larger than chemically synthesized drugs.
- They have tertiary and quaternary folding and post-translational modifications such as glycosylation.

Protein Structure Levels

Adapted from Boundless Biology
“No Two Snowflakes Are Alike”

Economic Burden of Anti-TNF Therapy

Annual Mean Expenditures per Person

- $10,364 for CD
- $7,827 for UC

vs.

- $4,314 for non-IBD

$p < 0.05$

Health Plan Paid Costs by Cost-driver Category and Pharmacy Cost for CD

- Adalimumab
- Infliximab
- Others

- Pharmacy
- Outpatient
- Inpatient
- Other

18.40%
12.30%
14.80%

How Much Do Biologics Cost?

- Biologics cost an estimated $1.2 B. to develop
- Biologic manufacturing costs are not publicly disclosed
- Insurance discounts and rebates are confidential


Global Sales of Biologic Drugs 2004-2011

Global expenditure on biologics in 2012 was $169 B., representing 18% of all medicines prescribed.

How Much Will Biosimilars Cost?

- Biosimilar prices in the EU have been on average approximately 30% less expensive than their reference products.

- Due to lack of a single payor system in the U.S., the relative costs of biosimilars will be determined by negotiations between the manufacturers and payors. At least a 20% saving is expected by switching to biosimilars.

  - Pharmaceutical Commerce, Biosimilars: why deep discounts may become the dominant paradigm, Feb 22, 2016.

Global Socioeconomics And Potential Savings With Biosimilars

The US could save $250 B. between 2014 and 2024 if just the 11 likeliest biosimilars would enter the market.

The Looming Biologics Patent Cliff


Biologics Price Competition And Innovation Act of 2009

SEC. 7002. APPROVAL PATHWAY FOR BIOSIMILAR BIOLOGICAL PRODUCTS.

(a) LICENSURE OF BIOLOGICAL PRODUCTS AS BIOSIMILAR OR INTERCHANGEABLE.—Section 351 of the Public Health Service Act (42 U.S.C. 262) is amended—

“(2) The term ‘biosimilar’ or ‘biosimilarity’, in reference to a biological product that is the subject of an application under subsection (k), means—

“(A) that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and

“(B) there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.
FDA Abbreviated Approval Pathway For Biosimilars

FDA uses a risk-based, totality-of-the-evidence approach to determine biosimilarity of the proposed product.

- Comparative clinical study to investigate whether there are clinically meaningful differences between the proposed biosimilar and the originator.

- Comparative clinical study to evaluate potential differences in immunogenicity between the proposed biosimilar and the originator.

- Comparative human PK / PD study between the proposed biosimilar and the originator.

- Comparative structural and functional characterization of the proposed biosimilar and the originator.

Weighted reliance on analytical similarity.

FDA, Beyond the Finish Line: Biosimilars in the US, Presented on Oct 2015
Extrapolation

- Clinical trials in one indication used as rationale for clinical use in other indications for which the originator biological product is approved

- Requires appropriate scientific justification

- FDA approved the two Infliximab biosimilars for the treatment of IBD even in the absence of randomized data
Are Providers Comfortable With Extrapolation?

Published Studies on The Efficacy And Safety of CT-P13 in IBD

<table>
<thead>
<tr>
<th>Author Reference</th>
<th>Country, Year</th>
<th>CD UC</th>
<th>Switch</th>
<th>Fail, %</th>
<th>LOR, wk</th>
<th>Stop, %</th>
<th>SAEs, %</th>
<th>ADA, %</th>
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<tbody>
<tr>
<td>Kang et al.16</td>
<td>Korea, 2014</td>
<td>8</td>
<td>9</td>
<td>3/5</td>
<td>12.5</td>
<td>11</td>
<td>8</td>
<td>6</td>
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<tr>
<td>Jung et al.17</td>
<td>Korea, 2015</td>
<td>52</td>
<td>69</td>
<td>25/27</td>
<td>10.8</td>
<td>14</td>
<td>54</td>
<td>5.5</td>
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<tr>
<td>Gao et al.18</td>
<td>Hungary, 2016</td>
<td>126</td>
<td>94</td>
<td>na</td>
<td>20.5</td>
<td>—</td>
<td>14</td>
<td>7.5</td>
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<tr>
<td>Park et al.19</td>
<td>Korea, 2015</td>
<td>95</td>
<td>78</td>
<td>64/16</td>
<td>25.5</td>
<td>11</td>
<td>30</td>
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<tr>
<td>Slewczynski et al.20</td>
<td>Poland, 2016</td>
<td>32</td>
<td>7</td>
<td>32/7</td>
<td>—</td>
<td>18</td>
<td>12</td>
<td>2.5</td>
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<tr>
<td>Farkas et al.21</td>
<td>Hungary, 2015</td>
<td>18</td>
<td>21</td>
<td>na</td>
<td>30</td>
<td>8</td>
<td>ng</td>
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<tr>
<td>Johnson et al.22</td>
<td>Norway, 2015</td>
<td>46</td>
<td>32</td>
<td>na</td>
<td>21</td>
<td>ng</td>
<td>14</td>
<td>6.5</td>
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<tr>
<td>Keil et al.23</td>
<td>Czech R, 2016</td>
<td>30</td>
<td>22</td>
<td>—</td>
<td>4.5</td>
<td>ng</td>
<td>14</td>
<td>7.7</td>
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<tr>
<td>Gao et al.24</td>
<td>Hungary, 2016</td>
<td>184</td>
<td>107</td>
<td>na</td>
<td>49</td>
<td>ng</td>
<td>30</td>
<td>21.3</td>
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<tr>
<td>Levair et al.25</td>
<td>United Kingdom, 2016</td>
<td>134</td>
<td>134</td>
<td>1.5</td>
<td>0</td>
<td>16</td>
<td>1.5</td>
<td>41</td>
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<tr>
<td>Smith et al.26</td>
<td>Netherlands, 2016</td>
<td>57</td>
<td>24</td>
<td>53/24</td>
<td>6</td>
<td>0</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Kolat et al.27</td>
<td>Czech R, 2016</td>
<td>56</td>
<td>18</td>
<td>56/18</td>
<td>4</td>
<td>19</td>
<td>24</td>
<td>28.2</td>
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<tr>
<td>Farkas et al.28</td>
<td>Hungary + Czech R, 2016</td>
<td>63</td>
<td>na</td>
<td>17.5</td>
<td>ng</td>
<td>14</td>
<td>ng</td>
<td>ng</td>
</tr>
<tr>
<td>Murphy et al.29</td>
<td>Ireland, 2015</td>
<td>14</td>
<td>—</td>
<td>28.5</td>
<td>—</td>
<td>24</td>
<td>28.5</td>
<td>Sang and Hoop</td>
</tr>
</tbody>
</table>

In general, no clear signal of difference was seen between Infliximab and CT-P13.
### Systematic Review With Meta-Analysis: The Efficacy And Safety of CT-P13 in IBD

#### Table 1: Characteristics of observational studies of biosimilar of anti-TNFα necrosis factor αs (CT-P13) in IBD

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Study year (reference)</th>
<th>Study design</th>
<th>Name of biosimilar (injected dose in mg/kg)</th>
<th>Age at start (mean)</th>
<th>Disease and schedule of biosimilar</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td>Jiang et al. 2015</td>
<td>Prospective</td>
<td>CT-P13 5 mg/m² weekly or 5 mg/m² every 2 weeks</td>
<td>30.0</td>
<td>5 mg/kg in week 0, 2, 6, 14</td>
</tr>
<tr>
<td></td>
<td>Park et al. 2015</td>
<td>Prospective</td>
<td>CT-P13 5 mg/m² weekly or 5 mg/m² every 2 weeks</td>
<td>31.0</td>
<td>5 mg/kg in week 0, 2, 6, 14</td>
</tr>
<tr>
<td></td>
<td>Park et al. 2015</td>
<td>Retrospective</td>
<td>CT-P13 3 mg/m² weekly or 3 mg/m² every 4 weeks</td>
<td>30.0</td>
<td>3 mg/kg in week 0, 2, 6, 14</td>
</tr>
<tr>
<td>UC</td>
<td>Park et al. 2015</td>
<td>Prospective</td>
<td>CT-P13 5 mg/m² weekly or 5 mg/m² every 2 weeks</td>
<td>30.0</td>
<td>5 mg/kg in week 0, 2, 6, 14</td>
</tr>
<tr>
<td></td>
<td>Park et al. 2015</td>
<td>Retrospective</td>
<td>CT-P13 3 mg/m² weekly or 3 mg/m² every 4 weeks</td>
<td>30.0</td>
<td>3 mg/kg in week 0, 2, 6, 14</td>
</tr>
<tr>
<td></td>
<td>Park et al. 2015</td>
<td>Retrospective</td>
<td>CT-P13 1.5 mg/m² weekly or 1.5 mg/m² every 4 weeks</td>
<td>30.0</td>
<td>1.5 mg/kg in week 0, 2, 6, 14</td>
</tr>
<tr>
<td></td>
<td>Park et al. 2015</td>
<td>Retrospective</td>
<td>CT-P13 1.5 mg/m² weekly or 1.5 mg/m² every 4 weeks</td>
<td>30.0</td>
<td>1.5 mg/kg in week 0, 2, 6, 14</td>
</tr>
</tbody>
</table>

#### Table 2: Characteristics of observational studies switching from infliximab to biosimilar

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Study year (reference)</th>
<th>Study design</th>
<th>Name of biosimilar (injected dose in mg/kg)</th>
<th>Continuous concomitant medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td>Park et al. 2015</td>
<td>Prospective</td>
<td>CT-P13 5 mg/m² weekly or 5 mg/m² every 2 weeks</td>
<td>SASA, 30%, natalizumab 5%, metronidazole 10%</td>
</tr>
<tr>
<td></td>
<td>Park et al. 2015</td>
<td>Prospective</td>
<td>CT-P13 5 mg/m² weekly or 5 mg/m² every 2 weeks</td>
<td>SASA, 70%, natalizumab 5%, metronidazole 10%</td>
</tr>
<tr>
<td></td>
<td>Park et al. 2015</td>
<td>Retrospective</td>
<td>CT-P13 5 mg/m² weekly or 5 mg/m² every 2 weeks</td>
<td>SASA, 30%, natalizumab 5%, metronidazole 10%</td>
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<td></td>
<td>Park et al. 2015</td>
<td>Retrospective</td>
<td>CT-P13 5 mg/m² weekly or 5 mg/m² every 2 weeks</td>
<td>SASA, 70%, natalizumab 5%, metronidazole 10%</td>
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The PROSIT-BIO Cohort: A Prospective Observational Study of Patients with IBD Treated with Infliximab Biosimilar

- 680 consecutive IBD patients (373 CD, 307 UC) were enrolled from 25 centers
- 400 patients were anti-TNF naive, 171 had a previous exposure and 109 were switched to CT-P13 after a mean of 18 +/- 14 infusions of infliximab
- A total number of over 4,000 infusions were recorded
- One of the largest prospective cohort of IBD patients treated with CT-P13... no signals of difference in safety and clinical efficacy has been observed


Randomized, DB, Phase III Study Conducted in Patients With Moderate to Severe CD

- 220 patients in 58 study centers across 16 countries randomized to CT-P13 or Infliximab
- At Week 6, CDAI-70 response rate of CT-P13 was quite similar to that of Infliximab
- The number of patients with at least one treatment-emergent adverse event (TEAE) showed a similar proportion in the 2 treatment groups

<table>
<thead>
<tr>
<th>Table 1. Efficacy Results at Week 6 for Per-Protocol Population</th>
</tr>
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<tbody>
<tr>
<td></td>
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<td>------------------</td>
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<tr>
<td>CDAI-70 response n (%)</td>
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<td></td>
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<tr>
<td>CDAI-100 response n (%)</td>
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<tr>
<td></td>
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<tr>
<td>Clinical remission n (%)</td>
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</tr>
</tbody>
</table>

*95% confidence interval

Cross-immunogenicity: Antibodies to Infliximab in Remicade-Treated Patients With IBD Similarly Recognize The Biosimilar Remsima

- 125 patients' and controls' sera were tested. All 56 anti-Remicade ATI-negative were also negative for anti-Remsima ATI. All 69 positive anti-Remicade IBD sera were cross-reactive with Remsima. Anti-Remicade ATIs of patients with IBD (n=10) exerted similar functional inhibition on Remsima or Remicade TNF-α binding capacity

- **Conclusions-**
  - Anti-Remicade antibodies in patients with IBD recognize and functionally inhibit Remsima to a similar degree, suggesting similar immunogenicity and shared immunodominant epitopes


Interchangeability

- FDA defines as “Substitution for the reference product by a pharmacist without the intervention of the health care provider who prescribed the reference product”

- No biosimilar in the U.S. yet has **interchangeability** designation
Interchangeability

- No data to support interchangeability
- Break of tolerance and development of immunogenicity which can cause hypersensitivity reactions, neutralization with loss of response and autoimmunity
- Safety surveillance for individual drugs becomes very challenging when making multiple switches

Switching vs. Substitution

[Diagram showing transition study, substitution study (single switch), interchangeability study (multiple switches)]
NOR-SWITCH

482 pts stable on Infliximab for at least 6 months randomized 1:1

- **Main Study**
  - CT-P13
  - Infliximab

- **Open Label Extension**
  - CT-P13

- **W0**
- **W52**
- **W78**

- **Primary Endpoint:** Occurrence of disease worsening at W52
- **Assumptions:**
  - 30% disease worsening in the Infliximab arm
  - Non-inferiority margin: 15%

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Comparable trough serum levels, ADA (Remicade 7.1%, CT-P13 7.9%) and reported adverse events between Remicade and CT-P13

Figure. Occurrence of disease worsening during 52 weeks follow-up, overall and within the diagnoses in the Per Protocol Set.

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Status of U.S. Biosimilars For IBD

- **Biosimilars for Remicade**
  - Inflectra (infliximab-dyyb)
    - FDA approval: April 2016
  - Renflexis (infliximab-abda)
    - FDA approval: April 2017

- **Biosimilars for Humira**
  - Amjevita (adalimumab-atto)
  - Cyletezo (adalimumab-adbm)

Biosimilars Nomenclature

- In August 2015 FDA proposed a rule for naming biosimilars. The names include distinguishing suffixes (devoid of meaning), composed of four random lowercase letters (infliximab-\textit{hjmt}, infliximab-\textit{dyyb} and infliximab-\textit{abda})

- Intention- to avoid inaccurate perception of biosimilars efficacy

- Influences prescribing practice of biosimilars
Practical Considerations For Biosimilars

- Dosing is the same as the reference product
- Prior-authorization is expected to be the same for these agents
- Existing commercial therapeutic drug monitoring (TDM) assays will work with biosimilars
- Anti-drug antibody will cross react between a reference product and its biosimilar (and vice versa)
- No biosimilar in the U.S. yet has interchangeability designation

Clinical Scenarios For Biosimilars Use

<table>
<thead>
<tr>
<th>New Start</th>
<th>Prescriber choice of originator or biosimilar</th>
</tr>
</thead>
</table>
| Primary Nonresponder | Switching to a biosimilar SHOULD NOT BE CONSIDERED because it has the same MOA  
Prescriber should switch to another biologic with a different MOA |
| Stabilized Responder | Prescriber elects to maintain the originator  
Prescriber elects to switch to a biosimilar |
| Loss of Response | If attributed to high ADA titer then switching to a biosimilar SHOULD NOT BE CONSIDERED  
Prescriber should switch to another therapy |
Real Life Experience

CHANGES TO INFliximAB THERAPY OFFERINGS FOR SLHS INFUSION CENTERS – TRANSITION FROM REMICade TO INFLECTRA
GO-LIVE November 1, 2017

IMPORTANT TO KNOW: On November 1, Saint Luke’s Health System (SLHS) will be transitioning to Inflectra as the “preferred” product for patients requiring infliximab therapy in our outpatient infusion centers. For any new patient being initiated on infliximab therapy, providers should order Inflectra (infliximab-dyyb) rather than Remicade (infliximab). Remicade will remain available for only those outpatients already stabilized on Remicade and receiving maintenance therapy in our infusion centers.

Due to lower costs, Inflectra will be the preferred infliximab product for SLHS patients who are being initiated on this therapy. Remicade will remain on formulary for outpatients already stabilized on the drug but eventually will be phased out.

Other Resources

- American Gastroenterological Association- Biosimilars: www.gastro.org/biosimilars
- Crohn’s & Colitis Foundation: Biosimilars- What IBD Patients Should Know: www.crohnscolitisfoundation.org/resources/biosimilars.html
In 2017 CVS will remove several name brand drugs from it’s formulary because, they say, biosimilar generic drugs are just as good.

So, CVS executives should be okay having a biosimilar spouse... right?