Biosimilars: An Update on Clinical Trials (Review of Published and Ongoing Studies)

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ABSTRACT Biosimilars represent a new trend in the treatment of many immune-mediated inflammatory diseases. Regulatory requirements for approval of biosimilars are different from those of originators and rely mostly on the evidence generated from bioequivalence studies and in particular from RCTs. Our goal in this review was to search for relevant studies from randomized controlled trials on the biosimilars adalimumab, etanercept, infliximab and ustekinumab compared with their reference medication (publication in Medline) and ongoing studies in clinical trial registries. For infliximab biosimilars, we found data on patients with ankylosing spondylitis rheumatoid arthritis indicating no clinically relevant differences regarding efficacy and safety, as well as data on inflammatory bowel diseases and psoriasis. In addition, three registered studies of adalimumab biosimilars and just one study of an etanercept biosimilar were being carried out in patients with psoriasis. Ongoing studies on adalimumab, etanercept, and infliximab biosimilars in patients with rheumatoid arthritis were also identified. The conclusion seems to be that there are only 4 clinical trials on psoriasis (3 for the adalimumab biosimilar and 1 for etanercept biosimilar) and 1 clinical trial for PsA, CD, UC, RA, and AS (with the Infliximab biosimilar). Thus, the real and unique advantage of biosimilars is the low price derived from the special design studies despite the high technology used in fabrication process. Although not all ongoing biosimilar trials may have been registered, the present situation in terms of registered trials is quite unsatisfactory and provision of further clinical data and inclusion of patients in patient registries will be crucial.

KEY WORDS: biosimilar, review, clinical trial, biologic, psoriasis, adalimumab, etanercept, infliximab, Remsima, Inflectra

INTRODUCTION
The development of biologic drugs has enhanced the spectrum of treatments available for immune-mediated inflammatory diseases. However, despite their clear clinical benefit, use of biologics is often hindered by their high costs. As the patent for many TNF-alpha antagonists has expired or will soon expire, the development of biosimilars may lower treatment cost and increase patient treatment options. With the introduction of the first biosimilars we also have to introduce new terms such as extrapolation, interchangeability, traceability, and substitution in order to understand the real concept of bioequivalence (1,2). Regarding long-term safety, there are some issues with immunogenicity that can occur even in later stages (more than a year).
The first biosimilar of the monoclonal antibody infliximab CT-P13 was approved in September 2013 by the European Medicines Agency (EMA) under the brand name of Remsima and Inflectra (1,2). This product was approved for all of Remicade’s indications, although the comparative clinical trials were only conducted in patients with RA and AS (3). The patent protection for Enbrel and Humira will expire in most European countries on February 1st, 2015 and April 16th, 2018, respectively, and several biosimilars of etanercept and adalimumab are currently undergoing clinical trials (1-4).

There are many differences among different countries regarding criteria for regulatory approval of biosimilars. The economic advantage is real, but bioequivalence cannot be equated to therapeutic equivalence and should be demonstrate with further post marketing studies (4).

METHODS

We systematically reviewed published trials on the efficacy and safety of biosimilars in the literature as well as planned and ongoing trials in registries.

Eligibility criteria

Randomized controlled trials investigating biosimilars compared with their reference drugs (adalimumab, etanercept, infliximab, ustekinumab) in chronic inflammatory diseases (PsO, PA, CD, UC, AS, RA) were included. Non-original data and studies with healthy patients were excluded. No language restrictions were applied.

Literature search

Published RCTs were searched for in the literature by using the Medline (PubMed) database, and the following trial registers were used for ongoing/planned trials:

- www.controlled-trials.com
- www.clinicaltrials.gov
- www.anzctr.org.au
- http://apps.who.int/trialsearch
- www.clinicaltrialsregister.eu

Search items included various terms used for the relevant diseases – ankylosing spondylitis, Crohn’s disease, ulcerative colitis, rheumatoid arthritis, psoriatic arthritis, and psoriasis vulgaris in combination with biosimilars.

Study selection and data extraction

Two reviewers independently screened abstracts/titles for relevance and extracted data from the full texts or from records of the registries. Results were compared and differences resolved in discussion and by checking the data source.

Available study characteristics of both published trials and ongoing trials were retrieved for more detailed analysis. Study characteristics included patient characteristics, numbers, phase, disease, intervention, the definition of primary and secondary outcomes, efficacy and safety outcomes, and data on immunogenicity.

RESULTS

Published RCTs

A total of seventy-two publications were identified using the eligibility criteria. There were no trials providing data on the treatment of patients with psoriasis with biosimilars. Two studies were included, both on CT-P13 as a biosimilar to infliximab: PLANETAS, a pharmacokinetic study on 250 patients with AS and PLANETRA, a Phase 3 RCT with 606 patients with RA (5,6).

Using a 20% improvement from baseline ACR score (ACR20) at week 30 as the primary endpoint and additional efficacy, immunogenicity, safety, PK, and PD parameters as secondary endpoints, the PLANETRA study showed the equivalence of CT-P13 with infliximab in terms of ACR20 response at week 30 in active patients with RA with inadequate response to MTX treatment (6,7). Overall, CT-P13 was well tolerated, and the safety profile of CT-P13 was comparable with that of infliximab.

The primary outcome of the PLANETAS study was pharmacokinetic equivalence, with additional secondary outcomes such as a 20% improvement from baseline in the ASAS group criteria. The equivalence in terms of pharmacokinetics as well as clinical efficacy was demonstrated (5,8,9).

The risk of bias was rated as low for both studies (5-9).

Planned/ongoing RCTs

One hundred and twenty nine publications were identified; seventeen studies were included (Table 1, 2, 3, 4, 5, and 6).

Adalimumab: there were three completed RCTs of two adalimumab biosimilars as well as 3 ongoing registered RCTs of 3 adalimumab biosimilars (10-15). Two of the completed trials involve the adalimumab
Biosimilar ABP 501 versus adalimumab (Humira) in 530 patients with RA and 350 patients with psoriasis and one phase 1 trial involving the adalimumab biosimilar BCD-057 in 94 healthy individuals (10,12,14). Ongoing trials of adalimumab biosimilars involve SB5, M923, and GP2017 versus adalimumab in 490 patients with RA and 964 patients with psoriasis (11,13,15).

Etanercept: there were two completed RCTs of 2 etanercept biosimilars (CP2015 and HD2013) versus etanercept (Enbrel) in 546 patients with psoriasis and 300 patients with RA, and 2 ongoing RCTs registered (16-19). A trial on the etanercept biosimilar SB4 versus etanercept (Enbrel), including 498 patients with RA and a trial on the CHS-0214 biosimilar versus the originator in 486 patients with RA were registered (17,19). Completion was scheduled for November 2014 (no published studies) and October 2015, respectively. At present, these studies are in the phase of data collection for primary outcome measures.

Infliximab: four ongoing RCTs and one completed RCT of infliximab biosimilars were identified (20-23). A trial on the infliximab biosimilar SB2 with 584 patients with RA was registered in August 2013, with a scheduled completion date set for November 2014 (20). No data have been published yet. Another trial

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Table 1. Randomized controlled trials investigating biosimilars compared with their reference drugs in chronic inflammatory diseases

<table>
<thead>
<tr>
<th>NCT number</th>
<th>Intervention</th>
<th>Phase</th>
<th>Enrollment</th>
<th>Study start</th>
<th>Estimated primary competition date</th>
<th>Primary outcome</th>
<th>Secondary outcome</th>
<th>Comment</th>
<th>Sponsor</th>
<th>Disease</th>
<th>Reference product</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02452151</td>
<td>Inflectra 5 mg/kg BW or 10 mg/kg BW 4 to 6 doses</td>
<td>4</td>
<td>300</td>
<td>August 2015</td>
<td>August 2016</td>
<td>Relapse rate</td>
<td></td>
<td>Pts treated with infliximab for at least 12 weeks prior to inclusion</td>
<td>Onze Lieve Vrouwe Gasthuis</td>
<td>CU</td>
<td>Infliximab</td>
</tr>
<tr>
<td>NCT02148640</td>
<td>CT-P13 with same dose and frequency as pre-inclusion treatment with innovator infliximab</td>
<td>4</td>
<td>500</td>
<td>October 2014</td>
<td>April 2016</td>
<td>DAS28</td>
<td>ASDAS Partial Mayo score</td>
<td>PASI</td>
<td>Diakonhjemmet Hospital</td>
<td>RA</td>
<td>Infliximab</td>
</tr>
<tr>
<td>NCT01936181</td>
<td>SB2 3 mg/kg at week 0, 2, 6 then every 8 weeks</td>
<td>3</td>
<td>584</td>
<td>August 2013</td>
<td>August 2014</td>
<td>ACR20</td>
<td>ACR50 DAS28</td>
<td>Pts on MTX for at least 6m, stable dose of MTX 10-25mg QW for at least 6w</td>
<td>Samsung Bioepis Co., Ltd</td>
<td>RA</td>
<td>Infliximab</td>
</tr>
<tr>
<td>NCT01895309</td>
<td>SB4 50mg QW for 24w Etanercept 50mg QW for 24w</td>
<td>3</td>
<td>498</td>
<td>June 2013</td>
<td>November 2014</td>
<td>ACR20</td>
<td>ACR50 DAS28</td>
<td>Pts with MTX for at least 6m, stable dose of MTX 10-25</td>
<td>Samsung Bioepis Co., Ltd</td>
<td>RA</td>
<td>Etanercept</td>
</tr>
</tbody>
</table>
using NI-071 in 230 patients with RA, was registered in July 2013 (21). The already-approved CT-P13 is currently involved in 2 ongoing trials involving patients with IBD, RA, AS, and psoriasis (22,23).

**DISCUSSION**

In the ever-expanding market of biosimilars, it is important for us as clinicians to be confident about the requirements for the approval of biosimilars. This reassurance comes from the evidence that has been generated before marketing authorization, and in particular from RCTs as an important part of it. Unfortunately, at present there is rather limited evidence provided by the clinical trials, especially on psoriasis and psoriatic arthritis, which would help a dermatologist feel more comfortable about prescribing biosimilars.

For example, the first biosimilar Inflectra or Remsima was approved for all Remicade’s indications based on studies on rheumatoid arthritis and ankylosing spondylitis and is being used today in dermatology for psoriasis as well as in gastroenterology for inflammatory bowel diseases (2-4).

Table 2. Randomized controlled trials investigating biosimilars compared with their reference drugs in chronic inflammatory diseases

<table>
<thead>
<tr>
<th>NCT number</th>
<th>Intervention</th>
<th>Phase</th>
<th>Enrolment</th>
<th>Study start</th>
<th>Estimated primary competition date</th>
<th>Primary outcome</th>
<th>Secondary outcome</th>
<th>Comment</th>
<th>Sponsor</th>
<th>Disease</th>
<th>Reference product</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02016105</td>
<td>Ongoing, not recruiting GP2017 80 mg at wo, followed by 40 mg every other week</td>
<td>3</td>
<td>448</td>
<td>December 2013</td>
<td>July 2015</td>
<td>PASI75</td>
<td>PASI50 PASI90 PASI10HR QoL</td>
<td>Sandoz</td>
<td>Pso</td>
<td>Adalimumab</td>
<td></td>
</tr>
<tr>
<td>NCT01891864</td>
<td>Completed GP2015 50 mg BIW for 12 w, thereafter 50 mg QW</td>
<td>3</td>
<td>546</td>
<td>June 2013</td>
<td>June 2014</td>
<td>PASI75</td>
<td>PASI50 PASI90 PASI Inj site reaction Immunogenicity</td>
<td>Sandoz</td>
<td>Pso</td>
<td>Etanercept</td>
<td></td>
</tr>
<tr>
<td>NCT02581345</td>
<td>Active, Recruiting M923 GP2015 50 mg BIW for 12 w, thereafter 50 mg QW</td>
<td>3</td>
<td>516</td>
<td>September 2015</td>
<td>September 2016</td>
<td>PASI75</td>
<td>PASI PASI50 PASI90 sPGA DLQI PK AEs Immunogenicity</td>
<td>Baxalta US Inc.</td>
<td>Pso</td>
<td>Adalimumab</td>
<td></td>
</tr>
</tbody>
</table>

Ustekinumab: no published or ongoing RCTs in patients with psoriasis or other indications were identified.
marketing studies regarding biosimilar immunogenicity which is the main concern for biosimilars.

All these considerations are linked to the particularities and differences in the approval process and the clinical trials of biosimilars in comparison with the originator.

**Clinical trials of biosimilars**

Requirements for approval of a biosimilar include physicochemical, biologic, and preclinical studies to establish bioequivalence, with clinical development focused on confirming and resolving any remaining uncertainties regarding bioequivalence (2,3,24).

Because the experience with the reference product serves as the base, the primary goal of biosimilar development is to demonstrate that the purity, potency, and safety of the biosimilar are similar to the reference product. However, one or more clinical studies are required to demonstrate the safety of the biosimilar (24-29).

Clinical development of the biosimilar begins with studies to demonstrate comparable pharmacokinetics and pharmacodynamics with the reference product in a relevant population. Also included in early clinical development are investigations that focus on safety, including immunogenicity. Once PK, PD, and immunogenic similarity to the reference product has been demonstrated, at least one phase 3 clinical comparability trial is conducted to confirm similar efficacy and safety in a sensitive population (24-26).
Phase 3 clinical comparability trials are intended to resolve uncertainties that remain regarding the efficacy and safety of the biosimilar in comparison with the reference product following completion of physicochemical, biologic, and preclinical investigations, as well as PK, PD, and immunogenicity investigations in humans (28,29). These trials provide a head-to-head comparison with the reference product, with the goal of demonstrating that the proposed biosimilar has neither decreased, nor increased activity relative to the reference product. Study design elements must be determined carefully as they are critical determinants of detecting clinically meaningful differences between the biosimilar and the reference product.

In dermatology, published direct data on patients with psoriasis are missing. However, information on biosimilars in patients with psoriasis is currently being investigated in 2 completed trials involving an Adalimumab biosimilar, ABP501, and an etanercept biosimilar – GP2015, with results not yet available. Furthermore, there are also 3 ongoing clinical trials on patients with psoriasis, including the already approved infliximab biosimilar CT-P13 as well as the adalimumab biosimilars GP2017 and M923.

Regarding the already approved infliximab biosimilar CT-P13, clinical data that contributed to its approval were generated by PLANETAS and PLAN-
ETRA, two pivotal randomized clinical trials which directly compared CT-P13 and the reference product in AS and RA (5,6). In these randomized clinical trials, the two agents were shown to be highly similar in terms of PK, efficacy, and safety. However, post-marketing surveillance is needed to further evaluate the safety profile of this biosimilar, and there are currently 3 ongoing phase-4 clinical trials involving patients with psoriasis, RA, AS, CD, and UC. Two of them are interventional phase-4 studies, and their purpose is to also assess the safety and efficacy of switching from Remicade to the biosimilar Remsima in patients with rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Crohn’s disease, and chronic plaque psoriasis, with approximately 500 patients to be enrolled to assess the efficacy of an infliximab-biosimilar (Inflectra) compared with an infliximab-innovator (Remicade) in patients with inflammatory bowel disease in remission.

At present there are two post-marketing observational studies on patients with inflammatory bowel diseases, RA, AS, and psoriasis that have been prescribed Inflectra (infliximab) or Remicade (infliximab) for treatment.

Our research found that there were no trials on biosimilars for ustekinumab.

**CONCLUSION**

For infliximab biosimilars, we found data on patients with ankylosing spondylitis and rheumatoid arthritis that indicated no clinically relevant differences regarding efficacy and safety, as well as data on inflammatory bowel diseases and psoriasis. While there were three registered studies of adalimumab biosimilars, we found just one study on an etanercept biosimilar being carried out in patients with psoriasis. Ongoing studies on adalimumab, etanercept, and infliximab biosimilars in patients with rheumatoid arthritis were also identified.

As to psoriasis, evidence is currently being sought for the adalimumab biosimilars ABP 501, GP2017, and M923 in approximately 400 patients, and for the etanercept biosimilar GP2015 in 270 patients.

Although data regarding RCTs on biosimilars is still limited, it has been expanded over the last years. Consequently, this will enable the EMA to consider direct evidence from patients with psoriasis in the approval of biosimilars in dermatology. The only real advantage of biosimilars is the low cost, but this consideration cannot allow us to ignore an inferior therapeutic result or side effects. Risk management protocols and standardization assays are also needed for long term follow-up.
Although not all ongoing biosimilar trials may have been registered, the present situation in terms of registered trials is quite unsatisfactory and will leave clinicians with some degree of uncertainty with respect to their treatment decisions. As a consequence, provision of further clinical data and inclusion of patients in patient registries will be crucial. Undoubtedly, the advent of biosimilars will reduce acquisition costs of treatment and at the same time have an impact on the prescribing patterns of clinicians and management of patients.

**Abbreviations:**


**Table 6. Randomized controlled trial investigating CT-P13 compared with its reference drug**

<table>
<thead>
<tr>
<th>Study name</th>
<th>Study ID</th>
<th>Year</th>
<th>Drug</th>
<th>Number randomized</th>
<th>Study duration</th>
<th>Disease</th>
<th>ASDAS:3.8 (SD:0.8)</th>
<th>Endpoint1</th>
<th>Endpoint2</th>
<th>Endpoint3</th>
<th>AEs</th>
<th>Infusion related events</th>
<th>Serious AE</th>
<th>Withdrawal due to AE</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLANETAS Study Park 2012</td>
<td>NCT01220518</td>
<td>2013</td>
<td>CT-P13 5 mg/kg bw at w0, 2, 6 and then every 8 w</td>
<td>125</td>
<td>54w</td>
<td>AS according to the 1984 modified New-York classification criteria for ≥3m prior to screening</td>
<td>70.5% (79/112)</td>
<td>51.8% (58/112)</td>
<td>54.7%</td>
<td>27.4% (32/117)</td>
<td>22.9% (25/109)</td>
<td>W30: DR-infusion reaction: 3.9%</td>
<td>6.4% (8/125)</td>
<td>Celtrion Inc.</td>
<td></td>
</tr>
<tr>
<td>IFX 5mg/kg bw at w0, 2, 6 and then every 8 w</td>
<td>125</td>
<td>54w</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Comments: All patients were premedicated with an antihistamine (chlorfeniramine 2-4 mg or dose of equivalent anyihistamine such as cetirizine 10 mg) 30-60 min prior to the start of infusion at the investigator’s discretion; test for equivalence based on pharmacokinetics

**References:**


