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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 Pso, 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

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

NCT number	Intervention	Phase	Enrollment	Study start	Estimated primary completion date	Primary outcome	Secondary outcome	Comment	Sponsor	Disease	Reference product
NCT02452151 Active, non-recruiting	Inflectra 5 mg/kg BW or 10 mg/kg BW 4 to 6 doses Infliximab 5 mg/kg BW or 10 mg/kg BW 4 to 6 doses	4	300	August 2015	August 2016	Relapse rate		Pts treated with Infliximab for at least 12 weeks prior to inclusion	Onze Lieve Vrouwe Gasthuis	CU CD	Infliximab
NCT02148640 Recruiting	CT-P13 with same dose and frequency as pre-inclusion treatment with innovator infliximab Infliximab (Remicade) with same dose and frequency as prior to inclusion	4	500	October 2014	April 2016	DAS28 ASDAS Partial Mayo score PASI			Diakonhjemmet Hospital	RA AS CD UC Pso	Infliximab
NCT01936181 Active, non-recruiting	SB2 3 mg/kg at week 0, 2, 6 then every 8 weeks Remicade 3 mg/kg at week 0, 2, 6 then every 8	3	584	August 2013	August 2014	ACR20	ACR50 DAS28	Pts on MTX for at least 6m, stable dose of MTX 10-25mg QW for at least 6 w	Samsung Bioepis Co., Ltd	RA	Infliximab
NCT01895309 Active, not recruiting	SB4 50mg QW for 24w Etanercept 50mg QW for 24w	3	498	June 2013	November 2014	ACR20	ACR50 DAS28	Pts with MTX for at least 6m, stable dose of MTX 10-25	Samsung Bioepis Co., Ltd	RA	Etanercept

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

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

NCT number	Intervention	Phase	Enrollment	Study start	Estimated primary competition date	Primary outcome	Secondary outcome	Comment	Sponsor	Disease	Reference product
NCT02016105 Ongoing, not recruiting	GP2017 80 mg at w0,followed by 40 mg every other week Adalimumab 80 mg at wo, followed by 40 mg every other week for 33 w	3	448	December 2013	July 2015	PASI75	PASI50 PASI90 PASI10HR QoL		Sandoz	Pso	Adalimumab
NCT01891864 Completed	GP2015 50 mg BIW for 12 w, thereafter 50 mg QW Etanercept 50 mg BIW for 12 w, thereafter 50 mg QW	3	546	June 2013	June 2014	PASI75	PASI50 PASI90 PASI Inj site reaction Immunogenicity		Sandoz	Pso	Etanercept
NCT02581345 Active, Recruiting	M923 Humira	3	516	September 2015	September 2016	PASI75	PASI PASI50 PASI90 sPGA DLQI PK AEs Immunogenicity		Baxalta US Inc.	Pso	Adalimumab

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).

Ustekinumab: no published or ongoing RCTs in patients with psoriasis or other indications were identified.

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).From this experience, which is probably still limited in the number of patients, we can conclude that there is no specific safety concern today that was raised and no specific lack of efficacy either. There are also ongoing centered post-

Table 3. Randomized controlled trials investigating biosimilars compared with their reference drugs in chronic inflammatory diseases

NCT number	Intervention	Phase	Enrollment	Study start	Estimated primary competition date	Primary outcome	Secondary outcome	Comment	Sponsor	Disease	Reference product
NCT02167139 Ongoing non-recruiting	SB5 40 mg every other week Humira 40 mg every other week	3	490	May 2014	May 2015	ACR20	ACR50 Das28		Samsung Bioepis Co., Ltd.	RA	Adalimumab
NCT02115750 Ongoing, non-recruiting	CHS-0214 50 mg QW for 24 w Etanercept 50 mg QW for 24 w	3	486	May 2014	October 2015	ACR20	Not stated	Pts with a stable dose of MTX of 8-25 mg QW	Coherus Biosciences, Inc.	RA	Etanercept
NCT02395055 Completed	BCD-057 40 mg at w0 Adalimumab 40 mg at w0	1	94	June 2015	October 2015	Max concentration of adalimumab after BCD-057 /humira single inj AUC	Time of max concentration ada, half-life of ada, volume of distribution, clearance of ada, AEs,SAEs, etc.	Purpose: pharmacokinetics tolerability and safety after single subcutaneous injection of BCD-057 in healthy volunteers.	Biocad	Healthy	Adalimumab
NCT01936181 Active, non-recruiting	SB2 3 mg/kg BW at w0, 2, 6, then every 8 w Infliximab 3 mg/kg BW at w0, 2, 6 then every 8 w	3	584	August 2013	November 2014	ACR20	ACR50, DAS28	Pts with MTX for at least 6m, stable dose of MTX 10-25mg QW for at least 4w	Samsung Bioepis Co., Ltd.	RA	Infliximab

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).

Table 4. Randomized controlled trials investigating biosimilars compared with their reference drugs in chronic inflammatory diseases

NCT number	Intervention	Phase	Enrollment	Study start	Estimated primary competition date	Primary outcome	Secondary outcome	Comments	Sponsor	Disease	Reference product
NCT01270997 Completed	HD203 25 mg BIW for 48 w Etanercept 25 mg BIW for 48 w	3	300	December 2012	May 2012	ACR20	ACR50,ACR70, safety, immunogenicity	Pts. with concomitant MTX treatment	Hanwha chemical	RA	Etanercept
NCT01970488 Completed	ABP 501 40 mg every other week for 50 w	3	350	October 2013	March 2015	PASI percentage improvement	PASI75, Spga, BSA,SAE, laboratory values, vital signs, ADA		Amgen	Pso	Adalimumab
NCT01927263 Completed	NI-071 100 mg/vial for 54w Infliximab 100 mg/vial for 54 w	3	230	July 2013	March 2015	DAS28	ACR20, ACR50, ACR70, ACR core-set changes, long term safety, immunogenicity	Pts. on MTX 6-16 mg QW for 2 w for at least 12 w prior to the screening visit	Nichi-Iko Pharmaceutical Co. Ltd.	RA	Infliximab
NCT01970475 Completed	ABP 501 40 mg every other week for 22 w Adalimumab 40 mg every other week for 22 w	3	530	October 2013	November 2014	ACR20	DAS28, ACR50, ACR70, AE, SAE, vital signs, lab values	Pts. With MTX for at least 12 w, stable dose of MTX 7.5-25 mg QW for at least 8 w; pts with inadequate response to MTX	Amgen	RA	Adalimumab

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-

Table 5. Randomized controlled trial investigating CT-P13 compared to its reference drug

Infliximab/CT-P13 biosimilar – rheumatoid arthritis																		
Study name	Study ID	Drug	Year	Number randomized	Study duration	Disease	Severity	Endpoint 1	Result	Endpoint 2	Result	Endpoint3	Result	AEs	Infusion related reactions	Serious adverse events	Withdrawal due to AE	Sponsor
PLANETRA Study Yoo 2013	NCT01217086	CT-P13 3mk/kg bw at w0, 2, 6,every 8 w + MTX 12.5-25 mg/w + folic acid	2013	302 304	54 w	RA, prior unsuccessful treatment with\mtx for at least 3 m	PGA of disease activity: 64.7(SD: 14.3)	ACR20	w30 60.9% (184/302) w54 57% (172/302)	ACR50	w30 35.1% (106/302) W54 33.1 (100/302)	Pts wit ADAs	w30 48.4% (122/252)	W30: TEAEs:60.1 DR-TEAEs: 35.2 W54: DR -TEAEs: 43.4	W30:6.6 (20/301) W54:7.6 (23/302)	W30: TEAEs:10 (30/301) W54: TEAEs: 13.9 (42/302)	9.3 (28/302)	Celtrion Inc.
		IFX 3mg/kg bw at w0,2,6,every 8w+MTX 12.5-25mg/w+folic acid		304			PGA of disease activity:65 (SD:13.5)		W30 58.6% (178/304) W54 52% (158/304)		W30: 34.2% (104/304) W54: 31.6% (96/304)		W30: 48.2% (122/253)	W30: TEAEs: 60.8DR-TEAEs:35.9 W54: DR-TEAEs: 44.7	W30:8.3 (25/301) W54: (31/300)	W30: TEAEs:7 (21/301) W54: TEAEs: 10.3 (31/300)	9.2 (28/304)	

Comments: All patients were premedicated with an antihistamine (chlorfeniramine 2-4 mg or dose of equivalents antihistamine) 30-60 min prior to the start of infusion at the investigator`s discretion; ACR20 at w30 – equivalence: if the 95% CI is within ±15%

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 have 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.

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

Infliximab/CT-P13 biosimilar – ankylosing spondylitis																		
Study name	Study ID	Year	Drug	Number randomized	Studty duration	Disease	Severity	Endpoint1	Result	Endpoint2	Result	Endpoint3	Result	AEs	Infusion-related events	Serious AE	Withdrawal due to AE	Sponsor
PLANETAS Study Park 2012	NCT01220518	2013	CT-P13 5 mg/kg bw at w0, 2, 6 and then every 8 w	125	54w	AS according to the 1984 modified New-York classification criteria for ≥3m prior to screening	ASDAS:3.8 (SD:0.8)	ASAS20	W30: 70.5% (79/112)	ASAS40	W30: 51.8% (58/112) W54: 54.7%	Pts.with ADAs	W30: 27.4% (32/117) W54: 22.9% (25/109)	W30 TEAEs: 64.8%	W30: DR-infusion reaction:3.9%	4.8% (6/125)	6.4% (8/125)	Celtrion Inc.
			IFX 5mg/kg bw at w0, 2, 6 and then every 8 w	125			ASDAS:3.9 (SD:1.1)		W30: 72.4% (84/116)		W30: 47.4% (55/116) W54: 49.1%		W30: 22.5% (25/111) W54: 26.7% (28/105)	W30: TEAEs: 63.9%	W30: DR-infusion reaction:4.9%	6.4% (8/125)	4.0% (5/125)	
Comments: All patients were premedicated with an antihistamine(chlorfenirmanine 2-4 mg or dose of equivalent anyihistamine such us cetirizine 10 mg) 30-60 min prior to the start of infusion at the investigator`s discretion; test for equivalence based on pharmacokinetics																		

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:

ACR20/50: American College of Rheumatology (20% and 50%), ADA: anti-drug antibodies, ASDAS: Ankylosing Spondylitis Disease Activity score, BW: body weight, m-month/s, MTX: methotrexate, pts: patients, PGA: Physician Global Assessment, SD: Standard Deviation, TEAE: treatment-emergent adverse events, w: week, AE: adverse event, BSA: body surface area, DAS 28: disease activity score 28, HRQol: health-related quality of life, IGA: investigator's Global Assessment, PASI: Psoriasis Area and Severity Index, QW: once weekly, sPGA: static Physician Global Assessment, IBD: inflammatory bowel diseases, CD: Crohn's disease, UC: ulcerative colitis, RA: rheumatoid arthritis, Pso; psoriasis, AS: ankylosing spondylitis, RCT: randomized control trial, PK: pharmacokinetics, PD: pharmacodynamics

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