Biosimilars 2017: What We Need to Know

Miguel Regueiro, M.D.
Professor of Medicine
IBD Clinical Medical Director
Senior Medical Lead, Specialty Medical Homes
University of Pittsburgh Medical Center

Disclosures

Consultant:
• Abbvie
• Amgen
• Janssen
• Miraca laboratories
• Pfizer
• Takeda
• UCB

Research Grants:
• Abbvie
• Janssen
• Takeda

Why even have this talk?

Why not stick with what we know and love!

What will biosimilars mean for us?

In the last decade we were finally getting comfortable with biologics – now come along the biosimilars

Annual Revenue Due to Adalimumab

One approach to healthcare costs is similar to Themos’s car

Maybe we can get away with...

“It is likely that biosimilars will be widely used for the treatment of IBD due to their cost savings and comparable efficacy.”

Papamichael et al. Review article: pharmacological aspects of anti-TNF biosimilars in inflammatory bowel diseases. AP&T 2015

Ha, Christina; Kornbluth, Asher
Inflammatory Bowel Diseases. 22(10):2513-2526, October 2016.

Biosimilars: Confusion

• Are They Generics?
• How Similar Can They Be?
• Were They Tested in Humans Prior To Approval?
• Will They Get “Blanket Approval” For All Indications?
• Will Prescribers Control What Patients Get?
• How Much Cheaper Will They Be?

Biosimilars

• Biosimilars are a similar copy of an originator biologic therapy. NOT GENERICS. The originator is also sometimes called “the reference product” or “innovator.”

<table>
<thead>
<tr>
<th>What should be the same?</th>
<th>What is different?</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Strength</td>
<td>✓ They are NOT an identical copy in every way (glycosylation may differ)</td>
</tr>
<tr>
<td>✓ Route of administration</td>
<td></td>
</tr>
<tr>
<td>✓ Effectiveness</td>
<td></td>
</tr>
<tr>
<td>✓ Safety profile</td>
<td></td>
</tr>
</tbody>
</table>
What are the clinical efficacy data comparing a Biosimilar to Reference antiTNF?

Note: no comparative studies in IBD, all data extrapolated from AS/RA

Indication

1. Rheumatoid arthritis
2. Ankylosing spondylitis
3. Psoriatic arthritis
4. Psoriasis
5. Ulcerative colitis
6. Crohn's disease

Biosimilars Can be Extrapolated to Other Indications

- Comparison studies of a biosimilar that show equivalent efficacy and safety to the originator in one indication may be extrapolated to all indications for the originator.

EXAMPLE: biosimilar infliximab that works equally well in rheumatoid arthritis can be extrapolated and receive FDA approval without any additional studies for Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriasis and psoriatic arthritis.

Adapted from: US Biologics Price Competition and Innovation Act of 2009
Interchangeable Biosimilars

• "Interchangeable" designation of biosimilars may allow for free exchange with originator biologics with no greater risk of adverse effects or diminished efficacy
• Statute allows pharmacy substitution of interchangeable biosimilars without prescriber intervention
• Subject to each state’s laws and regulations governing drug
• FDA determines whether a biosimilar is interchangeable or not
  – Requires studies of cross-over between originator and biosimilar

Adapted from: US Biologics Price Competition and Innovation Act of 2009

…patients who developed Anti-Drug Antibody to either infliximab or CT-P13 will not benefit from switching to the other drug…..”

Papamichael 2015 AP&T

Biosimilars for IBD

Inflectra™ is the first FDA approved biosimilar for inflammatory bowel disease
  – Has biosimilarity to Infliximab (Remicade®)
  – Not interchangeable (per regulatory)
  – Studied in:
    • Ankylosing Spondilitis
    • Rheumatoid Arthritis
  – Extrapolated to:
    • Crohn’s disease (in adults and children)
    • Ulcerative colitis (in adults)
  – Not available yet, projected 2018

Amjevita™ is the second FDA approved biosimilar (adalimumab) for inflammatory bowel disease

Clinical Response 33% - 100% (most > 60%) and Remission 38% - 100% (most > 65%): remember no IBD head-to-head BSM vs Reference

Table 2 | Efficacy and safety of infliximab biosimilar CT-P13 in IBD

<table>
<thead>
<tr>
<th>IBD type</th>
<th>N</th>
<th>Country</th>
<th>CT-P13 dose (mg/kg)</th>
<th>Study type</th>
<th>Follow-up (weeks)</th>
<th>WAB (%)</th>
<th>Prior anti-TNF (%)</th>
<th>Inflammation reaction (%)</th>
<th>Adverse events (%)</th>
<th>Clinical response (%)</th>
<th>Clinical remission (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD 3</td>
<td>5</td>
<td>Korea</td>
<td>8</td>
<td>Retrospective, single-centre</td>
<td>8</td>
<td>67</td>
<td>33</td>
<td>0</td>
<td>0</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td>CD 16</td>
<td>5</td>
<td>Hungary</td>
<td>62.5</td>
<td>Prospective, multi-centre</td>
<td>4</td>
<td>6</td>
<td>81</td>
<td></td>
<td>0</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>CD 32</td>
<td>5</td>
<td>Poland</td>
<td>10</td>
<td>Retrospective, single-centre</td>
<td>10</td>
<td>NR</td>
<td>42</td>
<td>8</td>
<td>0</td>
<td>69 (5/6)</td>
<td>NR</td>
</tr>
<tr>
<td>CD 38</td>
<td>5</td>
<td>Korea</td>
<td>62</td>
<td>Retrospective, single-centre</td>
<td>54</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>99 (8/8)</td>
<td>84</td>
</tr>
<tr>
<td>UC 12</td>
<td>5</td>
<td>Korea</td>
<td>8</td>
<td>Retrospective, single-centre</td>
<td>8</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>UC 22</td>
<td>5</td>
<td>Poland</td>
<td>60</td>
<td>Prospective, single-centre</td>
<td>16</td>
<td>26.6</td>
<td>7.5</td>
<td>2</td>
<td>75</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>UC 32</td>
<td>5</td>
<td>Poland</td>
<td>10</td>
<td>Retrospective, single-centre</td>
<td>10</td>
<td>17</td>
<td>10 (2/2)</td>
<td>0</td>
<td>15 (2/2)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>UC 42</td>
<td>5</td>
<td>Korea</td>
<td>60</td>
<td>Retrospective, multi-centre</td>
<td>54</td>
<td>55</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>12 (2/2)</td>
<td>8 (1/1)</td>
</tr>
</tbody>
</table>

2016: The First Monoclonal Biosimilars Received US FDA Approval

• Food and Drug Administration approved biosimilar for infliximab (-dyyb) on April 5, 20161 and adalimumab (-atto) on September 23, 2016.2
• Approved for most but not all of the same indications
• Launch: "Pfizer press release 10/17/16: "Pfizer Inc. (NYSE-PFE) announced today that the company will begin shipment of INFLECTRA® (infliximab-dyyb) for injection, a biosimilar of REMICADE® (infliximab) to wholesalers in the United States (U.S.) in late November 2016." 3
• Price? : "INFLECTRA will be introduced at a 15% discount to the current wholesaler acquisition cost (WAC) of REMICADE®, its reference product." 3


HOW HAVE BIOSIMILARS PERFORMED IN IBD?

Papamichael et al. AP&T 2015

2016: The First Monoclonal Biosimilars Received US FDA Approval

• Food and Drug Administration approved biosimilar for infliximab (-dyyb) on April 5, 20161 and adalimumab (-atto) on September 23, 2016.2
• Approved for most but not all of the same indications
• Launch: "Pfizer press release 10/17/16: "Pfizer Inc. (NYSE-PFE) announced today that the company will begin shipment of INFLECTRA® (infliximab-dyyb) for injection, a biosimilar of REMICADE® (infliximab) to wholesalers in the United States (U.S.) in late November 2016." 3
• Price? : "INFLECTRA will be introduced at a 15% discount to the current wholesaler acquisition cost (WAC) of REMICADE®, its reference product." 3

Clinical Experience with CT-P13 in IBD: Updated Systematic Review

- 13 studies in Korea, Hungary, Czech, Norway, Netherlands, Italy involving at least 500 IBD patients who were switched from IFX to CT-P13
- Treatment persistency ranged 57%-88% at end of follow-up
- Adverse events in the range of expected
- Infusion reactions up to 6.6%
- ATI in the range of expected


Clinical Experience with CT-P13 in IBD: Prospective Study

- Prospective Italian study: PROSIT-BIO
  - 547 patients
  - Clinical response at 8 weeks
  - 90% in anti-TNF naïve
  - 89% in previous anti-TNF
  - 100% in switchers from IFX
  - Loss of response (median 4 months follow up)
  - 17.8% anti-TNF naïve
  - 29.1% anti-TNF experienced
  - Only 7.9% in switchers
  - Infusion reactions occurred twice as often in IFX exposed if drug holiday had been >4 months

Fiorino G et al, Inflamm Bowel Dis 2017;23:233-43

Prospective Trial of Switching From Originator Infliximab to CT-P13: NOR-SWITCH

- 481 Norwegian patients with CD, UC, SpA, RA, PsA, Ps
- Stable, on IFX ≥6 months
- Randomized 1:1 to continued IFX or CT-P13 for 52 weeks
- Primary endpoint: clinical worsening
  - ...worsening in disease specific composite measure or consensus between investigator and patient leading to major change in therapy
- Non-inferiority, margin of 15%

Concluding statement from recent systematic review in the Annals of Internal Medicine:

“Preliminary evidence supports the biosimilarity and interchangeability of biosimilar and reference TNF inhibitors.”

Infliximab: Remicade® indications not included in biosimilar Inflectra™ FDA approval

<table>
<thead>
<tr>
<th>Condition</th>
<th>Remicade®</th>
<th>Inflectra™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Crohn’s Disease</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Pediatric Crohn’s Disease</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Adult Ulcerative Colitis</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Adult Rheumatoid Arthritis</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Adult Polyarticular Arthritis</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Adult plaque Psoriasis</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Adalimumab: Humira® indications not included in biosimilar Amjevita™ FDA approval

<table>
<thead>
<tr>
<th>Condition</th>
<th>Humira</th>
<th>Amjevita</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Crohn’s Disease</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Pediatric Crohn’s Disease</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Adult Ulcerative Colitis</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Adult Rheumatoid Arthritis</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Juvenile Idiopathic Arthritis</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Adult Polyarticular Arthritis</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Adult Psoriatic Arthritis</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hidradentitis Suppurativa</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Adult Uveitis</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>