Patiënten-onderzoeken naar overstappen
Wat leren we van trials en registries

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Disclosure statement

• Independent PhD researcher of the MABEL Fund

• MABEL Fund
  • Market Analysis of Biologics and Biosimilars following Loss of Exclusivity
  • Collaboration between KU Leuven, Belgium and the Erasmus University Medical Center, the Netherlands
  • Prof. I. Huys, Prof. S. Simoens, Prof. P. Declerck, Prof. A.G. Vulto
  • Supported by pharmaceutical companies via an unrestricted grant

• https://pharm.kuleuven.be/clinpharmacotherapy/mabel
To switch or not to switch: that is the biosimilar question

Silvio Danese and Laurent Peyrin-Biroulet

Biosimilar monoclonal antibodies are now being accepted in clinical practice by IBD specialists. However, switching patients already undergoing originator biologic treatment to biosimilars has been debated due to lack of controlled studies. The NOR-SWITCH study now provides novel clinical evidence in switching from originator to biosimilar in patients with IBD.

Refers to Jorgensen, K. K. et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet 389, 2304–2310 (2017)

Patients were followed for 52 weeks. The two treatment groups were similar for major baseline demographic and disease characteristics; disease-specific measures suggested low disease activity at baseline.

The primary study end point of disease worsening occurred in 53 (26%) patients in the infliximab originator group and in 61 (30%) patients in the CT-P13 group, a risk difference of –4.4%, with a 95% CI of –12.7% to 3.9%, within the pre-specified noninferiority margin of 15%. Additionally, remission occurred in 123 (61%) patients in the infliximab originator group and 126 (61%) patients in the CT-P13 group, an adjusted rate difference of 0.6% (95% CI –7.5% to 8.8%). Looking specifically at patients with Crohn’s disease, disease worsening occurred in 14 (21%) patients in the infliximab originator group and in 23 (36%) patients in the CT-P13 group, a risk difference
Attitudes are changing in the medical and regulatory community

Federal Agency for Medicines and Health Products (FAMHP)
If the prescriber decides to move from one to the other (original/original; original/biosimilar; biosimilar/original or biosimilar/biosimilar, often also called "switch" in this context), then this must be done with the necessary follow-up and the modification must be recorded accurately. The exclusion of INN prescription avoids switching without follow-up by the prescriber. However, since the biosimilar medicinal product can only be authorised if it has the same safety and efficacy profile as the reference medicinal product, relevant changes in treatment are not expected upon switching from the reference product to a biosimilar medicinal product (or vice versa).

Danish Medicines Agency (LIS)
Would it be problematic to switch to a biosimilar medicinal product?
“No. The biosimilar medicinal product can only be authorised if it has the same efficacy profile as the reference medicinal product, and consequently you will not experience any changes in your treatment if you switch to a biosimilar medicinal product.”

ECCO 2016
- Switching from the originator to a biosimilar in patients with IBD is acceptable. Studies of switching can provide valuable evidence for safety and efficacy. Scientific and clinical evidence is lacking regarding reverse switching, multiple switching, and cross-switching among biosimilars in IBD patients.
- Switching from originator to a biosimilar should be performed following appropriate discussion between physicians, nurses, pharmacists, and patients, and according to national recommendation. The IBD nurse can play a key role in communicating the importance and equivalence of biosimilar therapy.

ESMO 2017
Interchangeability and switching should only be permitted if
- the physician is well-informed about the products;
- the patient is fully briefed by the physician; and
- a nurse is closely monitoring the changes and tracking any adverse events.
Interchangeability: European perspective

Interchangeability of Biosimilars: A European Perspective

Pekka Kurki¹ · Leon van Aerts² · Elena Wolff-Holz³ · Thijs Giezen⁴ · Venke Skibell⁵ · Martina Weise⁶

“.. a state-of-the-art demonstration of biosimilarity, together with intensified PMS, is a sufficient and realistic way of ensuring interchangeability of EU-approved biosimilars under supervision of the prescriber. In the authors’ opinion, biosimilars licensed in the EU are interchangeable if the patient is clinically monitored, will receive the necessary information, and, if needed, training on the administration of the new product.”

"We have found no evidence from clinical trial data or post marketing surveillance data that switching to and from different biopharmaceuticals leads to safety concerns."

More and more (complex) biosimilars are entering the market

<table>
<thead>
<tr>
<th>Active substance</th>
<th>Authorized biosimilars by EC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>Amgevita, Cyltezo, Imraldi, Solymbic</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>Inhixa, Thorinane</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>Abseamed, Binocrit, Epoetin Alfa Hexal, Retacrit, Silapo</td>
</tr>
<tr>
<td>Epoetin zeta</td>
<td></td>
</tr>
<tr>
<td>Etanercept</td>
<td>Benepali, Erelzi</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Accofil, Filgrastim Hexal, Grastofil, Nivestim, Ratiogrestim, Tevagrestim, Zarzio</td>
</tr>
<tr>
<td>Follitropin alfa</td>
<td>Bemfola, Ovaleap</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Flixabi, Inflectra, Remsima</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>Lusduna, Abasaglar</td>
</tr>
<tr>
<td>Insulin lispro</td>
<td>Insulin lispro Sanofi</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Ritemvia, Blitzima, Rituzena, Riximyo, Rixathon, Truxima</td>
</tr>
<tr>
<td>Somatropin</td>
<td>Omnitrope</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>Movymia, Terrosa</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Ontruzant</td>
</tr>
</tbody>
</table>

38 biosimilar products authorized in EU

23 distinct biosimilars (=38 products) for 13 different RPs

RP, reference product.
EMA: Biosimilar medicines. Accessed 11 December 2017
Can patients under treatment with a reference biological safely be switched to its biosimilar version? What is the current evidence?

**Systematic literature review of switching studies**
- Switch from reference biological medicine to biosimilar
- All therapeutic classes with a biosimilar authorized by EMA or in registration
- Sources:
  - Biomedical databases: Embase, Medline, Cochrane, Web of Science
  - Search strings validated by Medical library Erasmus MC & MGAS KUL
  - 1853 articles screened
  - Conference abstracts, posters, ClinicalTrials.gov, snowballing
Switch studies for different therapeutic classes

- **Haematopoietic growth factors**
  - Epoetin alfa/zeta
  - Filgrastim

- **Endocrinologically acting medicines**
  - Follitropin alfa
  - Insulin glargine/lispro
  - Somatropin

- **Anti-TNFs**
  - Adalimumab
  - Etanercept
  - Infliximab

- **LMWH**
  - Enoxaparin

- **mAbs in oncology**
  - Rituximab
  - Trastuzumab

LMWH, low-molecular-weight heparin; mAb: monoclonal antibody
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## Applied selection criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Patients under treatment with a biological medicine</td>
<td>- Bio-naïve patients</td>
</tr>
<tr>
<td></td>
<td>- Healthy volunteers</td>
</tr>
<tr>
<td>- Switching from a biological reference product to its biosimilar version</td>
<td>- No switch</td>
</tr>
<tr>
<td></td>
<td>- Switch between different INNs</td>
</tr>
<tr>
<td></td>
<td>- Switch between small-molecule and generic medicine</td>
</tr>
<tr>
<td>- Studies with efficacy and/or safety measurement (phase III clinical trial, real</td>
<td>- Non clinical study</td>
</tr>
<tr>
<td>world clinical study, qualitative study measuring patient experience)</td>
<td>- Study without intervention (literature review, expert opinion, guideline, meta-</td>
</tr>
<tr>
<td></td>
<td>analysis, drug-utilization study without clinical or pharmaco-therapeutical outcome</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

INN, international non-proprietary name.  
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Number of switch trials

Overall 109 studies including a switch from RP → biosimilar

Bulk of the data for anti-TNF

GH: growth hormone, mAb, monoclonal antibody, RP: reference product, TNF: tumor necrosis factor
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Overall (N studies=109) 15 248 patients switched from RP to biosimilar* in a monitored setting

*For epoetin: from different ESA → biosimilar.
ESA, erythropoiesis-stimulating agents; GH, growth hormone; mAb, monoclonal antibody; RP, reference product.
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A substantial part of switch trials are single arm studies
### Different possible designs of switch studies

<table>
<thead>
<tr>
<th>Design Description</th>
<th>Reference (R)</th>
<th>Biosimilar (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single switch, single arm</td>
<td>R</td>
<td>B</td>
</tr>
<tr>
<td>Single switch, parallel arm</td>
<td>Rand.</td>
<td>R</td>
</tr>
<tr>
<td>Single switch, parallel arm</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Single switch, cross-over</td>
<td>B</td>
<td>R</td>
</tr>
<tr>
<td>Multiple switch/alternating</td>
<td>B</td>
<td>R</td>
</tr>
</tbody>
</table>
Single arm studies/registries are hard to interpret

Kaplan–Meier survival curve based on the use of IFX in all patients with CD

Is the **observed decrease in efficacy** due to:
- the **normal course** in duration of response?
- the **switch** (development of ADAs)?

**ADA**, antidrug antibodies.

**Single arm studies and registries lead to limited evidence**

*Need for hard, objective endpoints*
Even well-designed trials may not be sensitive to detect small differences in efficacy

Median time to relapse CD after **treatment withdrawal** in infliximab responders

**Figure 2.** Kaplan–Meier time-to-relapse curve of the 115 included patients. The median ± SE follow-up time was 28 ± 2 months. There were 52 patients with confirmed relapse. The median time to relapse was 16.4 months.
Anti-drug antibody measurement in switch studies

N studies with ADA and/or TL measurement
N studies with no ADA/TL measurements/reportings

17

Overall N

GH
Epoetin
Filgrastim
Anti-TNF
Insulin
mAb in onco

46
63
13
1
3
1
2
6
0

ADA or TL not systematically measured during switch studies

GH, growth hormone; mAb, monoclonal antibody; TL, trough level.
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Overview reported final conclusion of authors switch studies

- N studies concluded comparable efficacy and safety
- N studies concluded differences in safety/efficacy/retention/dose

GH, growth hormone; mAb, monoclonal antibody
Manuscript in preparation.
## Results for switch studies rituximab (N=5)

<table>
<thead>
<tr>
<th>Switch</th>
<th>N</th>
<th>Indication</th>
<th>Study design</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTX → BCD-020*</td>
<td>80</td>
<td>Rheumatoid arthritis</td>
<td>Double blind RCT, partial cross over</td>
<td>24w</td>
</tr>
<tr>
<td>RTX → CT-P10</td>
<td>20</td>
<td>Rheumatoid arthritis</td>
<td>Open label extension phase I</td>
<td>24w</td>
</tr>
<tr>
<td>RTX → CT-P10</td>
<td>109</td>
<td>Rheumatoid arthritis</td>
<td>Open label extension phase III</td>
<td>24w</td>
</tr>
<tr>
<td>RTX → GP2013</td>
<td>53</td>
<td>Rheumatoid arthritis</td>
<td>Double blind RCT, parallel arm</td>
<td>24w</td>
</tr>
<tr>
<td>RTX → PF-05280586</td>
<td>125</td>
<td>Rheumatoid arthritis</td>
<td>Double blind RCT, parallel° arm</td>
<td>3 x 24 w</td>
</tr>
<tr>
<td>RTX → CT-P10°</td>
<td>recruiting</td>
<td>LTB follicular lymphoma</td>
<td>Double blind RCT, parallel arm</td>
<td>NR</td>
</tr>
</tbody>
</table>

- Overall, no indications of safety issues or loss of response
- Switch studies in non-oncology indications
- Concomittant MTX

*Trend of higher rate of AEs in switch arm for BCD-020, BCD-020 is approved in Russia and India, not in EU/US, °only during 1st 24 w of treatment, clinicaltrials.gov NCT02260804 – recruiting status, no results yet, not included in review, LTB: low tumour burden Manuscript in preparation
Results for switch studies trastuzumab (N=1)

<table>
<thead>
<tr>
<th>Switch</th>
<th>N</th>
<th>Indication</th>
<th>Study design</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRZ → ABP 980</td>
<td>171</td>
<td>Adjuvant EBC</td>
<td>Phase III randomized, parallel arm</td>
<td>NR*</td>
</tr>
</tbody>
</table>

Biosimilar ABP 980 in patients with early breast cancer: Results of single switch from trastuzumab to ABP 980

von Minckwitz G, Turdean M, Zhang N, Santi P, Hanes V German Breast Group, Neu-Isenburg, Germany; Emergency County Hospital Cluj, Cluj-Napoca, Romania; Amgen, Inc., Thousand Oaks, CA; Centro de Estudos de Hematologia Oncologia, Sao Paulo, Brazil

Background: Analytical, functional, and pharmacokinetic similarity between ABP 980 and trastuzumab (TRAS) has been demonstrated. Here we report results from the single switch treatment arm in the adjuvant phase of the corresponding clinical study.

Methods: The objective of this randomized, multicenter, double-blind study was to compare ABP 980 with TRAS in women with HER2-positive early breast cancer. Patients were randomized 1:1 to intravenous ABP 980 or TRAS (breast and sentinel node or axillary lymph node dissection) in a 3-weekly schedule. Following surgery, patients who initially received TRAS were to undergo a single switch to receive ABP 980 Q3W for up to 1 year (IP) in the neoadjuvant phase. Allocation occurred at random. The objective of the single switch was to evaluate safety and tolerability of switching from TRAS to ABP 980.

"Switching from TRAS to ABP 980 following surgery was safe in patients with breast cancer. Switching did not increase the frequency or severity of AEs and no unexpected safety signals were noted, and it did not increase the incidence of developing ADAs."
Overview reported final conclusion of authors switch studies

- N studies concluded comparable efficacy and safety
- N studies concluded differences in safety/efficacy/retention/dose

GH, growth hormone; mAb, monoclonal antibody
Manuscript in preparation.
Overview reported final conclusion of authors switch studies

<table>
<thead>
<tr>
<th>Ref</th>
<th>Switch</th>
<th>N</th>
<th>Study design</th>
<th>Follow-up</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>EPO → biosimilar</td>
<td>163</td>
<td>Retrospective matched control study</td>
<td>24 weeks</td>
<td>Demonstrated a <strong>dosing penalty</strong> when switching, 40% higher doses required to maintain anemia control</td>
</tr>
<tr>
<td>2.</td>
<td>Insulin → biosimilar</td>
<td>24</td>
<td>Retrospective chart review</td>
<td>Median of 33 weeks</td>
<td>Indicated a small increase in insulin dose after switch</td>
</tr>
</tbody>
</table>

- **GH**: growth hormone; **mAb**: monoclonal antibody

Manuscript in preparation.
## Anti-TNF switch studies concluding differences between groups

<table>
<thead>
<tr>
<th>Ref</th>
<th>Switch</th>
<th>Indication</th>
<th>N</th>
<th>Design</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>IFX → biosimilar</td>
<td>RA, SpA, IBD, other*</td>
<td>260</td>
<td>Prospective, single switch, single arm</td>
<td>Mean of 34 weeks</td>
</tr>
<tr>
<td>2.</td>
<td>IFX → CT-P13</td>
<td>RA, AS, PsA</td>
<td>89</td>
<td>Prospective, single switch, parallel arm**</td>
<td>Median of 33 weeks</td>
</tr>
<tr>
<td>3.</td>
<td>IFX → CT-P13</td>
<td>RA, AS, PsA</td>
<td>192</td>
<td>Prospective, single switch, single arm</td>
<td>6 months</td>
</tr>
<tr>
<td>4.</td>
<td>IFX → CT-P13</td>
<td>CD, UC</td>
<td>133</td>
<td>Prospective, single switch, single arm</td>
<td>12 months</td>
</tr>
<tr>
<td>5.</td>
<td>IFX → CT-P13</td>
<td>PsA, AS, RA, CD with associated SpA</td>
<td>23</td>
<td>Single switch, single arm</td>
<td>Mean 1.7 months</td>
</tr>
</tbody>
</table>

**prospective cohort of IFX naïve patients and retrospective cohort of patients treated with originator as controls

4 of 5 switch studies for anti-TNF that concluded differences after switching/between groups reported a high number of discontinued treatment mainly driven by worsening in PROs potentially due to attribution/nocebo effect

Real world studies: the experience of Cochin university hospital

<table>
<thead>
<tr>
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<th>Design</th>
<th>Follow-up</th>
</tr>
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<td>RA, SpA, IBD, other*</td>
<td>260</td>
<td>Prospective, single arm, single switch</td>
<td>Mean of 34 w</td>
</tr>
</tbody>
</table>

- 23% patients discontinued biosimilar
- In discontinuation cases: 80% of patients experienced inefficacy
  - SpA patients: significant increase in PRO measures
  - Patients who switched back to originator saw subjective disease activity measures improved
- No changes in trough levels or objective parameters (CRP, swollen joints)

*20 patients with other rheumatic diseases, 8 patients with uveitis, 6 patients with ‘other’
Registries: the example of DANBIO

<table>
<thead>
<tr>
<th>Switch</th>
<th>Indication</th>
<th>N</th>
<th>Study design</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>infliximab → CT-P13</td>
<td>RA, SpA, PsA</td>
<td>802</td>
<td>Registry</td>
<td>3 m (disease activity), 6 m (ADA + TL), 1 y (retention rate)</td>
</tr>
</tbody>
</table>

- **ACR 2016 - preliminary data**
  - ~6% stopped treatment due to LOE or AE
  - ‘further investigation warranted before non-medical switch can be recommended’

- **1 year data – full report**
  - Disease activity and flare rates similar pre/post switch
  - CT-P13 retention rate *slightly lower* (difference of 3.4%) compared with IFX in historic cohort

- **TL + ADA measurements in 231 pts**
  - No difference in ADA or serum IFX at 3 and 6 months

Comparison with historic cohort of IFX pts


ADA: antidrug antibody; AE: adverse events; LOE: loss of efficacy.
Based on current evidence, **no clear indication** that switching from originator biologicals to biosimilars leads to **safety issues or loss of response**

**Data on switching are accumulating:**
- Combination of clinical trial extension studies, registries, real world studies
- Studies across various disease indications and products
- Bulk of the data for anti-TNF (CT-P13)

**Current switch studies have limitations:**
- Most trials **insufficiently sensitive** (underpowered, short follow-up) to identify differences in efficacy or rare adverse events
- **Registries/single arm studies** give **limited evidence**
- Little data on **multiple switching/alternating**
- No data on **switching between biosimilars**
Take home message

- **Residual uncertainty:**
  - Thus far, no evidence that switching has lead to safety issues
  - No evidence to exclude any risk
  - More data needed? What type of evidence is needed? Unrealistic burden of proof?
  - Harmonization of different approaches of switching studies/switching in clinical practice

- A key concern when switching is **potential increase in immunogenicity**:
  - **Determine ADAs** in relation to clinical outcomes or trough levels/implement TDM
  - No issues identified so far

- Continued **pharmacovigilance** and traceability remains key, as is the case for all biologicals
Bedankt voor uw aandacht!

Vragen?

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