Explaining the Return on Investment of Biologic Therapy in IBD

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Director of the Inflammatory Bowel Disease Clinic
Professor of Medicine
University of Calgary
This is inflammatory bowel disease...

Crohn’s Disease

Ulcerative Colitis
For decades, there were many unmet needs in IBD...Need for:

- Rapid relief of symptoms
- Avoidance of steroids
- Avoidance of time off work for admission / hospital treatment
- Sustained efficacy for long-term control
- Avoidance of surgery
- Normal quality of life
- Restored control over daily life
Before anti-TNF therapies were available...

- The nature of IBD was less well understood and acknowledged
- Treatment focused on reducing symptoms and managing disease flares
- The outlook for patients was very different
  - Limited treatments
  - High hospitalization, disability and surgery rates
  - Increased mortality rates
Before anti-TNF therapies were available...

- Ashamed
- Desperate
- Afraid
- Lack on Control
- Lack of Hope
Impact of IBD on patients’ lives

Proportion of patients who feel their condition was controlling their lives

- UC (n=451): 53%
- Asthma (n=305): 19%
- Migraine (n=305): 37%
- RA (n=309): 44%

Psychological impact of UC

- Worry about long-term effects: 84%
- Making life more stressful: 82%
- Feel: 70%
- Sometimes always feel depressed: 62%

*p < 0.05 vs other chronic conditions

Internet survey designed to assess a variety of disease impact indices
Work Disability in UC and CD

Norwegian population-based study of UC and CD patients (n=518) receiving disability pension (DP)

In UC patients, the proportion of individuals receiving a DP because of conditions other than IBD was predominant in all age groups except for 30- to 39-year-olds. In contrast, IBD was the predominant cause of CD patients receiving a DP except in the youngest patient group.

UC=ulcerative colitis; CD=Crohn's disease; RR=relative risk; CI=confidence interval; IBD=inflammatory bowel disease.

Productivity Burden of IBD

Productivity assessed in Dutch IBD cohort (COIN study):
• Only 54%-61% of patients were employed
• 13-18% missed work due to illness
• 10 days of work missed per year
• Annual productivity losses: €1,304 – €1,580
• Out of pocket expenses: €228-300

van der Valk et al. (2014) Gut
Burden of Illness of IBD in Canada

- Canada has highest prevalence of IBD in the world
- Burden of illness:
  - Poor quality of life
  - Hospitalizations and surgery
  - Increased mortality risk
  - Productivity losses
- High cost burden to society
Burden of Illness of IBD in Canada

Direct Costs of IBD (2012) - $1.2B

- Hospital Outpatient: $100,949,449
- Hospital Inpatient: $60,740,737
- Physician Visits: $394,814,790
- Prescription Drugs: $521,465,012
- Other Health Care: $131,729,320
- Out of Pocket Expenses: $9,408,866

Indirect Costs of IBD (2012) - $1.6B

- Short Term Work Loss: $978,911,459
- Long Term Work Loss: $300,090,320
- Premature Mortality: $92,783,205
- Caregivers Work Loss: $180,722,115
- Out of Pocket Expenses: $110,273

Rocchi et al. (2012) *Can J Gastroenterol*
Impact of IBD in Canada

Disability assessed from Manitoba IBD Database:

- ~20% on disability in CD
- ~11% on disability in UC

Israeli et al. (2014) Clin Gastroenterol Hepatol
Anti-TNFs have improved patient outcomes in IBD

Before anti-TNFs...

- Progressive nature of CD less well understood and acknowledged
- Treatment focused on reducing symptoms and managing disease flares
- Outlook for patients was very different
  - Limited treatments
  - High surgery / hospitalisation rates
  - High mortality rates

Now...

- Timely drug intervention
- Long-term sustainability (scheduled maintenance)
- Steroid-free, deep remission
- Complete mucosal healing
- Reduction in long-term complications
- Decreased hospitalisations and surgeries
Explaining the ROI of Biologics

**Opportunities:**

1. Revolutionary in the treatment of chronic inflammatory conditions
2. Effective
3. Safe
4. Good patient satisfaction
5. **Linked to improvements in workplace productivity, absenteeism and decreased disability claims**

**Challenges:**

1. **Cost: $20K+/yr**
   
   1. Payers are predicting increasing costs with biologics as indications broaden and more products come to market
   
   2. The impact of cost containment
High-Cost Biologics, National 2014

For biologics, a small share of claims represent a large share of cost.

Source: Telus Health Solutions, Data Trends and National Benchmarks; Perspective Overview. Presented March 25, 2015.
Biologics Improve Productivity

• 34.7% vs 16.5% in remission at Week 54 for REMICADE® and placebo, respectively

• 6.6 hours of fully productive time lost every week for patients not in remission

• Employment and disability advantages for patients in remission

Reinisch et al. (2007) Inflamm Bowel Dis
Biologics, when combined with a Patient Assistance Programs, improve Long-Term Disability

Number of patients with Crohn's Disease self-reported being on disability before entering a patient assistance program in Canada in 2012 (n=517)

Before

- Yes: 34%
- No: 66%

After

- Yes: 10%
- No: 90%

What is an Anti-TNF?

**Biological characteristics**

- **Fab**
  - Antigen binding
  - Heavy chain
  - Light chain

- **Fc**
  - Effector functions
    - ADCC
    - CDC

**Physicochemical characteristics**

- Amino acid modifications
  - Deamidation, oxidation, glycation, isomerization

- Fragmentation
  - Cleavage in hinge region, Asp-Pro

- Aggregation

- Primary and higher order structure
  - Glycosylation
    - Fucosylation, sialylation, mannose
  - Disulfide Bonds
    - Free thiols, disulfide shuffling, thioether

- C-terminal heterogeneity
  - Lysine processing, Proline amidation
High Complexity of Monoclonal Antibodies

**Aspirin**  
Molecular weight = 80 daltons  
0 amino acids

**Erythropoietin**  
Molecular weight = 30,000 daltons  
166 amino acids

**Antibody (IgG)**  
Molecular weight = 150,000 daltons  
~1,300 amino acids
Manufacturing of biopharmaceuticals

Source of variation between manufacture of innovator biopharmaceutical and biosimilar

- Use of different vector
- Different cell expression system
- Different cell line, growth media & method of expansion
- Different operating conditions
- Different binding and elution conditions
- Different methods, reagents, reference standards

- Cloning of specific gene sequence into viral or non-viral vector
- Transfer into host cell for expression
- Protein production
- Protein recovery through filtration and centrifugation
- Protein purification by chromatography
- Protein characterisation and stability
SEB Landscape* in The Near Future

<table>
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<tr>
<th>REMICADE®</th>
<th>HUMIRA®</th>
<th>ENBREL®</th>
<th>RITUXAN®</th>
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<td>REMSIMA™ (Celltrion)</td>
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<td>NI-071 (Nichi-Iko/Sanofi)</td>
<td>BI 695501 (Boehringer Ingelheim)</td>
<td>HD203 (Hanwha Chemicals)</td>
<td>MabionCD20 (Mabion SA)</td>
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*As of April 2015

## SEBs Are Not Generics

<table>
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<th>Generics</th>
<th>SEBs</th>
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<tbody>
<tr>
<td>Small molecule drug</td>
<td>Large complex molecule</td>
</tr>
<tr>
<td>Chemically synthesized</td>
<td>Manufactured in living system</td>
</tr>
<tr>
<td>Fully characterized molecule</td>
<td>Challenging to fully characterize</td>
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<tr>
<td>Mechanism of action well understood</td>
<td>May not be well understood</td>
</tr>
<tr>
<td>Can be duplicated exactly</td>
<td><strong>Challenging to duplicate exactly</strong></td>
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<tr>
<td>Active ingredient is chemically identical to reference product</td>
<td>Active ingredient is <em>highly similar</em> to reference product</td>
</tr>
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<td>Approved on the basis of analytical similarity and bioequivalence</td>
<td>Approved on the basis of extensive in vitro comparability testing and reduced non-clinical and clinical comparability testing (toxicity, pharmacokinetics, safety, and efficacy)</td>
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## Interchangeability/Substitution

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<tr>
<th>Health Authority</th>
<th>Position</th>
<th>References in notes.</th>
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<tr>
<td><strong>SEBs are not generic biologics</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>Outside of mandate for interchangeability (Provincial decision)</strong>&lt;br&gt;• <strong>BC</strong>: Pharmacists can interchange products that are bioequivalent (generics only); information regarding SEBs is emerging and until further evidence is available, the pharmacist should consult with HC and the manufacturer&lt;sup&gt;2&lt;/sup&gt;&lt;br&gt;• <strong>AB</strong>: No interchangeability for SEBs&lt;sup&gt;3&lt;/sup&gt;&lt;br&gt;• <strong>QC</strong>: Order of Pharmacists considers a switch from innovator to SEB to be a therapeutic substitution which is currently beyond the scope of practice for Quebec pharmacists&lt;sup&gt;6-7&lt;/sup&gt;&lt;br&gt;• Rest of Canada is still unknown</td>
<td><strong>2007</strong>: Decision on using SEBs should be made by qualified health care professional&lt;sup&gt;4&lt;/sup&gt;&lt;br&gt;<strong>2012</strong>: SEBs are not the same as generics, which have simpler chemical structures and are considered to be identical to their reference medicines&lt;sup&gt;5&lt;/sup&gt;</td>
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<td><strong>SEB authorization is not a declaration of pharmaceutical or therapeutic equivalence</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>Outside of mandate for interchangeability (Country decision)</strong></td>
<td><strong>BPCI Act clearly distinguishes biosimilarity and interchangeability</strong>&lt;sup&gt;8&lt;/sup&gt;&lt;br&gt;• The regulatory approval of the biosimilarity of two products does not imply their interchangeability&lt;sup&gt;8&lt;/sup&gt;&lt;br&gt;• Biosimilar authorization framework allows for possibility of interchangeable designation (multiple switches). An application for interchangeability must be submitted which demonstrates that the biosimilar meets the criteria for interchangeability&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Health Canada (HC) does not support automatic substitution</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td><strong>Outside of mandate for interchangeability (State decision to implement or not)</strong></td>
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Interchangeability: Health Canada’s Concerns Are Scientifically Based

1. Pharmaceutics: Drug substances of the biosimilar and reference are not identical
2. PK/PD: The biosimilar is not “bioequivalent” to the reference
3. Safety: As a consequence of their complexity and impurity profiles, automatic interchangeability of biologics or biosimilars could give rise to different clinical consequences
4. Immunogenicity: Repeated switches between biosimilars and originator products may increase immunogenicity with potentially negative effects
5. Clinical use: A biosimilar may or may not receive authorization for all indications or uses
6. Post-market: Data used in the demonstration of “similarity” are only valid at the time of market authorization due to possible significant post-market changes and “manufacturing drift”

SEBs: In a nutshell

1. SEBs are not generics.
2. The process is the product.
3. Biologics and SEBs are not currently interchangeable.
4. There is a need to generate further evidence on SEBs.
5. Cost savings are not expected to be as significant as those for generic drugs.
Cost containment Measures

• With drug costs increasing, some plans are shifting to contain the costs of biologics.

• Typical measures:
  ▫ Special authorization forms
  ▫ Tiering: Where the patient is required to try 1 biologic before another.

• Biologics treat complex conditions, and broad cost containment measures may not be in the best interests of the patient.
Patient Support Programs by Innovators: What You and Your Patients Can Expect

• **Treatment initiation**
  - Manage reimbursement, liaise with insurers and help with completion of paperwork
  - Ensure cost is not a barrier to therapy
  - Assists with scheduling and administering infusions

• **Ongoing treatment**
  - Update medical orders
  - Monitor adverse events
  - Track contraindications to biologic dosing

• **Communication**
  - Provide a consistent point of contact for patients
  - Provide post-infusion report to treating physician after every treatment

• **Disease support**
  - Living with chronic disease
  - Managing comorbidities
  - Exercise programs, diet, and nutrition
  - Partnership with patient associations
Patient Support Programs Improve Compliance Supporting Reduced Disability Rates

Number of patients with *Crohn's Disease* self-reported being on disability before entering a patient assistance program in Canada in 2012 (n=517)

Before

- Yes 34%
- No 66%

After

- Yes 10%
- No 90%

Patient Support Programs Improve Compliance Supporting Reduced Disability Rates

Number of patients with *Ulcerative Colitis* self-reported being on disability before entering a patient assistance program in Canada in 2012 (n=75)

Before

- Yes 31%
- No 69%

After

- Yes 3%
- No 97%

Conclusions

• IBD is a devastating disease who’s effects expand into the workplace

• Value of biologics goes beyond the cost of the products

• The entry of SEBs may not result in significant cost savings to plans
  • Complex manufacturing process
  • Different implications than generic paradigm
  • Health Canada does not support automatic substitution
Questions