Biosimilars: Something New or Déjà Vu?

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Disclosures

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Overview

• Definitions
  • Biosimilars
  • Biomimics

• Biosimilars for inflammatory diseases

• Biopharmaceuticals
  • Structure
  • Changes in manufacture

• Regulatory aspects
  • Clinical trials
  • Extrapolation of indications
  • Immunogenicity
  • Interchangeability

• Economic aspects
Biosimilarity and Biosimilars

• Regulatory definition of biosimilarity (United States)
  • “The biologic product is highly similar to the reference product notwithstanding minor differences in clinically inactive components,” and
  • “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”

• A biosimilar is a legitimate copy of a biopharmaceutical that no longer is protected by patent, which has:
  • Undergone rigorous analytical and clinical assessment, in comparison to its reference product, and
  • Been approved by a regulatory agency according to a specific pathway for biosimilar evaluation

# Current State of Biosimilars Market

<table>
<thead>
<tr>
<th>Class</th>
<th>Reference Drug</th>
<th>European Union</th>
<th>United States</th>
<th>Canada</th>
<th>Australia</th>
<th>Japan</th>
<th>South Korea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythropoiesis-stimulating agents</td>
<td>epoetin alfa (Eprex®)</td>
<td>5</td>
<td></td>
<td>3</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>darbepoetin alfa (Aranesp®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granulocyte-colony stimulating factor</td>
<td>filgrastim (Neupogen®)</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Human growth hormone</td>
<td>somatropin (Genotropin®)</td>
<td>1</td>
<td></td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Follicle-stimulating hormone</td>
<td>follitropin alfa (Gonal-F®)</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF Inhibitors</td>
<td>infliximab (Remicade®)</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>etanercept (Enbrel®)</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>adalimumab (Humira®)</td>
<td>4</td>
<td>2</td>
<td></td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Insulins</td>
<td>insulin glargine (Lantus®)</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>insulin lispro (Humalog®)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>enoxaparin sodium (Lovenox®)</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N-terminal parathyroid hormone</td>
<td>teriparatide (Forteo®)</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-CD20 monoclonal antibody</td>
<td>rituximab (Rituxan®, MabThera®)</td>
<td>6</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>HER2 receptor inhibitor</td>
<td>trastuzumab (Herceptin®)</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>VEGF-A inhibitor</td>
<td>bevacizumab (Avastin®)</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td><strong>41</strong></td>
<td><strong>9</strong></td>
<td><strong>6</strong></td>
<td><strong>16</strong></td>
<td><strong>10</strong></td>
<td><strong>9</strong></td>
</tr>
</tbody>
</table>

Biosimilars for Inflammatory Diseases Approved by EMA & FDA


*Positive CHMP opinion. Pending EC decision.
What Is a Biomimic?

• A “biomimic” (or “intended copy”) is a replica of a biopharmaceutical that is *not* developed, assessed, or approved according to regulatory guidelines for biosimilars
  • Similarity *not* demonstrated by a stepwise and comprehensive comparability exercise
  • May have *differences* in primary structure from bio-originator
  • May *differ* from bio-originator in formulation, doses/dosing regimen, efficacy, safety, and immunogenicity, which may result in clinically significant differences
Marketed “Biomimics” Based On Biologic Agents Used to Treat Inflammatory Diseases

<table>
<thead>
<tr>
<th>Drug*</th>
<th>Manufacturer (location)</th>
<th>Marketed in</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rituximab biomimics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reditux™</td>
<td>Dr. Reddy’s Laboratories (India)</td>
<td>Bolivia, Chile, Ecuador, India, Paraguay, &amp; Peru</td>
</tr>
<tr>
<td>Novex®</td>
<td>Laboratorio Elea (Argentina)</td>
<td>Argentina &amp; Paraguay</td>
</tr>
<tr>
<td>Kikuzubam™</td>
<td>Probiomed (Mexico)</td>
<td>Withdrawn in March 2014 Bolivia, Chile, Mexico, &amp; Peru</td>
</tr>
<tr>
<td><strong>Etanercept biomimics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yisaipu®</td>
<td>Shanghai CP Goujian Pharmaceutical Co. (China)</td>
<td>China</td>
</tr>
<tr>
<td>Etanar™</td>
<td>Shanghai CP Goujian Pharmaceutical Co. (China)</td>
<td>Colombia</td>
</tr>
<tr>
<td>Etacept™</td>
<td>Shanghai CP Goujian Pharmaceutical Co. (China)</td>
<td>India</td>
</tr>
<tr>
<td>Etart™</td>
<td>Shanghai CP Goujian Pharmaceutical Co. (China)</td>
<td>Mexico</td>
</tr>
<tr>
<td>Infinitam™</td>
<td>Probiomed (Mexico)</td>
<td>Mexico</td>
</tr>
<tr>
<td>Altebrel™</td>
<td>AryoGen Biopharma (Iran)</td>
<td>Iran</td>
</tr>
</tbody>
</table>

Manufacturing Process for Bio-Originators & Biosimilars

Cloning into DNA Vector
- Possibly same gene sequence
- Probably different vector
- Different cell expression system

Transfer into Host Cell Expression
- Screening / Selection

Cell Expansion
- Different cell line, growth media, method of expansion

Cell Production in Bioreactors
- Different cell line, growth media, bioreactor conditions

Recovery through Filtration or Centrifugation
- Different operating conditions

Purification through Chromatography
- Different binding and elution conditions

Characterization and Stability
- Different methods, reagents, reference standards

Goals of “Stand-alone” and Biosimilar Development Are Different

“Stand-alone” Development Program, 351(a)  
Goal: To establish safety and efficacy of a new product

“Abbreviated” Development Program, 351(k)  
Goal: To demonstrate biosimilarity

“FDA intends to use a risk-based, totality-of-the-evidence approach to evaluate all available data and information submitted in support of the biosimilarity of the proposed product.”

All Biologics (Bio-originators & Biosimilars) Are Subject to Variability

Variability Can Be Due to Changes in

- Protein-folding variants
- Misfolding
- Aggregation
- Enzymatic cleavage
- Degradation
- Glycosylation
- Disulfide bond formation
- Phosphorylation
- Deamidation
- Oxidation
- Amino acid substitution
- Other

Biologics: Variability, Drift, & Evolution

• Normal batch-to-batch variability
  • Proven acceptable ranges (PARs) of variation are established during development
  • Product is monitored to assure that variation in quality attributes is within PARs
  • Does not pose safety or efficacy risk to patients

• Drift
  • Unintended alterations in manufacturing process result in deviation of product attributes over time

• Evolution
  • Deliberate process changes made by manufacturer & regulators for the manufacture of the drug substance and drug product
  • Changes to regulatory approval (e.g., technology, scale up production)
  • Changes are made to address deviations (trend) or a sudden deviation (shift)

Commercial Lots of Bio-originators Are Not Identical

- Small modifications in manufacturing processes may result in gradual changes
- Chemical characterization of different commercial lots of etanercept and rituximab produced between 2007 and 2011 revealed variations in both C-terminal lysine content & glycosylation

- Despite these differences, when product is within pre-specified proven acceptable ranges (PARs) of variation, it is marketed with no change in label

Changes in Bio-originator Manufacturing Process Result in Differences Compared to Initially Approved Product

Comparison of Pre- and Post-Change Batches of Rituximab

- Approximately 3-fold increase in nonfucosylated G0 glycans in later batches of rituximab resulted in more potent ADCC

ADCC = antibody-dependent cell-mediated cytotoxicity.
Biosimilar Development Goal:
Develop Product Highly Similar to Reference Product

Exercise to Claim Biosimilarity Must Demonstrate Equivalence within Prespecified Margins

Development of Biosimilars – Time Axis

Initial reference product quality range

Current reference product quality range

Reference product quality range over time

Range for control of biosimilar product

Demonstrating Biosimilarity: General Principles

• Biosimilar has been shown to be highly similar to reference product in extensive comparative analytical studies

• Biosimilar must demonstrate similar efficacy and safety, compared to reference product
  • PK/PD, and immunogenicity studies
  • Smaller, double-blind, parallel-group, active comparator clinical trial(s)

• No differences in safety or efficacy are expected between an approved biosimilar and its reference product

• Extrapolation of indications
  • Clinical efficacy and safety have already been demonstrated by reference product
  • No need to demonstrate efficacy of biosimilar in all indications
Analytical Characterization Methods for TNF Inhibitor Biosimilar

MOA = mechanism of action.
Infliximab-dyyb: An Approved Biosimilar Is Like Another Batch of Its Reference Product

Phase 1 Double-Blind RCT of Infliximab-dyyb (CT-P13) vs Infliximab Originator in Ankylosing Spondylitis

- 250 patients with active AS randomized 1:1 to receive either infliximab-dyyb or infliximab originator (5 mg/kg 2-hour IV infusion per dose)
  - Dose-loading phase: Weeks 0, 2, & 6
  - Maintenance phase: Weeks 14, 22, & 30
- Assessments
  - Ratios of geometric means of primary PK parameters between Weeks 22-30 were subjected to ANCOVA analysis at 90% CIs
  - ASAS20 & ASAS40 at Week 30
  - Safety (incidence of AEs)
- Primary endpoint: Ratio of geometric means of PK parameters in infliximab-dyyb & infliximab originator arms (Weeks 22-30)
  - AUC$_T$: 1.05 (90% CI 0.94 to 1.16)
  - C$_{max,ss}$: 1.02 (90% CI 0.95 to 1.09)

AS = ankylosing spondylitis; IV = intravenous; AE = adverse event.
Phase 3 Double-Blind RCT of CT-P13 vs Infliximab Originator in Rheumatoid Arthritis

- 606 patients with active RA despite previous DMARDs randomized 1:1 to receive either CT-P13 or Remicade (3 mg/kg 2-hour IV infusion per dose) + MTX & folic acid
  - Dose-loading phase: Wks 0, 2, & 6
  - Maintenance phase: Wks 14, 22, & 30
- Primary endpoint: Proportion of patients achieving ACR20 at week 30
  - Equivalence between treatments defined using exact binomial test with 95% CIs within margin of ±15%
- Secondary endpoints
  - ACR50/70
  - Incidence of AEs

RA = rheumatoid arthritis; IV = intravenous; AE = adverse event.
Patterns of Pharmacodynamic Response Over Time

• Demonstration of equivalent clinical responses during early, steep phase of time-response curve provides additional information on biosimilarity
  • Earlier portion of time-response curve affords greater sensitivity to detect differences in efficacy between study drugs than does plateau phase
  • Assessment of response to therapy over first 3 months of treatment allows comparison of rapidity of onset

Phase 3 Double-Blind RCT of SB4 vs Etanercept Originator in Rheumatoid Arthritis

- 596 patients with active RA despite MTX randomized 1:1 to receive either SB4 or etanercept originator SC weekly + MTX & folic acid for up to 52 weeks
- Primary endpoint: Proportion of patients achieving ACR20 at week 24
  - Equivalence between treatments: 95% CI of difference of ACR20 response rates between treatment groups had to be entirely contained within margin of ±15%
- Secondary endpoints
  - ACR50/70, ACR-N, AUC of ΔDAS28, EULAR response
  - Incidence of AEs and SAEs

Related TEAEs (to Week 24)

<table>
<thead>
<tr>
<th></th>
<th>SB4 (n=299)</th>
<th>Etanercept originator (n=297)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>83 (27.8%)</td>
<td>106 (35.7%)</td>
</tr>
<tr>
<td>Serious TEAEs</td>
<td>13 (4.4%)</td>
<td>13 (4.4%)</td>
</tr>
<tr>
<td>Injection site reactions (ISRs)*</td>
<td>22 ISRs in 11 pts (3.7%)</td>
<td>156 ISRs in 51 pts (17.2%)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*P<.001

ACR Response Rates to Week 24

RA = rheumatoid arthritis; SC = subcutaneous; EULAR = European League Against Rheumatism; TEAE = treatment-emergent adverse event.

Biosimilars: Extrapolation of Indications

• Extrapolation of data from a clinical trial of biosimilar conducted in one disease may be used to support approval for additional indications for which reference product is already licensed

• In which inflammatory disease(s) should a biosimilar be studied to provide adequate information for extrapolation of indications?

  • Rheumatoid arthritis
  • Juvenile inflammatory arthritis
  • Ankylosing spondylitis
  • Psoriatic arthritis

  • Psoriasis
  • Inflammatory bowel disease
    • Crohn’s disease
    • Ulcerative colitis
Biosimilars: Differential Immunogenicity

• **Greater immunogenicity** of proposed biosimilar, compared to reference product, would question biosimilarity

• **Lower immunogenicity** of proposed biosimilar would not preclude biosimilarity (eg, SB4 vs ETN: 0.7% vs 13.1% antidrug antibodies + to week 24)
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—

“(3) The term ‘interchangeable’ or ‘interchangeability’, in reference to a biological product that is shown to meet the standards described in subsection (k)(4), means that the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.
Demonstrating Interchangeability of a Biosimilar with a Reference Product: FDA Draft Guidance

• Postmarketing data

• Data from prospective, controlled switching study (or studies)
  • Design
    • Lead-in period of treatment with reference product followed by randomized two-arm period (switching arm vs non-switching arm)
    • At least three switches, with each switch crossing over to alternative product
  • Analysis
    • Primary endpoints: PK data ($C_{\text{max}}, T_{\text{max}}, C_{\text{trough}}, \text{AUC}_t$)
    • Secondary endpoints: Safety, immunogenicity, and efficacy
  • US-licensed reference product as comparator

Study Designs Comparing Bio-originators & Biosimilars

Transition study
Transition arm

- Bio-originator
- Biosimilar

Biosimilar treatment arm

- Biosimilar

Interchangeability study (multiple switches)
Switching arm

- Bio-originator
- Biosimilar
- Bio-originator
- Biosimilar

Non-switching arm

- Bio-originator

Phase 3 Double-Blind RCT of Etanercept-szzs (GP2015) vs Etanercept Originator in Psoriasis

Phase 3 RCT of Etanercept-szzs (GP2015) vs Etanercept Originator in Psoriasis

Adjusted PASI Response Rates for Continued vs Switched Treatment Groups (PPS)

PASI = Psoriasis Area and Severity Index.
Switching: European Experience
NOR-SWITCH: Continuing Infliximab Originator vs Switching to Infliximab-dyyb

- 52-week randomized, double-blind, non-inferiority phase IV trial

- Primary endpoint: Disease worsening* during 52-week follow-up
  
  *According to worsening in disease-specific composite measures and/or a consensus between investigator & patient leading to major change in treatment.

- Noninferiority margin: 15%

- Exploratory subgroup analyses: Disease worsening within each of the 6 diagnoses

NOR-SWITCH: Forest Plot of Risk Difference According to Disease

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Infliximab originator n=202</th>
<th>Infliximab-dyyb n=202</th>
<th>Risk difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn’s disease</td>
<td>14 (21.2%)</td>
<td>23 (36.5%)</td>
<td>-14.3% (-29.3 – 0.7)</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>3 (9.1%)</td>
<td>5 (11.9%)</td>
<td>-2.6% (-15.3 – 10.0)</td>
</tr>
<tr>
<td>Spondyloarthritis</td>
<td>17 (39.5%)</td>
<td>14 (33.3%)</td>
<td>6.3% (-14.5 – 27.2)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>11 (36.7%)</td>
<td>9 (30.0%)</td>
<td>4.5% (-20.3 – 29.3)</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>7 (53.8%)</td>
<td>8 (61.5%)</td>
<td>-8.7% (-45.4 – 28.1)</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>1 (5.9%)</td>
<td>2 (12.5%)</td>
<td>-6.7% (-26.7 – 13.2)</td>
</tr>
<tr>
<td>Overall</td>
<td>53 (26.2%)</td>
<td>61 (29.6%)</td>
<td>-4.4% (-12.7 – 13.2)</td>
</tr>
</tbody>
</table>

NOR-SWITCH: Similar Immunogenicity with & without Switching

Antidrug antibodies to infliximab originator and infliximab-dyyb were analyzed with in-house inhibition assays that only measure neutralizing antibodies. Antidrug antibodies were not analyzed in samples with concentrations of drug >5 mg/L because high drug concentrations cause interference in the assays for antidrug antibodies.

NOR-SWITCH: Similar Treatment-Emergent Events in Safety Population with & without Switching

<table>
<thead>
<tr>
<th></th>
<th>Infliximab originator (n=241)</th>
<th>Infliximab-dyyb (n=240)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUSAR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serious AE</td>
<td>32/24 (10%)</td>
<td>27/21 (9%)</td>
</tr>
<tr>
<td>AE</td>
<td>422/168 (70%)</td>
<td>401/164 (68%)</td>
</tr>
<tr>
<td>AE resulting in study drug discontinuation*</td>
<td>18/9 (4%)</td>
<td>9/8 (3%)</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>10/10 (4%)</td>
<td>5/4 (2%)</td>
</tr>
</tbody>
</table>

Data are number of events/number of patients (%)

* Patients could have other primary reason for study drug discontinuation.
SUSAR = serious unexpected serious adverse reaction.
### Outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RA (n=403)</th>
<th>Changes Over Time</th>
<th>PsA (n=120)</th>
<th>Adjusted absolute 1-year retention rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Δ Pre-switch</td>
<td>Δ Postswitch</td>
<td>p Value</td>
</tr>
<tr>
<td>DAS28</td>
<td>(n=276)</td>
<td>0.1 (-0.2 to 0.5)</td>
<td>0.0 (-0.4 to 0.4)</td>
<td>0.8</td>
</tr>
<tr>
<td>HAQ (0-3)</td>
<td>(n=265)</td>
<td>0.0 (0.0-0.1)</td>
<td>0.1 (-0.1 to 0.1)</td>
<td>0.3</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td></td>
<td>0 (-1 to 2)</td>
<td>0 (-2 to 3)</td>
<td>0.4</td>
</tr>
<tr>
<td>Patient’s VAS global score, mm</td>
<td></td>
<td>0 (-7 to 9)</td>
<td>0.046</td>
<td></td>
</tr>
<tr>
<td>PsA (n=120)</td>
<td></td>
<td>-3 (-12 to 4)</td>
<td>0 (-7 to 11)</td>
<td>0.01</td>
</tr>
<tr>
<td>DAS28</td>
<td>(n=81)</td>
<td>(n=169)</td>
<td>-0.4 to 0.6</td>
<td>0.10</td>
</tr>
<tr>
<td>HAQ (0-3)</td>
<td></td>
<td>0 (0.0-0.1)</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td></td>
<td>0 (-1 to 2)</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>Patient’s VAS global score, mm</td>
<td></td>
<td>0 (-7 to 9)</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>AxSpA (n=279)</td>
<td></td>
<td>0 (-4 to 5)</td>
<td>0 (-4 to 7)</td>
<td>0.3</td>
</tr>
<tr>
<td>BASDAI, mm</td>
<td>(n=60)</td>
<td>0 (-4 to 5)</td>
<td>0 (-4 to 7)</td>
<td>0.3</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td></td>
<td>0 (-1 to 1)</td>
<td>0 (-1 to 2)</td>
<td>0.2</td>
</tr>
<tr>
<td>Patient’s VAS global score, mm</td>
<td></td>
<td>1 (-4 to 8)</td>
<td>-1 (-7 to 7)</td>
<td>0.7</td>
</tr>
<tr>
<td>ASDAS</td>
<td>(n=169)</td>
<td>0.0 (-0.3 to 0.4)</td>
<td>0.0 (-0.3 to 0.3)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Numbers are medians (interquartile ranges) unless otherwise stated (%)

**VAS** = visual analogue scale.


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**Adjusted absolute 1-year retention rates**

- **Infliximab-dyyb: 83.4% (95% CI 80.8 to 86.2)**
- **Historical IFX originator cohort: 86.8% (95% CI 84.8 to 88.8)**

* p=0.03
Nocebo Effect

• Nocebo = “I will harm” (Latin)
• Symptoms and/or physiological changes that follow administration of an inert, chemically inactive substance that patient believes to be an active drug
• Refers to distressing symptoms that accompany placebo administration in ~25%
• May also account for side effects experienced by patients taking an active drug
• Misattribution of bodily symptoms to a drug is more likely to occur in:
  • Patients who expect to experience distressing side effects
  • Patients who have experienced side effects to other drugs in the past
  • Patients with anxiety, depression, and somatization
  • Patients with erroneous information and misunderstandings about drug
• Address by education; avoid imparting negative expectations about a drug; open, collaborative discussion; reassurance; and encouragement of patient

BIO-SWITCH: Biosimilar Discontinuation Due to Subjective Outcomes

• Multicenter, prospective cohort study of 192 patients (75 RA, 50 PsA, 67 AS) switched from infliximab to infliximab-dyyb
• Patients informed by brief letter followed by phone call
• Discontinuation rate within 6 months of switch: 24%
• No change in DAS28-CRP score from baseline to 6 months
  • 2.2 (SD 0.9) to 2.2 (SD 0.8), ∆ = 0 (95% CI: -0.1 to 0.2)
• Increase in BASDAI score from baseline to 6 months
  • 3.8 (SD 2.0) to 4.3 (SD 2.1), ∆ = +0.5 (95% CI: 0.1 to 0.9)
• Nocebo effect: Increases in DAS28 due to subjective assessments (TJC, patient global disease activity); not to changes in objective measures (SJC, CRP)

BIO-SPAN: BIOsimilar Switch - Study on Persistence & Role of Attribution & Nocebo

- 625 pts (433 RA, 128 PsA, 64 axSpA) in Netherlands agreed to open label nonmandatory transition from etanercept originator to SB4 with structured communication strategy
  - All patients informed that lower costs & fewer injection site reactions were reason for transitioning
  - Rheumatology & pharmacy staff trained how to counsel pts about biosimilars & how to discuss possible nocebo response
- Compared to historical cohort of 600 etanercept originator-treated patients (67% included in both cohorts)
- Primary outcome: Adjusted hazard ratio (HR) between SB4 discontinuation in transition cohort & etanercept originator discontinuation in historical cohort = 1.57 (95% CI 1.05 to 2.36)
  - Crude 6-month etanercept originator retention rate in historical cohort = 92% (95% CI 90% to 94%)
  - Crude 6-month SB4 retention rate in transition cohort = 90% (95% CI 88% to 93%)

Legislation on Biologics & Biosimilar Substitution: 2013-2018

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See NCSL reports for details at www.ncsl.org


- Any biologic product under consideration for substitution must first be approved as “interchangeable” by FDA
- Prescriber would be able to prevent substitution by stating “dispense as written” or “brand medically necessary”
- Notification
  - Prescriber must be notified of any allowable substitution made at a pharmacy
  - Patient must be notified that a substitution or switch has been made
    - In some states, patient consent would be required before any such switch is made
- Documentation
  - Pharmacist and prescriber must retain records of substituted biologic medications
  - State must maintain a public or Web-based list of permissible interchangeable products
- Legislation in some states
  - Requires pharmacist to explain cost or price of reference biologic and interchangeable biosimilar to patient
  - Provides immunity for pharmacists who make a substitution in compliance with state law

Nonproprietary Naming of Biologic Products

• Specific nomenclature should clearly identify biologic products to:
  • Improve pharmacovigilance
  • Differentiate among biologic products that have not been determined to be interchangeable

• All biologic products (bio-originators and biosimilars) will have a nonproprietary name that includes a unique suffix composed of four lowercase letters that is devoid of meaning
  • Example: For products sharing core name *infliximab*, proper names will be:
    • infliximab-hjmt (Remicade)
    • infliximab-dyyb (Inflectra™)
    • infliximab-abda (Renflexis™)

• Naming convention is applicable to both previously licensed and newly licensed biologic products

Justification for Biosimilars

• The potential risk to the individual of switching to a lower-cost biosimilar should be outweighed by the potential benefit to society of expanding access to care for all
Potential Benefits of Biosimilars

• Availability of biosimilars should decrease cost of treating patients

• Lower-priced biosimilars introduce market competition
  • Provoke discounts & rebates for bio-originators
  • Multiple biosimilars of same reference product drive price down

• Biosimilars should be more readily available to patients for whom the bio-originator had been inaccessible

• Greater global access to effective biopharmaceuticals should reduce disability, morbidity, and mortality associated with inflammatory diseases

Impact of Biosimilar Competition in Europe

“The increased competition resulting from biosimilars entering the market affects not just the price of the respective biosimilar’s reference product, but also the price of the whole product class. It can have almost as large an impact on the total market price as it has on the biosimilar/reference product price.”

Infliximab Biosimilars for RA in Norway

2014 Norwegian national hospital tender for biologicals:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost NOK</th>
<th>Cost US$</th>
<th>Discount c/w Remicade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab (Remicade)</td>
<td>84,787</td>
<td>14,131</td>
<td>---</td>
</tr>
<tr>
<td>Infliximab (Inflectra)</td>
<td>56,987</td>
<td>9,497</td>
<td>32%</td>
</tr>
<tr>
<td>Infliximab (Remsima)</td>
<td>51,588</td>
<td>8,598</td>
<td>39%</td>
</tr>
</tbody>
</table>

Based upon 75 kg patient treated with infliximab 3 mg/kg iv q8 weeks

2015 Norwegian national hospital tender for biologicals:
69% price reduction for Remsima compared to Remicade

Graph kindly provided by Prof. TK Kvien.
Comparison of US Biosimilar & Generic Drug Average Share of Sales & Price Discount (6 Months after Launch)

<table>
<thead>
<tr>
<th></th>
<th>Price discount vs originator</th>
<th>Share of sales vs originator*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic Drug Average</td>
<td>≥40%</td>
<td>≥75%</td>
</tr>
<tr>
<td>filgrastim-sndz</td>
<td>15%</td>
<td>~10%</td>
</tr>
<tr>
<td>infliximab-dyyb</td>
<td>15%</td>
<td>~2%</td>
</tr>
<tr>
<td>Infliximab-abda</td>
<td>35%</td>
<td>???</td>
</tr>
</tbody>
</table>

*Does not include rebates or other contracted reductions.

Average Selling Price (ASP) of Infliximab-dyyb Decreased in 2017 While ASP of Reference Product Increased

Centers for Medicare and Medicaid CMS Medicare Part B Drug Average Sales Price Report
(updated December 12, 2017)

| Quarter | infliximab (Remicade) | infliximab-dyyb (Inflectra) |
|---------|-----------------------|-----------------------------
| Q1 17   | $946                  | $776                       |
| Q2 17   | $946                  | $807                       |
| Q3 17   | $809                  | $809                       |
| Q4 17   | $822                  | $753                       |
| Q1 18   | $810                  | $738                       |

*Q1 2017 and Q2 2017 reflect Wholesale Acquisition Cost (WAC) for infliximab-dyyb; first ASP for infliximab-dyyb became available in Q3 2017.

Discounts & Rebates

• Reference product manufacturer reduces price through discounts & rebates to lower than biosimilar price

• If payer designates lower-priced reference product as being preferred over biosimilar(s), then competition is stifled

• If biosimilar manufacturer cannot gain market share & withdraws from market → reference product price likely will rise

• Payer may need to purchase biosimilar at slightly higher acquisition price to preserve competitive market
The “Rebate Trap”

<table>
<thead>
<tr>
<th></th>
<th>Pre-Biosimilar</th>
<th>Post-Biosimilar 50% of Patients Switch</th>
<th>100% of Patients Switch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference biologic list price, US $</td>
<td>50 000</td>
<td>50 000</td>
<td>50 000</td>
</tr>
<tr>
<td>Reference biologic postrebate price, US $</td>
<td>25 000</td>
<td>NA (no longer offering rebate)</td>
<td>NA (no longer offering rebate)</td>
</tr>
<tr>
<td>Biosimilar price, US $</td>
<td>NA</td>
<td>10 000</td>
<td>10 000</td>
</tr>
<tr>
<td>Patients taking branded biologic, No.</td>
<td>1000</td>
<td>500</td>
<td>0</td>
</tr>
<tr>
<td>Patients taking biosimilar, No.</td>
<td>NA</td>
<td>500</td>
<td>1000</td>
</tr>
<tr>
<td>Payer cost, US $</td>
<td>25 000 000</td>
<td>30 000 000</td>
<td>10 000 000</td>
</tr>
</tbody>
</table>
Potential Payer Incentives to Encourage Biosimilar Use

• Give biosimilar preferred formulary status
  • Minimal or no requirement for prior authorization
  • Tier 1
• Minimal or waived copayment for patient
Summary

• Objective of biosimilar development program is to establish biosimilarity, not to re-establish benefit
  • Biosimilars undergo a rigorous regulatory approval process with extensive analytical studies & an abbreviated clinical program
  • Stepwise & comprehensive comparative approach to demonstrating biosimilarity is designed to “reduce residual uncertainty,” based upon “totality-of-the-evidence”

• Biosimilars are highly similar to their reference products, like another batch of the bio-originator

• A biosimilar approved according to a regulatory pathway for biosimilars should be as effective and as safe as its reference product

• Availability of biosimilars introduces market competition that drives down cost of biopharmaceuticals
Conclusion

• It is safe, effective, and cost-effective (in most countries) to switch to a biosimilar

• If the actual cost of a biosimilar is not lower than that of its reference product (after discounts & rebates), the availability of the biosimilar introduces market competition that results in effective treatment for patients with the reference product at a lower cost