Biosimilars

Douglas White, MD, PhD
Gundersen Health System
La Crosse
Biosimilars

- Manufacturing and Drift
- Safety
- FDA Approval and Extrapolation
- Naming and Post-Marketing Surveillance
- Interchangeability and Switching
- Payers, Trump Administration, Courts
The Making of a Biologic

DNA (gene that codes for a mAb)

Immortalized Cell

DNA -> RNA (transcription)
RNA -> protein (translation)
Post-translational modifications
- glycosylation
- methionine oxidation
- deamidation
- disulfide bond modification
- phosphorylation
- others

Many options:
- murine
- human
- CHO (etanercept)
- other

pH
Media
Scale
Temp
O2
Cell density
Osmolality

Efficacy
Stability
Immunogenicity

mAb

Purification
Stabilizers
Precipitation/Aggregation

Precipitation/Aggregation
Drift – Unavoidable in Manufacturing

• Variation, related to altered manufacturing processes, in the structure, efficacy and safety of a biologic

• Drift causes lot-to-lot variability in all biologics
  – even at a single manufacturer
  – including originator infliximab (35x!), etanercept and rituximab

• Potential implications for biosimilars:
  – Failure of a drug to work as intended
  – Less favorable safety profile
    • “biomimics” and “biocopies”
  – Improvements (!) in efficacy and/or safety
    • type-I interferon receptor agonist

In Spite of Drift, Safety Looks Good

• No major post-marketing safety signals in US with originator biologics so far
• Favorable results from biosimilar safety studies
• Development of anti-drug antibodies (ADA) and immunogenicity are comparable between originators and biosimilars
ABSTRACT NUMBER: 19L

Biosimilar Infliximab (CT-P13) Is Not Inferior to Originator Infliximab: Results from a 52-Week Randomized Switch Trial in Norway

Guro Løvik Goll1,2, Inge C Olsen3, Kristin K Jorgensen4, Merete Lorentzen5, Nils Bolstad6, Espen A. Haavardsholm7, Knut EA Lundin8, Cato Mork9, Jorgen Jahnson4, Tore K Kvien3 and the NOR-SWITCH study group, 1Dept of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, 2Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, 3Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, 4Dept of Gastroenterology, Akershus University Hospital, Lorenskog, Norway, 5Dept of Dermatology, Rikshospitalet, Oslo, Norway, 6Department of Medical Biochemistry, OUS-Radiumhospitalet, Oslo, Norway, 7Diakonhjemmet Hospital, Oslo, Norway, 8Dept of gastroenterology, Rikshospitalet, Oslo, Norway, 9Dept of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway

Meeting: 2016 ACR/ARHP Annual Meeting
Date of first publication: October 22, 2016
Keywords: biosimilars, Clinical Response, infliximab, Late-Breaking 2016, randomized trials and treatment
Trough drug levels and the frequencies of reported adverse events including infusion reactions were similar (data not shown).
A Cautionary Tale

- Recombinant Human Erythropoietin
  - Anemia of chronic kidney disease
  - European Union, not US
  - Originator drug (not a biosimilar)
- 1998 SQ use associated with increase in PRCA
- Definitive cause “still being discussed”
- Manufacturing changes -> altered immunogenicity
  - Stabilizer (polysorbate-protein instead of human-serum albumin)
  - Packaging (pre-filled syringe with leachables in the rubber stopper might have acted as an adjuvant)
- Patients mount an antibody response against erythropoietin
- After these factors were remedied, the number of cases decreased by 90%

- ACR Biosimilars Position Statement
### Table 3: Efficacy of infliximab and CT-P13 in relation to ADA status

<table>
<thead>
<tr>
<th>Disease (response criteria)</th>
<th>Treatment</th>
<th>Response rate (%)&lt;sup&gt;‡&lt;/sup&gt;</th>
<th>ADA-negative patients</th>
<th>ADA-positive patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CT-P13 5mg/kg</td>
<td>61.0</td>
<td>37.9</td>
<td></td>
</tr>
<tr>
<td>AS (ASAS40)</td>
<td>Infliximab 5mg/kg</td>
<td>54.7</td>
<td>36.4</td>
<td></td>
</tr>
<tr>
<td>RA (ACR20)</td>
<td>Methotrexate + CT-P13 (3mg/kg)</td>
<td>73.9</td>
<td>53.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methotrexate + infliximab (3mg/kg)</td>
<td>67.2</td>
<td>48.1</td>
<td></td>
</tr>
</tbody>
</table>

<sup>‡</sup> More ADA-negative patients achieved ASAS40 or ACR20 responses compared with ADA-positive patients.

<sup>‡</sup> Results from the PLANETAS and PLANETRA studies. <sup>14,15</sup> Abbreviations: ACR20, 20% response by ACR criteria; ADA, antidrug antibody; AS, ankylosing spondylitis; ASAS40, 40% response by Assessment of Ankylosing Spondylitis International Society criteria; RA, rheumatoid arthritis.
Immunogenicity: Biosimilars Match Originator

**Figure 3** | ADA induction after treatment with infliximab or CT-P13. Comparative induction of ADAs against reference infliximab and CT-P13 in patients with ankylosing spondylitis (left) and rheumatoid arthritis (right) during two clinical studies (PLANETAS and PLANETRA, respectively). ADAs were assessed by electrochemical-luminescent immunoassay technology (Meso Scale Discovery). Abbreviation: ADA, antidrug antibody.

Dorner & Kay 2015 Nat Rev Rheum
Biosimilars Are More Complex than Generics

Figure 4. Comparison of the small-molecule drug aspirin and biologic products

- **Small Molecule Drug**
  - Aspirin
  - 21 atoms

- **Small Biologic**
  - Human Growth Hormone
  - ~3000 atoms

- **Large Biologic**
  - Monoclonal antibody
  - ~25,000 atoms

INCREASING COMPLEXITY

www.hospira.es/en/about_hospira/biologics/biosimilars_generic_drugs
Separate Approval Pathways

**Small-Molecule Generics**
- Less complex
- Regulated by Federal FDC Act
- Abbreviated approval via Hatch-Waxman amendments in 1984

**Biosimilars**
- Vastly more complex
- FDA experience since 1980’s (recombinant insulin, hGH)
- Regulated by the PHS Act
- Abbreviated approval via Biologics Price Competition and Innovation Act

> “Congress has left FDA and the courts considerable latitude in defining these terms.”¹

.Framework:
- Part of the ACA 2010
- Defines key terms
  - Biosimilar
  - Interchangeable

Abbreviated Approval of CT-P13 in the US

- Had already been approved in 66 countries
- >23k patient-years of experience as of July 2015

Data Review

Feb 2016
Arthritis Committee

Apr 2016
Full FDA

Approved with Extrapolation
Several Layers of Data Are Required by the FDA for Biosimilar Approval
FDA Approval of CT-P13 (Infliximab-dyyb)

• Two clinical trials paved the way:
  – PLANETRA
    • 606 adults with RA from 19 countries in Europe, Asia, Latin America, Middle East
  – PLANETAS
    • 250 adults with Ank Spond from 10 countries in Europe, Asia and Latin America

• Extrapolated to psoriasis, PsA, UC (adult only), CD, ped CD
• Arthritis Advisory Committee - not allowed to vote by disease, rather asked to approve for all indications or reject
• Once licensed, a biosimilar loses status at the FDA and would have to go through normal channels for additional indications
## FDA-Approved Biosimilars in the US

<table>
<thead>
<tr>
<th>Name</th>
<th>Manufacturer</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>filgrastim-sndz</td>
<td>Sandoz</td>
<td>5/6/2015</td>
</tr>
<tr>
<td>infliximab-dyyb*</td>
<td>Celtrion</td>
<td>4/5/2016</td>
</tr>
<tr>
<td>etanercept-szms*</td>
<td>Sandoz</td>
<td>8/30/2016</td>
</tr>
<tr>
<td>adalimumab-atto*</td>
<td>Amgen</td>
<td>9/23/2016</td>
</tr>
</tbody>
</table>

*Complete or near-complete extrapolation
*Random suffixes
What’s with the Funny Suffixes?

• Push by biosimilar manufacturers for identical names (to match originator) to improve market uptake
  – Some support from FTC (competition)

• ACR and other groups argued successfully for unique names to allow for pharmacovigilance (post-marketing surveillance)

• Final FDA guidance announced Jan 12, 2017
  – Unique suffixes (originators too)
  – Random, non-meaningful, non-memorable
  – Aligns with WHO
Can They “Switch” My Patient?

• **Switching** – prescriber changes the drug
• **Substitution** – someone other than prescriber changes the drug (FDA-preferred terminology)
• **Interchangeable** – status granted to a biosimilar by the FDA that allows substitution
  – No biosimilars are interchangeable in the US (yet)
  – Substitution of interchangeable biosimilars is regulated by state law
  – Draft FDA guidance for establishing interchangeability was released Jan 2017 (triple switch studies proposed)

• **Non-Medical Switching** aka Payer Substitution – formulary changes that force patients to switch, even when no medical indication for switching exists
Themes in State Biosimilar Legislation

STATE LAWS AND LEGISLATION RELATED TO BIOLOGIC MEDICATIONS AND SUBSTITUTION OF BIOSIMILARS

11/15/2016

Richard Cauchi

For several decades, every state has regulated the use of brand-name and generic prescription drugs through statutes and agency or board rules. These state actions include when and how generics may be substituted for brand-name prescriptions, by pharmacists or others. Generic drugs typically have active ingredients that are identical to those of their brand-name counterpart. These traditional drugs include familiar pills used regularly by tens of millions of Americans as well as some specialty drugs.

Biologic medicines are much more complex than traditional chemically synthesized drugs. Biologics are manufactured from living organisms by programming cell lines to produce the desired therapeutic substances and consist of large molecules. Common biologics in use today include injectable treatments for arthritis, medicines for cancer, diabetes, Crohn's disease, psoriasis, the Hepatitis B vaccine and pending stem cell therapies.

TABLE OF CONTENTS

"Right to Try" State Actions
Typical Features of State Legislation
2013 – 2016 State Laws
Mandatory Prescription Drug Substitution Laws
Recent news - 2015-16
"Right to Try" State Actions
Appendix: Definitions

RESOURCES

Biosimilars PDF edition

Themes in State Biosimilar Legislation

Notification:
• Most bills specify 5 business days (after substitution)
• No state bills call for advanced or immediate notification
• Generally, notification will be made through an EHR. If not available, then fax, phone, email etc.

Mandatory Substitution:
• Some states appear to mandate dispensation by cost

DAW:
• Many states have provisions to write “dispense as written” or “brand medically necessary” to prevent substitution
How Are Payers Responding?

Outside Rheumatology:
• CVS and UHC formularies for 2017:
  – Brand name G-CSF is out, biosimilar filgastrim-sndz is in
  – Brand name insulin glargine is out, biosimilar is in

Rheumatology:
• Ascension proposal – Infliximab-dyyb preferred
• UHC policy – Remicade preferred
Ascension Proposal

Operate 141 hospitals in 24 states

Measure of Success
- Elimination of Remicaide use

To: Office of the President
    Solutions Subsidiary Leaders
    Leadership Community Council
    Clinically Integrated Operating Community
    Ministry Operating Executives
    Ascension Medical Group Dyad Leaders

cc: Chief Clinical Officers
    Chief Medical Officers
    Chief Nursing Officers
    Chief Information Officers
    Pharmacy Directors

From: Roy Guharoy, PharmD, MBA
      Vice President, Clinical Integration, Chief Pharmacy Officer

      Greg James, MD, MBA
      Co-Chair, Care Excellence Committee

Date: December 21, 2016

Subject: Comment Period for Therapeutic Clinical Directives
Policy Update

• Beginning April 1, 2017, Remicade will be the preferred infliximab product for UnitedHealthcare®.

• UnitedHealthcare® will require both new and current commercial members, who are receiving infliximab therapy, to use Remicade.

• Members who are...currently using Inflectra™, will be required to...transition to Remicade to continue benefit coverage....
Which Path for Manufacturers?
Trump Administration

• Repealing the ACA
• Many new appointments (FDA, HHS, CMS) with broad latitude to (re-)interpret regulations
• Funding to prevent backlogs at FDA (BsUFA II)
• New Executive Orders (ex. EO January 30, 2017)
  – For every new regulation, must eliminate 2 old ones
  – Encourage housecleaning
  – Will reduce the number of rules, but the rules will get bigger
  – May impact FDA regs around interchangeability and naming
  – Opportunity for ACR to influence what regulations are retired
RheumPAC
Advocacy Is a Joint Effort.
Patent Litigation: The Last Hurdle?

- I don’t even pretend to understand
- July 2015: United States Court of Appeals for the Federal Circuit (located in Wash DC) ruled on Amgen v Sandoz
- Dec 2016: Supreme Court refused to hear Amgen v Apotex ("patent dance")
- Jan 2017: Supreme Court agreed to hear Amgen v Sandoz
- Expected arguments in Apr, decision in June
- Stay tuned....