

Biosimilars: A Review of Published Randomized Control Trials Comparing Biosimilars with their Reference Products

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Abstract

Biosimilars represent a therapeutic revolution for many immune-mediated inflammatory diseases. Biosimilars have different regulatory requirements than those of originators. These regulatory requirements are based on the evidence generated from bioequivalence studies, and in particular from RCTs.

The goal of our review was to search for published randomized control trials that investigate biosimilars compared to their reference medicine (infliximab, adalimumab, etanercept, ustekinumab) in chronic inflammatory diseases (psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, by using the Medline (PubMed) databases. Nineteen randomized control trials investigating biosimilars compared to their reference drug were included. As of November 2017, five anti-TNF biosimilar agents have been granted approval and are available on the market for patients with an inflammatory disease in the European Union. The Infliximab biosimilars CT-P13 (Remsima, Inflectra) and SB2 (Flixabi), the etanercept biosimilars SB4 (Benepali) and GP2015 (Elrezi) and adalimumab biosimilars ABP501 (Amgevita, Solymbic), SB5 (Imraldi) and BI 695501 (Cyltezo). Evidence of equivalence between biosimilars and reference drugs was supported by head-to-head randomized clinical trials: two published randomized clinical trials for SB2, SB4, GP2015, ABP501, SB5, BI695501 and three published randomized control trial in the case of CT-P13 and ABP 501. Although not all randomized clinical trials comparing biosimilar to its reference product have been published, the present situation is satisfactory and provision of further clinical trials awaited.

Keywords: Biosimilar; Review; Clinical trial; Infliximab; Adalimumab; Etanercept; Inflectra

Abbreviations: EU: European Union; RCTs: Randomized Control Trials; Pso: Psoriasis; PsA: Psoriatic Arthritis; CD: Crohn's Disease; UC: Ulcerative Colitis; AS: Ankylosing Spondylitis; RA: Rheumatoid Arthritis; IFX: Infliximab; ETN: Etanercept; ADL: Adalimumab; ACR: American College of Rheumatology; PK: Pharmacokinetics; PD: Pharmacodynamics; AUC_{inf} : Area Under the Concentration-Time Curve from Time Zero to Infinity; AUC_{last} : Area Under the Concentration-Time Curve from Time Zero to the Last Quantifiable Concentration; EU-INF: EU-Sourced Infliximab; US-INF: US-Sourced Infliximab; SDAI: Simple Disease Activity index; CDAI: Clinical Disease Activity index; LDAS: Low Disease Activity Score; C_{max} : Maximum Plasma Drug Concentration; T_{max} : Time to Reach C_{max} ; ADA: Antidrug Antibodies; PASI: Psoriasis Area and Severity Index; PASI50/75/90/100: 50/75/90/100 Improvement in PASI; TEAE: Treatment-Emergent Adverse Events; PGA: Physician Global Assessment; EULAR: European League against Rheumatism; DAS28: Disease Activity Score 28; ESR: Erythrocyte Sedimentation Rate; ASAS: Assessment of Spondyloarthritis; ACR20/50/70: 20%/50%/70% Improvement in American College of Rheumatology Score

Introduction

Biosimilars represent a therapeutic revolution for many immune-mediated inflammatory diseases. Given the high cost of the reference biological drugs along with their recent patent expiry, biosimilars have gained ground in the therapeutic armamentarium of many immune-mediated inflammatory disease, as they enable significant cost savings for the healthcare systems and at the same time increase earlier access to otherwise expensive biological therapy.

A biosimilar drug is defined by the World Health Organization as a "biotherapeutic product similar in terms of quality, safety and efficacy to an already licensed reference therapeutic product whose license has expired" [1].

Owing to the fact that the efficacy of the original biologic drug has already been confirmed, the development of a biosimilar should fulfill rigorous step-wise process aimed at demonstrating that the investigated biosimilar is highly similar to the reference product. In this regard, regulatory agencies have developed guidelines for proving biosimilarity which consist mainly in bioequivalence studies and in particular randomized control trials [2-4].

Development and clinical trials of biosimilars

Data requirements necessary to support regulatory approval of a biosimilar begin with nonclinical development (physicochemical, biologic), as well as preclinical development (animal studies) aimed at establishing biosimilarity with the reference drug. Additionally, clinical equivalence studies are required in order to demonstrate that the efficacy, safety and immunogenicity of the proposed biosimilar are similar to the reference product and also confirming and resolving any remaining uncertainties regarding biosimilarity. These clinical studies begin with phases I head-to-head clinical studies which demonstrate comparable pharmacokinetics to and pharmacodynamics in relevant population [5-7].

Early clinical development also involves investigations that focus on safety, including immunogenicity. After similarity of the biosimilar with the reference drug in terms of PK, PD and immunogenicity have

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been demonstrated in phase 1 clinical studies, at least one head-to-head phase 3 clinical comparability trial is performed aimed at confirming similar efficacy and safety in a sensitive population [7,8].

The purpose of these phase 3 clinical comparability trials is to resolve uncertainties with regard to efficacy and safety of the biosimilar compared to its reference drug that remain after competition of physicochemical, biologic and preclinical investigations, as well as, P_d , P_k and immunogenicity investigations. These trials provide a head-to-head comparison of biosimilar with the reference drug, aimed at demonstrating that the proposed biosimilar has neither increased nor decreased activity compared to its to the reference product [9-11].

Post-marketing monitoring is also implemented, for example through pharmacoepidemiological studies, to ensure continual monitoring of long-term safety.

Trial designs for biosimilars development have similar designs with other biologic drugs with regard to patient population selection, sample size, study duration, end points.

However study design elements must be considered carefully as they are critical determinants of detecting clinically meaningful differences between the biosimilar and the reference product [5-12].

Methods

A systematic review of the literature was carried out in order to collect all published randomized control trials that investigate biosimilars with their reference medicine (infliximab, adalimumab, etanercept, ustekinumab) in chronic inflammatory diseases (Psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis) by using the Medline (PubMed) databases.

Search key words used to identify all relevant articles included various terms used for the relevant diseases- psoriasis, psoriatic arthritis, ankylosing spondylitis, rheumatoid arthritis, Crohn's disease, ulcerative colitis in combination with biosimilars.

Abstracts/titles of the studies were independently screened by two reviewers and full-text articles were extracted for more detailed analysis. Each study included was individually reviewed in order to retrieve available study characteristics including patient characteristics, number, phase, disease, efficacy, safety outcomes and data on immunogenicity.

Results

A total of one hundred and two publications were identified using eligibility criteria.

Nineteen randomized control trials investigating biosimilars compared to their reference drug were included (Table 1 Included as supplementary data).

Infliximab biosimilars

To date, two infliximab biosimilars, CT-P13 (Remsia and Inflectra) and SB2 (Flixabi) have been approved in the European Union [13-15].

CT-P13 was approved in the EU in 2013 for use in the treatment of adult CT-P13 patients with RA, PsA, psoriasis, ulcerative colitis, Crohn's disease [13,14].

Evidence of equivalence between CT-P13 and reference infliximab was provided by 3 randomized, clinical trials: PLANETAS (a phase 1 double-blind, parallel-group study), PLANETRA (a phase 3 double-blind, multicentre study involving 605 patients with RA) and a

supportive Japanese phase 1/2 study [16-23].

The first randomized, phase 1 study (PLANETAS) was performed on 250 patients with AS. In this study, the CT-P13 pharmacokinetic was demonstrated to be similar to that of the original drug. Moreover, the 2 biosimilar drugs showed good performance in terms of efficacy and safety [19].

Subsequently, a phase 3, double-blind study (PLANETRA) study was performed in 604 RA patients. Two groups of patients were randomized to receive original infliximab or CT-P13 at the same dose and methotrexate. The two patients groups revealed similar response rate, drug-related adverse events and development rate of anti-drug antibodies at the end of the study [16].

In PLANETRA study extension, a total of 455 patients with RA from the previous study were treated up to week with the aim of assessing efficacy and safety of continuing CT-P13 or switching from reference infliximab to CT-P13 in patients who had completed 54 weeks of treatment. The results from PLANETRA study extension reported that response rates were maintained and did not significantly differ in the switch and maintenance groups [17].

Regarding immunogenicity, in both PLANETAS and PLANETRA studies, anti-drug antibodies against infliximab and CT-P13 were measured and during the extension phase, anti-drug antibodies incidence was comparable between maintenance and switches groups [16-23].

Further support for the comparable efficacy of CT-P13 and reference infliximab comes from a small phase 1/2 study in 101 Japanese patients with RA [23].

All these data further support the extrapolation of CT-P13 to all the indications for which infliximab is approved. SB2 (Flixabi) is an infliximab biosimilar that has recently received marketing authorization in the EU in May 2016 for use in the treatment of adult patients with RA, PsA, psoriasis, ulcerative colitis, Crohn's disease [15].

Evidence of equivalence between and reference infliximab sourced from 2 randomized clinical trials: A phase 1, parallel, three-arm, single-blind study of 159 healthy volunteers and a phase 3, double-blind trial of 584 patients with RA [24-27].

Both studies have demonstrated similarity in terms of PK, PD, efficacy, safety, immunogenicity between the 2 drugs.

Etanercept biosimilars

To date, there are 2 etanercept biosimilars approved in the EU: SB4 (Benepali) and GP 2015 (Elrezi) [28,29].

SB4 is an etanercept biosimilar that has been approved in the EU in 2016 for use in the treatment of adult patients with RA, PsA, AS, psoriasis, non-radiographic axial spondyloarthritis [28].

The equivalence of SB4 and reference etanercept was determined in 2 RCT: a phase 1, single-blind, three-way study of 138 healthy volunteers and a phase 3, double-blind trial. The latter was conducted on 596 patients with RA, and consisted of 52 week main study and an additional 48 week transition (switching) study. The 2 drugs have proven similarity in terms of efficacy, tolerability profiles, adverse events, immunogenicity [30-32].

GP2015, a further etanercept biosimilar was submitted for approval in the EU in December 2015 and gained approval in April 2017 [29].

Evidence of equivalence between GP2015 and reference etanercept was provided by 2 randomized control trials: a phase 1, two-sequence,

two-period, cross-over study in 54 healthy male subjects and a phase 3, double blind study which involved 531 patients with moderate to severe plaque psoriasis (EGALITY) [33,34].

The phase 1 pharmacokinetic study was conducted in 54 healthy male subjects and has proven pharmacokinetic equivalence of the two drugs [33].

The phase 3 study (EGALITY) was conducted in 531 patients with moderate to severe plaque psoriasis and consisted of 4 periods. This trial met its end points for equivalence of efficacy. Likewise, secondary end point, drug related adverse events and anti-drug antibodies were comparable between GP2015 and reference etanercept [34].

Adalimumab biosimilars

To date, there are 3 adalimumab biosimilars approved in the EU: ABP501 (Amgevita and Solymbic), SB5 (Imraldi) and BI695501 (Cyltezo) [35-38].

Evidence of equivalence between ABP 501 and reference adalimumab sourced from 3 RCTs: a phase 1, single-dose study in 501 healthy adults and 2 phase 3, randomized, double-blind studies, performed in patients with moderate to severe plaque psoriasis and moderate to severe RA, respectively. Both studies have demonstrated that ABP501 is similar to adalimumab in clinical efficacy, safety and immunogenicity [39-42].

In the phase 1 study, after a single 40 mg SC injection, the PK of ABP 501 was similar to that of and adalimumab and the safety and tolerability profiles were also similar [39].

Evidence of equivalence between SB5 and reference adalimumab was demonstrated in 2 RCTs: a phase 1, single-blind single-dose study in 59 healthy subjects which demonstrated pharmacokinetic similarity, and a phase 3 randomized, double-blind study performed in patients with RA which demonstrated comparable efficacy, safety and immunogenicity to reference adalimumab [43,44].

Evidence of equivalence between BI695501 and reference adalimumab comes from 2 randomized clinical trials: a phase 1, single dose study in 109 healthy subjects and a phase 3 randomized, double-blind studies performed in patients with moderate to severe rheumatoid arthritis [45-47].

Conclusion

As of November 2017, five anti-TNF biosimilar agents have been granted approval and are available on the market for patients with as inflammatory disease in the European Union. The infliximab biosimilars CT-P13 (Remsima, Inflectra) and SB2 (Flixabi), the etanercept biosimilars SB4 (Benepali) and GP2015 (Elrezi) and adalimumab biosimilars ABP501 (Amgevita, Solymbic), SB5 (Imraldi) and BI 695501 (Cyltezo). They all have shown close comparability to their reference medicinal products in terms of physical, biologic and clinical characteristics. The first biosimilar was infliximab biosimilar CT-P13 which was approved in September 2013 by the European Medicines Agency, followed by etanercept biosimilar SB4 in January 2016, infliximab biosimilar SB2 in May 2016, adalimumab biosimilar ABP501 on March 2017, etanercept biosimilar GP2015 on April 2017 and adalimumab biosimilars SB5 and BI695501 on October and November, respectively [47].

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