Health Technology Assessment for Similar but not Interchangeable Products

Subsequent Entry Biologics (SEBs)

• The prescribers perspective

Dr. Wayne P. Gulliver  MD, FRCPC, FACP
Professor of Dermatology & Medicine, Memorial University of Newfoundland
3 most important attributes for Patient and Doctor

- Safety
- Safety
- Safety
Overview of Psoriasis

- Worldwide prevalence: 0.1–3.0% population (NL 10,000 cases-2% - WG -3500)
- Significant impairment in QoL for many patients similar to IHD, DM and asthma
- Affects a person's self-esteem and sociability
- DLQI – 2 min validated tool
  - assist the clinical consultation, patient evaluation and monitoring and to help with clinical decision making process
- Chronic plaque-type most common form (75%) (form found in PsA)
- Majority of patients will have mild disease
- Mean age of onset = 30 years (M=F)
- 75% disease onset before age 40 years
- Earlier age of onset, more severe disease

IHD, Ischemic heart disease; DM, Diabetes mellitus; QoL, Quality of life; PsA Psoriatic arthritis; DLQI, Dermatology life quality index
Psoriasis is NOT a 12 Week Disease!
PASI 75 @ Week 12 – HC\FDA Requirement

Anti-TNF Treated Patient

- Is there a skin vs. joints disconnect?
- What about responses at 24, 36, 52 weeks? Longer???
Efficacy Overview (8-16 wks) moderate-to-Severe Psoriasis (PASI 75)

- Infliximab 5 mg/kg (80%)
- Adalimumab 40mg qwkly (81%)
- Adalimumab 40mg eow (71%)
- PUVA (70%)
- CSA 5 mg/kg/d (70%)
- MTX 15 mg/wk (60%)
- Etanercept 50 mg 2x/wk (49%)
- Etanercept 25 mg 2x/wk (34%)
- CSA 2.5-4 mg/kg/d (28%)
- Ustekinumab 45 mg q3m (67%)
- Alefacept 15 mg/wk (17%)

<One head to head trial>
PASI 75 With Extended Treatment: Anti-TNF Psoriasis Trials

Note: Not intended as head to head comparisons

- Infliximab (5 mg, q8w)
- Etanercept 50 mg BIW
- Etanercept 25 mg BIW
- Adalimumab 40 mg EW
- Adalimumab 40 mg EOW
- Etanercept 50 mg BIW --> 25 mg BIW

Overall Efficacy: PASI 75 Responses Through Year 3

PHOENIX 1

Week 0 - 40

Week 76 – Year 3

Percent of Patients

45 mg, n = 255

Ustekinumab 45 mg

90 mg, n = 256

Ustekinumab 90 mg

*Includes only patients randomized to ustekinumab at Week 0; Placebo crossover patients are re-included after Week 28
†Excludes patients withdrawn from ustekinumab at Week 40 until 12 weeks after retreatment

REVEAL - Example of a PASI 90 positive response:

**Fig 4.** Photographs of patient randomized in period A to adalimumab. **A,** Baseline (Psoriasis Area and Severity Index [PASI] score = 25.2). **B,** Week 4 (PASI score = 5.9; 77% improved from baseline). **C,** Week 16 (PASI score = 1.2; 95% improved from baseline).
PHOENIX 2: Clinical results over 1 year obtained with ustekinumab 90 mg every 12 weeks

Infliximab shows rapid and significant improvement on nail psoriasis

Week 0

Week 24

Adalimumab: Before & After
### Number of Subjects Who Discontinued Study Agent Through Year 4

<table>
<thead>
<tr>
<th>Reason for Discontinuation</th>
<th>Ustekinumab 45 mg</th>
<th>Ustekinumab 90 mg</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects randomized at Week 0</td>
<td>606</td>
<td>606</td>
<td>1212</td>
</tr>
<tr>
<td>Subjects who discontinued study agent</td>
<td>160 (26.4%)</td>
<td>146 (24.1%)</td>
<td>306 (25.2%)</td>
</tr>
<tr>
<td>Reason for discontinuation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event</td>
<td>44 (7.3%)</td>
<td>48 (7.9%)</td>
<td>92 (7.6%)</td>
</tr>
<tr>
<td>Worsening of psoriasis</td>
<td>0 (0.0%)</td>
<td>1 (0.2%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Unsatisfactory therapeutic effect</td>
<td>13 (2.1%)</td>
<td>15 (2.5%)</td>
<td>28 (2.3%)</td>
</tr>
<tr>
<td>Landmark visit nonresponder per protocol</td>
<td>31 (5.1%)</td>
<td>17 (2.8%)</td>
<td>48 (4.0%)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>19 (3.1%)</td>
<td>24 (4.0%)</td>
<td>43 (3.5%)</td>
</tr>
<tr>
<td>Death</td>
<td>4 (0.7%)</td>
<td>6 (1.0%)</td>
<td>10 (0.8%)</td>
</tr>
<tr>
<td>Other</td>
<td>49 (8.1%)</td>
<td>36 (5.9%)</td>
<td>85 (7.0%)</td>
</tr>
</tbody>
</table>

- Placebo crossover subjects are included after crossover to ustekinumab.
- Landmark non-responder:<PASI 50 at wk 28

Data on file, COBI.
Results

Baseline

Week 244 / 5 years

Week 52

DLQI = 0
BSA = 0–1%
Figure 8. Rates of Other Malignancies Compared to SEER (2010 Analyses)

- Through the 2010 Analyses, the rate of other malignancies was consistent with those expected in the general U.S. population using the SEER Database (see below)

*The expected number of patients with malignancies is based on the SEER Database (2009), adjusted for age, gender, and race.
† Indicates Standard Incidence Ratio (SIR) with 95% CI.
**Since cervical carcinoma in situ is not captured in SEER, a single case in 90 mg is not included in this analysis.

For PHOENIX 2, patients who were dose escalated from 45 mg to 90 mg were switched to the corresponding column following dose escalation.

Reich K, et al. Presentation at World Congress of Derm 2011. FC07-03.
# Meta-Analysis: Risk Difference of MACE for Anti-TNF vs. Placebo in RCTs

<table>
<thead>
<tr>
<th>Biologic Therapy</th>
<th>Placebo</th>
<th>Risk Difference, Events per Person-Year (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Source</strong></td>
<td><strong>Events, No.</strong></td>
<td><strong>Person-Years</strong></td>
</tr>
<tr>
<td>Etanercept</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td>Menter et al.14</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td>Strober et al.15</td>
<td>0</td>
<td>32</td>
</tr>
<tr>
<td>Infliximab</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Chauchari et al.20</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Gottlieb et al.21</td>
<td>0</td>
<td>38</td>
</tr>
<tr>
<td>Reich et al.22</td>
<td>0</td>
<td>139</td>
</tr>
<tr>
<td>Menter et al.23</td>
<td>0</td>
<td>168</td>
</tr>
<tr>
<td>Etanercept</td>
<td>0</td>
<td>112</td>
</tr>
<tr>
<td>Leonardi et al.24</td>
<td>0</td>
<td>112</td>
</tr>
<tr>
<td>Gottlieb et al.25</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>Papp et al.26</td>
<td>0</td>
<td>90</td>
</tr>
<tr>
<td>Tyring et al.27</td>
<td>0</td>
<td>72</td>
</tr>
<tr>
<td>Van de Kerkhof et al.28</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>Bagel et al.29</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>0</td>
<td>22</td>
</tr>
<tr>
<td>Gordon et al.30</td>
<td>1</td>
<td>22</td>
</tr>
<tr>
<td>Menter et al.31</td>
<td>0</td>
<td>250</td>
</tr>
<tr>
<td>Asahina et al.32</td>
<td>0</td>
<td>57</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>1078</td>
<td>494</td>
</tr>
</tbody>
</table>

**Heterogeneity:** $\chi^2 = 0.96, df = 14; P > .99; I^2 = 0\%$

**Test for overall effect:** $z = 0.07, P = .94$

**Test for subgroup differences:** $\chi^2 = .07, P = .94$

Biologic treatment may save lives

<table>
<thead>
<tr>
<th></th>
<th>Biological agents</th>
<th>Methotrexate</th>
<th>Other therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death, myocardial infarction and stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence rate (95% CI)</td>
<td>6.0 (2.7–13.4)</td>
<td>17.3 (12.3–24.3)</td>
<td>44.5 (34.7–57.0)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.20 (0.09–0.47)</td>
<td>0.57 (0.37–0.87)</td>
<td>Ref.</td>
</tr>
<tr>
<td>HR adjusted for age and sex (95% CI)</td>
<td>0.28 (0.12–0.64)</td>
<td>0.65 (0.42–1.00)</td>
<td>Ref.</td>
</tr>
<tr>
<td>HR adjusted for age, sex, medication, comorbidity and socioeconomic status (95% CI)</td>
<td>0.29 (0.12–0.68)</td>
<td>0.73 (0.47–1.14)</td>
<td>Ref.</td>
</tr>
</tbody>
</table>

Danish real-world cohort study. J Internal Medicine 2012, in press

Industry sponsored Registries for systemic therapies in Psoriasis

- Registry including all therapies but targeting mainly Ustekinumab and Infliximab:
  - **PSOLAR** - established in 2009
    - USA
    - Canada
    - Mexico
    - Europe

- Registries for specific biologics:
  - **RESULTS** (T45). For Infliximab. Established 2002
  - Observe-5. For Etanercept.
  - **ESPRIT**. For Adalimumab.
### European Registries for systemic therapies in Psoriasis (independent from industry)

<table>
<thead>
<tr>
<th>Country</th>
<th>Italy</th>
<th>Sweden</th>
<th>Germany</th>
<th>Israel</th>
<th>UK</th>
<th>Netherlands</th>
<th>Spain</th>
<th>France</th>
<th>Denmark</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>PsoCare</td>
<td>Psoreg</td>
<td>PSOBEST</td>
<td>Clalit</td>
<td>BADBIR</td>
<td>PRESTON</td>
<td>BIOBADA DERM</td>
<td>PSOBIO-RAPSOBIO</td>
<td>DermBio</td>
</tr>
<tr>
<td>Type</td>
<td>Prospective cohort</td>
<td>Prospective cohort</td>
<td>Prospective cohort</td>
<td>Prospective Cohort and data mining</td>
<td>Prospective Cohort Biologics vs conventional</td>
<td>Prospective cohort</td>
<td>Retrospective &amp; prospective with controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapies</td>
<td>All systemic agents</td>
<td>All systemic agents</td>
<td>All systemic agents</td>
<td>All systemic agents</td>
<td>All systemic agents</td>
<td>All systemic agents</td>
<td>All systemic agents</td>
<td>Biologics</td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>16,151*</td>
<td>&lt; 2,000</td>
<td>&lt; 2,000</td>
<td>&lt; 2,000</td>
<td>&lt; 2,000</td>
<td>&lt; 2,000</td>
<td>&lt; 2,000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other countries with registries: Portugal, Tunisia, Switzerland
KEY ISSUES: Immunogenicity
Unwanted Immunogenicity

Proteins → Patients

Induce antibodies

Neutralise biological effects and compromise further therapy *e.g.*, Factor VIII

Alter pharmacokinetics

Cross-react with native protein and induce adverse reactions *e.g.*, EPO (PRCA)

No effect

Health Canada evaluates comparability for a single manufacturer/product before and after process changes – to ensure that patient outcomes will not be affected.¹

Health Canada considers an SEB a standalone product as it does not require the assessment of similarity between an SEB and reference biologic drug after approval²

Source: adapted from Dr. Amy Rosenberg (FDA)

¹Kay J, et al., Health Canada/BIOTECanada Summit on regulatory and clinical topics related to subsequent entry biologics (biosimilars), Biologicals (2012)
Immunogenicity is a Concern with Biologics

The complexity of the antigen determines the number of epitopes on the antigen and the number of antibody molecules that can bind to the antigen at any one time.


TNF Inhibitors: A Molecular Comparison

Etanercept

- Fc region of Human IgG1
- Extracellular Domain of Human p75 TNF receptor
- A human soluble receptor

Infliximab

- Mouse (Binding site for TNF)
- Human (IgG1)

Adalimumab

- Contains human CDR regions

Human (IgG1)

A chimeric monoclonal antibody

A human monoclonal antibody
Factors Affecting Immunogenicity

- Protein structure and aggregation
- Post-translational modifications
- Formulation
- Contaminants and impurities
- Route, dose, frequency, duration of administration
- Patient genetics (MHC)
- Associated diseases and concomitant therapies
- Immune modulatory effects of protein

Summary Immunogenicity

• Process changes adverse event - Eprex; pure red cell aplasia
• Changes in product impact efficacy
• Immunogenicity Vedolizumab - 40% produced auto antibodies – need for new dose ranging trial
• Infliximab biosimilar - urticaria
• Omnitrope increased related adverse events, increased auto antibodies
KEY ISSUES:

*Interchangeability/Substitution*
Withdrawal of Generic Budeprion for Nonbioequivalence

Janet Woodcock, M.D., Mansoor Khan, R.Ph., Ph.D., and Lawrence X. Yu, Ph.D.
SWITCH Trial in Chron’s Disease
Leuven Cohort (N=73)

- Prospective and randomized
- Patients on controlled maintenance IFX therapy (≤ 6 months) with elective switch to ADA for reasons of convenience
- All five sAEs were related to complicated Chron’s disease and occurred in patients randomized to adalimumab
- Dose optimization or interruption of treatment occurred in 17/36 patients (47%) in the ADA group and in 6/37 patients (16%) in the IFX group (p=0.006)
- Elective switching in patients with long-standing remission is associated with very poor results: loss of tolerance and loss of efficacy within 1 year
- Adherence to the first anti-TNF agent is recommended
Psoriasis switch Data

Efficacy and safety of adalimumab in patients with plaque psoriasis who have shown an unsatisfactory response to etanercept

Robert Bissonnette, MD, FRCPC,a Chantal Bolduc, MD, FRCPC,a Yves Poulin, MD, FRCPC,b Lyn Guenther, MD, FRCPC,c Charles W. Lynde, MD, FRCPC,d and Catherine Maari, MD, FRCPCa
Montreal and Quebec, Quebec, and London and Markham, Ontario, Canada
Summary of Data: Omnитrope (Somatotropin)

• Adverse events more common in Omnитrope (SBE)

• Treatment related hypothyroidism 14% vs. 4%

• Growth hormone antibodies more common Omnитrope (SBE) 56% vs. 2% (no RCTs single open label study for 9 months)
Expert Opinion on Extrapolation

- The mechanism of action for REMICADE® in Rheumatoid Arthritis is not necessarily similar in IBD\(^1,2\). Therefore, clinical outcomes in one indication may not be applicable in another

- “... the mechanisms of action of the TNFa antagonists are not completely understood, and that subtle molecular differences in a biologic drug may alter binding to targets in the body and lead to different clinical effects”\(^1\) (Brian G. Feagan, MD, FRCPC: Kay et al, 2012)

- “it may not be possible to extrapolate clinical data for a monoclonal antibody in one rheumatologic indication to other rheumatologic indications because of differences in dose, duration of therapy, efficacy of monotherapy vs. combination therapy, and stated claims of efficacy for those indications”\(^1\) (Jiang Wang, MD, PhD, Health Canada: Kay et al, 2012)

\(^{1}\)Kay J, et al., Health Canada/BIO-TECanada Summit on regulatory and clinical topics related to subsequent entry biologics (biosimilars), Ottawa, Canada, 14 May 2012. Biologicals (2012)

Biopharmaceuticals and biosimilars in psoriasis: What the dermatologist needs to know

Bruce E. Strober, MD, PhD, Katherine Armour, MD, Ricardo Romiti, MD, Catherine Smith, MD, Paul W. Tebbey, PhD, Alan Menter, MD, and Craig Leonardi, MD

Farmington, Connecticut; Victoria, Australia; São Paulo, Brazil; London, United Kingdom; Dallas, Texas; St Louis, Missouri
Position Statement on Generic Therapeutic & Biosimilar Substitution

(1) in the case of biosimilars, the biosimilar has a unique nonproprietary name to eliminate confusion, to allow providers to accurately track the therapeutic in a patient’s permanent record, and to allow for the collection of adverse event information;

(2) in the case of biosimilars, the biosimilar has been designated by the Food and Drug Administration as interchangeable\(^1\) with the prescribed biologic for the specified indicated use;

(3) the prescribing physician provides explicit permission to the pharmacist that a generic therapeutic or biosimilar may be used as a substitute to the original therapeutic or biologic medication;

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\(^{1}\) Interchangeability is defined in the Patient Protection and Affordable Care Act (ACA) as a biosimilar product that shows sufficient data to demonstrate that the product: 1) is a biosimilar to the reference product, 2) can be expected to produce the same clinical result as the reference product in any given patient, and 3) would have no enhanced risk in terms of safety and efficacy when switching or alternating between a biosimilar and reference product, when compared to the risk and effectiveness profile of the reference product.
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<table>
<thead>
<tr>
<th>Substitutability/Interchangeability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No substitutability/Interchangeability declaration by HC</strong></td>
</tr>
<tr>
<td><strong>Regulation:</strong> no declaration of substitutability/interchangeability by HC</td>
</tr>
<tr>
<td><strong>Quality:</strong> In view of the complexity and sensitivity of biologics to the manufacturing process, two biologics cannot be exactly the same</td>
</tr>
<tr>
<td><strong>Safety:</strong> As a consequence of their complexity and impurity profile, automatic substitution of biologicals could give rise to different (and sometimes unexpected) clinical consequences</td>
</tr>
<tr>
<td><strong>Health care: Interchangeability remains a provincial decision</strong></td>
</tr>
<tr>
<td><strong>Clinical Practice:</strong> The decision to treat a patient with a RBD or an SEB is within the authority of a qualified healthcare professional, and in the best interest of his/her patients</td>
</tr>
</tbody>
</table>
Points of Discussion
Subsequent entrance biologics.

• Lower cost possible

• Loss of efficacy with substitution probable

• Increased adverse events (Onmitrope example confirms) probable

• Viewed as new chemical entities definite