Clinical research with biosimilars in The Netherlands

Lissy de Ridder; Pediatric gastroenterologist
Biosimilars Nederland, Amsterdam 3 september 2015
CONFLICT OF INTEREST

Involved in industry sponsored studies, investigator initiated studies and/or consultancies with Shire, Merck, Janssen biologics, Abbvie and Hospira
Biosimilars: development and research

Somewhere far away?
Biosimilar research in Nederland

Or in our backyard?
INDUSTRY INITIATED TRIALS
CD3.4 Study in IBD patients (Hospira/Celltrion)

• The primary objective:
  • To demonstrate that IFX biosimilar is noninferior to IFX originator at Week 6 (Dose 3), in terms of efficacy, as determined by the CDAI-70 response rate

• Secondary objectives:
  • To evaluate long-term secondary efficacy of CT-P13 in comparison with Remicade up to Week 54
  • To evaluate overall safety of CT-P13 in comparison with Remicade up to Week 54

• Tertiary Objectives
  • To evaluate long-term tertiary efficacy of CT-P13 in comparison with Remicade up to Week 54.
  • To evaluate pharmacokinetics of CT P13 in comparison with Remicade up to Week 22.
    - To evaluate biomarkers (optional)

• 3 sites in Netherlands and 3 sites in Belgium participating in study
Study Design

- **Duration of patient’s participation**: at least 11 visits during 68 weeks (screening + treatment + follow-up)
- Random assignment in a 1:1:1:1 ratio to 4 groups:
  - IFX biosimilar during the whole treatment (53 patients)
  - IFX originator during the whole treatment (53 patients)
  - IFX originator, switch to IFX biosimilar at Week 30 (53 patients)
  - IFX biosimilar, switch to IFX originator at Week 30 (53 patients)

![Table of Doses](image)
Secure study (IFX4501)
9 Dutch hospitals

<table>
<thead>
<tr>
<th>Remicade treatment</th>
<th>Remsima treatment</th>
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<tr>
<td>For &gt; 30 weeks</td>
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Day 0

V1 visits

V2
8±1 weeks

V3
16±1 weeks

Design: open, GCP phase 4
Patients: RA, CU, CD
10 centres in NL
159 patients planned
11 patients included
SECURE study: primary objective

• To demonstrate that the infliximab serum concentration of Remsima is non-inferior to the infliximab concentration of Remicade,
• 16 weeks after switch from Remicade to Remsima
• in subjects with CD, UC or RA in stable remission for > 30 weeks
• measured by a bridging enzyme-linked immunosorbent assay (ELISA)
INVESTIGATOR INITIATED TRIALS
SIMILAR Trial

Santeon InflixMab biosimilar Research

A randomized, controlled, double blind, phase 4 noninferiority trial
to assess efficacy of Infliximab-biosimilar (Inflectra) compared to
Infliximab-innovator (Remicade) in patients with inflammatory
bowel disease in remission

j.m.jansen@olvg.nl
Rationale

• Is active switching of IBD patients in remission from Infliximab-innovator to Infliximab-biosimilar feasible?
Main Objective

• To compare the efficacy of Infliximab-biosimilar to Infliximab-innovator and to demonstrate its noninferiority up to 30 weeks, in patients with ulcerative colitis or Crohn’s disease in remission under treatment with infliximab for at least 12 weeks.

Secondary objectives:
• Evaluation of adverse effects.
• Evaluation of pharmacokinetics.
Study design

- A randomized, double-blind, multicentre, prospective study to assess the non-inferiority in efficacy of Infliximab-biosimilar (5mg/kg to 10mg/kg) compared to Infliximab-innovator (5mg/kg to 10mg/kg) in patients with CD or UC in remission under treatment with Infliximab for at least 12 weeks.
Nederlands Trial Register
St Maartenskliniek

• **Public Title**   The effect of switching treatment from innovator infliximab to infliximab biosimilar on efficacy, safety and immunogenicity in patients with rheumatoid arthritis, spondyloarthritis or psoriatic arthritis in daily clinical care

• **Scientific Title**   BIO-SWITCH study: Biosimilar of Infliximab Options, Strengths and Weaknesses of Infliximab Treatment CHange

• **ACRONYM**   BIO-SWITCH
BIO-SWITCH

• Inclusion criteria
• 1. A clinical diagnosis of either RA, SpA or PsA
• 2. Currently being treated with Remicade (1 or more infusions)
• 3. > 18 years of age
• 4. Ability to read and communicate well in Dutch
• 5. Informed consent
Paediatric IBD

Incurable, life changing disease
Aim of treatment

- Aiming at mucosal healing
- Prevent exacerbations
- Maximal efficacy and minimal toxicity
- Limit steroid use
- Optimal growth, normal pubertal development
- Prevent surgery

Persisting disease activity

Complications
Colon cancer

Treatment

Cancer (lymphoma)
Death (infection)
1992

1st Crohn’s disease patient worldwide treated with infliximab:
A child!

THE LANCET

Tumour-necrosis-factor antibody treatment in Crohn’s disease

Sir—We report a girl with Crohn’s disease who was not responsive to medical therapy but in whom complete but temporary remission could be achieved by treatment with tumour necrosis factor (TNF) monoclonal antibodies.

Bert Derkx, Jan Taminiau, Sandra Radema, Arnold Stronkhorst, Cees Wortel, Guido Tytgat, Sander van Deventer
Departments of Paediatric Gastroenterology, Nutrition, and Gastroenterology, Academic Medical Centre, 1105 AZ Amsterdam, Netherlands
Anti-TNF in Crohn’s disease

- 1995: DBRCT, adults, 1 infusion
- 1996: DBRCT, induction, adults with fistulizing disease
- 1999: DBRCT, ACCENT I, adults, maintenance
- 1999: DBRCT, ACCENT II, adults with fistulizing disease, maintenance
- 2007: RCT, REACH, children, infliximab maintenance
- 2009: SONIC, adults, naïve patients
- 2012: RCT, IMAGINE, children, adalimumab maintenance
Biosimilar research in children!
TISKids – Top down vs step up

**Inclusion:**
- 3-17 years of age
- Untreated Crohn
- Moderate-to-severe

**Exclusion:**
- Need for surgery
- Severe comorbidity

**Top-down**
- Azathioprine 2-3mg/kg/day
- Prednisolone
- Relapse

**Step-up**
- Azathioprine 2-3mg/kg/day
- Prednisolone
- Relapse

**RNA expression profiles**
- Peripheral Blood Lymphocytes
- Mucosal Biopsies

With support of ZonMw, Hospira, Crookids
Why would Top-down be better?

- Increased mucosal healing rates
  - viewed as the primary treatment goal
  - may result in less disease flares, complications, disease progression

- Higher quality of life and low risk of side effects

- Infliximab is more effective when given early after diagnosis

- Ceasing infliximab after 5 infusions may reduce healthcare costs
Top-down versus Step-up

Primary endpoint

Clinical remission (wPCDAI<12.5) without need for additional CD-related therapy or surgery
Secondary goals

• Study pharmacokinetic properties of IFX
• Identify predictive markers for IFX response
• Compare the cost-efficacy of Top-down versus Step-up
  – Correlate clinical disease activity with mucosal healing

• Sub-analysis:
  – Comparing EEN (+AZA) with prednisolon (+AZA)
To summarize, biosimilar..

- Developed in the Netherlands
- Industry initiated studies
- Investigator initiated studies
  - In adults
  - In children
Thanks for paying attention!
Clinical and endoscopic remission
• Remission is defined as a fecal calprotectin <250 mg/g in combination with the following:
  – CD: HBI score <5 with a SES-CD score ≤2.
  – UC: Total Mayo ≤2, with no individual subscore exceeding 1 point.

Relapse rate
• A colonoscopy will be performed in case of worsening of symptoms in combination with a fecal calprotectin >250 mg/g.
  • Endoscopy:
    – CD: SESS-CD score >2
    – UC: Mayo endoscopy score of ≥2.
    – A clinical need for change in treatment.