BIOSIMILARS – SIMILAR BUT NOT THE SAME

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Disclosures
- Speakers fees/Advisory Boards
  - AbbVie, Janssen, Takeda, Pendopharm, AstraZeneca, Actavis/Allergan
- Research Support
  - Robarts, AbbVie

The IBD treatment landscape

Anti-Tumor Necrosis Factors
- Infliximab
  - Remicade
- Adalimumab
  - Humira
- Golimumab
  - Simponi

Canadian Clinical UC Treatment Guidelines, 2015

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Canadian Clinical UC Treatment Guidelines, 2015
Alpha 4, Beta 7 integrin inhibitor

- Vedolizumab
- Entyvio
- Humanized monoclonal antibody that inhibits adhesion and migration of leukocytes into the gastrointestinal tract by preventing the alpha4beta7 integrin subunit from binding to mucosal addressin cell adhesion molecule-1 (MAdCAM-1).

Over the past several years, Subsequent Entry Biologics (SEBs) or biosimilars have been developed and are in the market place.

- These drugs are available in Canada and are in the market place.
- What does this mean for your patients?
- Who decides what drug your patients receive?

How do anti-TNFs work in the body?

Active IBD – No anti-TNF

Let's review what has happened to this point.
Biosimilars in the European Union, follow-on protein product in the United States and subsequent entry biologics (SEBs) in Canada

- SEBs are not generic biologics\(^1,2,3\)
- SEBs are made using a different host cell line and a different manufacturing process\(^1,2,3\)
- SEBs manufactured by different manufacturers are not identical to the innovative\(^1,2,3\) product or reference biologic drug (RBD) nor to each other\(^2\)
- SEB development fundamentally differs from manufacturing changes for innovator products and this is recognized in regulatory guidance by EMA\(^4\) and FDA\(^5\)

**Guideline on Similar Biological Medicinal Products Containing Biotechnology Derived Proteins as Active Substance: Quality Issues**

http://www.bio.org/articles/how-to-biosimilarize-a-biologic

**Guideline for Industry Scientific Considerations in Demonstrating Biosimilarity**


**US FDA. Guidance for Industry. Scientific considerations in demonstrating biosimilarity**


Health Canada Statements on Subsequent-Entry Biologics (SEB)

- SEBs are regulated as “New Drugs” by comparing to a reference product previously authorized and marketed in Canada with a reduced non-clinical and clinical package.
- The basis for accepting a reduced non-clinical and clinical data package for an SEB hinges on demonstrated similarity between the SEB and the suitable Reference Biologic Drug (RBD)
- SEBs are not generics (because biologics are more complex, SEB manufacturers cannot guarantee that their version is exactly identical to the original innovator’s version). Authorization of an SEB is not a declaration of pharmacological or therapeutic equivalence to the RBD
- Once a Notice of Compliance (NOC) is issued, the SEB is a new biologic drug and regulated accordingly. However, an SEB cannot be used as a RBD for another SEB submission

Biologics Are Far More Complex Than Conventional Medicines

- **Small Molecule** Medicine
  - Aspirin
  - 180 Daltons and 2 Zero Amino Acids
- **Biologic** Medicine
  - Human Growth Hormone
  - 22,125 Daltons and 391 Amino Acids. Non-Glycosylated Protein
  - 140,000 Daltons and 1,529 Amino Acids

- Biologics differ in size, manufacturing complexity, and in the way they interact with cells and other proteins in the body
- Different systems of approval are necessary for small molecule generics and subsequent entry biologics

What is a Biologic Drug Product?

Biologic = protein \(\text{molecule}\) + its specific manufacturing \(\text{process}\)

Biologic drug \(\text{product}\) = the biologic + the formulation + the delivery device

\[ \text{Molecule} + \text{BIOLIC} + \text{Process} \]

\(\text{Device} / \text{Delivery System}\)

Each process, molecule, and device = unique biologic product

**Two Different Processes Create Two Non-Identical Biologic Products**

START

Different systems for specific gene

Different vectors for gene

Different host cells to grow the protein

Different fermentation/culture conditions

Different downstream processing

Non-identical immunological properties in preclinical

END
**Manufacturing Change vs. Biosimilar Development**

Manufacturing Change of Innovator Biologics
Optimizing an approved process for a product that has previously undergone significant R&D and a full pre-clinical and clinical regulatory approval process

Each governed by different regulatory requirements

Biosimilar Development
Reverse engineering or recreating a version of the innovator’s product starting from published information and the product on the market

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**Indication Extrapolation**

Reference product has been approved for Indications A, B, C and D

1. Approval in Indication A
2. Extrapolation to other diseases or patient populations?
3. Indication B Indication C Indication D

Comparative CMC/quality, safety and efficacy studies of a subsequent entry biologic in a single disease or specific patient population (Indication A)
### CT-P13 Infliximab Indications by Type of Approval

<table>
<thead>
<tr>
<th>Indication</th>
<th>S. Europe 2012</th>
<th>US 2013</th>
<th>Canada 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid Arthritis (RA)</td>
<td>CT*</td>
<td>CT*</td>
<td>CT*</td>
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<tr>
<td>Ankylosing Spondylitis (AS)</td>
<td>CT**</td>
<td>CT**</td>
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<tr>
<td>Psoriatic Arthritis</td>
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<tr>
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<tr>
<td>Pediatric CD</td>
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</tr>
<tr>
<td>Ulcerative Colitis (UC)</td>
<td>E</td>
<td>E</td>
<td>-</td>
</tr>
<tr>
<td>Pediatric UC</td>
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</tbody>
</table>

CT-P13 approved with a complete data package including a single phase III or Phase I clinical trial.

* Exemplified indication without a phase I or III clinical trial. Dual (-) Not approved

These examples are not meant to provide a complete overview of all indication extrapolation decisions for CT-P13. Other publications have provided marketing authorization to CT-P13.

2. Consensus Paper: [ECCO-2013](http://www.ecco-ibd.eu/)

### Extrapolation: Health Canada Summary Basis of Decision

- Extrapolation from RA and AS to adult and pediatric IBD cannot be recommended due to the absence of clinical studies in IBD
- Observed differences in the level of afucosylation, FcγRIIIa receptor binding, and some in vitro Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) assays
- Differences in ability of ADCC induction could not be ruled out and ADCC cannot be ruled out as a mechanism of action in IBD
- Position supported by observation that ceruliumab pegol, an anti-TNF that lacks the ability to induce ADCC, displays only marginal efficacy in Crohn’s patients compared to other anti-TNFs.
- Pathophysiological differences between the rheumatic diseases and the IBDs making a direct extrapolation between the two groups challenging without clinical or PK/PD bridging data
- The safety profile of infliximab is also different between the rheumatic and inflammatory bowel diseases

#### From ECCO 2015: Biosimilar but not the same

**Objectives**

To compare surgery, readmission rates and other parameters of consecutive Remicade and Inflectra anti-TNF naïve IBD patients in a hospital in Ireland.

**Methods**

- Review of 36 consecutive IBD patients was completed.
- 14 Inflectra patients from January-July 2014.
- 22 Remicade patients from Dec 2011 to 2013.
- No differentiation between ulcerative colitis (UC), Crohn’s and indeterminate colitis (IC).
- Direct comparison of overall demographics, surgery rates, readmission rates, use of steroids, disease activity and CRP trends.

**Results**

- Significant differences in the following parameters:
  - Surgery
  - Hospital readmission
  - Median time to readmission (12 days Inflectra, 49 days Remicade/1 patient)
  - Steroid augmentation (60% Inflectra vs. 8% Remicade)
  - CRP over 8 weeks: 93% of Inflectra patients increase of CRP vs. 100% of Remicade decrease of CRP
  - Decrease in disease activity score in 57% of Inflectra pts vs. 95% of Remicade pts

**Conclusions**

- Study suggests biosimilars may be less efficacious as reference medicine.
- Highlights the need for large, prospective, RCTs of biosimilar IFX in IBD.
- Results reflect ECCO statement position about extrapolation and testing of biosimilars in IBD.

#### Interchangeability, Substitution and Switching

**Interchangeability**

- Health or Regulatory Authority Designation
  - Primarily a US standard: FDA can designate a subsequent entry biologic as interchangeable if...
    - It is expected to produce the same clinical result as the reference product in any given patient;
    - Repeated switching between subsequent entry biologic and reference product presents no greater safety or efficacy risk than continued use of the reference product

**Substitution** – Pharmacist Action

- When a pharmacist substitutes a certain prescribed product by another equivalent product
- If without the prescribing physician’s involvement, it is considered “automatic” or “involuntary” substitution

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2. Consensus Paper: [ECCO-2013](http://www.ecco-ibd.eu/)
Interchangeability and Substitution

Summary

- Given the limitations of post authorization data, it is currently impossible to conclude an absence of a risk of switching biologics.
- According to the FDA, approval of biosimilarity alone is insufficient to establish interchangeability or substitutability with the reference product.
- Some physicians have therefore expressed that interchangeability of mAbs should be evaluated on an individual basis by the treating specialist and should not be routinely recommended.

Interchangeability and Substitution

- Biosimilars are not generic copies of their reference product (RP).
- Can be developed through abbreviated clinical development pathway.
- Indication extrapolation is possible with adequate justification.
- Biosimilarity status does not imply interchangeability.
- Immunogenicity profile may differ from RP, and may only show when used in a larger, real-life patient population.
- Biomarks are not biosimilars of themselves after a manufacturing change fulfilling ICHQ6 specifications.

Summary cont...

- SEBs are not generics, as the manufacturing process is the product.
- SEBs may be less expensive than brand name biologics, but present uncertainty with respect to safety, efficacy, and extrapolation to other indications.
- SEBs should have unique names and should not be interchangeable or substitutable.
- Patient support programs are an important aspect of patient care and management with biologic drugs.
- There is a need for pharmacovigilance with SEBs, and registry programs are recommended to monitor for long-term safety and efficacy outcomes.

CAG position statement regarding SEBs for IBD

- SEBs may be a potentially effective and cost-saving option for the management of IBD that may serve to enhance access to biologic therapy.
- SEBs should be regarded as stand-alone products, and should be supported by well-designed nonclinical and clinical studies in a population relevant to Canadian patients.
- SEBs cannot be regarded as interchangeable with the reference biologic drug (RBD).
- Prescriptions for RBDs should not be automatically substituted for less expensive SEBs by dispensing pharmacies.
- SEBs should be supported by long-term pharmacovigilance data in a fashion similar to RBDs.
- Companies bringing SEBs to the Canadian market should be committed to improving patient care by acquiring new scientific data beyond what is required as a minimum to satisfy regulatory authorities and their commercial imperatives.
The impact of immunogenicity on an SEB? 
- No guarantee that our understanding of the impact of immunogenicity to infliximab and adalimumab will easily be extrapolated to an SEB that may be subtly different in molecular structure 
- How will clinical trials involving patients with IBD proceed and how will they be designed? 
- Will regulatory agencies require both induction and maintenance data or only induction data? 
- Where will these clinical trials be conducted?

Patient Support Programs - what our patients want
- Treatment initiation
  - Manage reimbursement issues
  - Cost barriers
  - Scheduling/administration of drug
- Ongoing treatment
  - Update medical orders
  - Monitor adverse events
  - Track contraindications
- Communication
  - Provide consistent point of contact
  - Post treatment reports
- Disease support
  - Living with chronic disease
  - Manage comorbidities
  - Exercise programs, diet, nutrition
  - Patient association partnerships

But why should we care...???

Quebec Listing For Inflectra/Remicade under “Prix le Plus Bas”
- INESSS states products are not interchangeable but listing as PPB allows pharmacists to dispense SEB without physician consent
- RAMQ suggests physicians use “Do Not Substitute” due to limits on infusion capacity and physician concerns about switching
- Quebec announces restrictions on “Do Not Substitute” effective April 24.

Discussion
- Should therapeutic substitution be allowed with Biologic products?
- Define any risk (to patient and prescriber) associated with therapeutic substitution policy? 
  - What are the risks to the patients and the prescriber associated with cost containment policy?
  - Should therapeutic substitution be allowed with Biologic products?
  - What criteria would you like to see in place to protect patient and physician concerns about switching?
  - How do we ensure therapeutic substitution is not being driven by a new business model or cost containment? What criteria would you like to see in place to protect patient and your choice of therapy? 
  - How does therapeutic substitution and cost containment policies impact innovation and investment?
  - What is the value of innovation, clinical trial research, and patient assistance programs? 
  - What role do these factors play in your message to the government?