Pharmacology of biosimilar candidate drugs in Rheumatology: a literature review

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ABSTRACT

Objective: To review current evidence concerning pharmacology of biosimilar candidates to be used in rheumatology.
Methods: A PubMed search up to August 2013 was performed using relevant search terms to include all studies assessing pharmacological properties of biosimilar candidates to be used in rheumatology. Data on study characteristics, type of intervention, pharmacokinetics (PK), pharmacodynamics (PD) and bioequivalence ratios was extracted.
Results: Of 280 articles screened, 5 fulfilled our inclusion criteria. Two trials, PLANETAS and PLANETRA, compared CT-P13 and infliximab in patients with active ankylosing spondylitis and rheumatoid arthritis, respectively. PK bioequivalence was demonstrated in the phase 1 PLANETAS trial by highly comparable area under the curve (AUC) and maximum drug concentrations (Cmax), whose geometric mean ratios fell between the accepted bioequivalence range of 80-125%. Equivalence in efficacy and safety was demonstrated in the phase 3 PLANETRA trial. Two phase 1 trials comparing etanercept biosimilar candidates TuNEX and HD203 in healthy volunteers showed a high degree of similarity in AUC and Cmax, with respective geometric mean ratios between PK bioequivalence range. The last included trial referred to GP2013, a rituximab biosimilar candidate, which demonstrated PK and PD bioequivalence to reference product in three different dosing regimens in cynomolgus monkeys.
Conclusion: Infliximab, etanercept and rituximab biosimilar candidates have demonstrated PK bioequivalence in the trials included in this review. CT-P13 has recently been approved for use in the European market and the remaining biosimilar candidates are currently being tested in patients with rheumatoid arthritis.

Keywords: Biosimilar; Pharmacokinetic; Pharmacodynamic; Infliximab; Etanercept; Rituximab

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INTRODUCTION

The development of biotechnological medicines has remarkably changed the treatment and prognosis of rheumatic patients[1]. However, these therapies represent a significant economic burden to healthcare systems worldwide: in 2009, the estimated global sales concerning biotechnologicals reached 93 billion dollars[2] and, in 2012, the top three selling tumor necrosis factor (TNF) alpha inhibitors reached 20 billion dollars of sales. With some of these medicines approaching patent expiry, many pharmaceutical companies are developing biosimilar compounds which are expected to reduce biotechnological-associated costs and improve drug access[3]. Biotechnological drugs are produced in living cells, have complex chemical structures (with tertiary and quaternary protein folding) and undergo post-translational modifications (like glycosylation). This renders impossible to precisely replicate the original biotechnological structure, hence biosimilars are not generics[4]. By definition, a biosimilar drug must be highly similar in terms of quality, efficacy and safety to its reference product. Efficacy and safety concerns were legitimately raised due to this structural variability and,

in 2005, the European Medicines Agency (EMA) issued its first guidelines on similar biological medicinal products[5]. In 2006, EMA approved Omnitrope®, a biosimilar of somatotropin, as the first biosimilar to be used in Europe, being rapidly followed by epoetin alpha, epoetin zeta and filgrastim biossimilars[6]. However, biopharmaceuticals used in rheumatology are incomparably more complex than these hormonal biosimilars: they have a much more intricate structure with a larger number of atoms and a heavier molecular weight, rendering it even more difficult to replicate. EMA guidelines were updated in 2012 for products containing monoclonal antibodies and they established all the non-clinical and clinical studies in which a biosimiliar candidate must demonstrate equivalence to the reference product, so that approval can be granted. In non--clinical studies, paramount *in vitro* biological comparability essays include: binding to target, Fc receptors (FcRn and Fc) and C1q complement protein; neutralization of soluble ligands; complement activation; and antibody and complement-dependent cytotoxicity. All dimensions of monoclonal antibodies are required to be assessed in non-clinical studies, even those that are not scientifically demonstrated to be important for the mechanism of action. *In vivo* comparative studies include pharmacology, efficacy and safety trials. Biosimilar guidelines state that if different mechanisms of action are considered or suspected to be relevant, pharmaceutical companies should provide relevant data to support similarity, including discussion of available literature related to the involved antigen receptors and mechanisms of action, potency assays, in vitro assays that describe the functionality of the molecule, and any relevant clinical data[7]. The totality of scientific evidence should be seen as a logical consequence of the comparability exercise principle with the original drug, which is founded in physiochemical and biological characterization.

Once non-clinical bioequivalence is demonstrated, biosimilar candidates undergo a rigorous pharmacokinetic (PK) and pharmacodynamic (PD) evaluation. PK study design varies according to factors like clinical context, safety and known PK characteristics of the original biotechnological. In general, single-dose crossover trials in healthy volunteers are preferred, although multiple-dosing trials in patients may be conducted in specific circumstances. The primary parameter for which bioequivalence must be demonstrated is the area under the curve (AUC), which reflects total body exposure after drug administration. Maximum drug concentration (Cmax) is also a primary outcome, usually when the biosimilar candidate is administered subcutaneously[7]. Although variability is expected with biosimilars, regulatory authorities, including EMA, have issued the acceptable variation boundaries: the 90% confidence interval (CI) for the ratio of the test and reference products should be contained within the interval of 80-125%[8]. For secondary PK parameters, such as time until maximum drug concentration (tmax), half-life (t1/2) and volume of distribution, CI for ratio or differences can be presented together with descriptive statistics but no acceptance range needs to be demonstrated. PD parameters may contribute to comparability of certain biosimilars, either as a support to previous PK data or as pivotal testing[7]. The glossary of the assessed pharmacological parameters can be found in Table I.

The purpose of this article was to review current evidence concerning pharmacology of biosimilar candidates.

METHODS

INCLUSION CRITERIA

We included all trials investigating pharmacological outcomes of biosimilar candidates intended to be used in rheumatology, either involving humans (healthy volunteers or patients) or other animals.

SEARCH STRATEGY

PubMed database was searched from inception to the 31st of August 2013. Although there were no language restrictions in the search strategy, papers for which no English, Portuguese, Spanish or French translation was available were later excluded. Reference lists of included studies were screened to identify any additional studies. The website of pharmaceutical companies responsible for biosimilar development was also accessed when convenient. The list of search terms and reasons for trial exclusion are available in the online supplementary appendix A.

TRIAL SELECTION AND DATA EXTRACTION

Titles and abstracts were assessed for inclusion suitability by one author (FA) and all potentially relevant papers were assessed by full text review. Details about the intervention (biosimilar vs reference product), study duration, number of participants included, PK and PD outcomes, and bioequivalence ratios were extracted.

TABLE I. GLOSSARY OF THE ASSESSED PHARMACOLOGICAL PARAMETERS IN THE INCLUDED TRIALS

Parameter	Abbreviation	Definition
Area under the curve	AUC	Measure of the extent of bioavailability for a drug given by a particular route, reflecting total body exposure to that drug. The AUC is dependent on the dose administered and the elimination rate of the drug
Clearance	CL	Factor that predicts the rate of drug elimination in relation to the drug concentration, measuring the ability of the body to eliminate the drug
Half-life	t1/2	Time required to change the amount of drug in the body by one-half during elimination. It also indicates the time required to attain 50% of steady state
Maximum drug concentration	Cmax	Maximum or "peak" concentration observed after drug administration
Minimum drug concentration	Cmin	Minimum or "trough" concentration observed after drug administration and just prior to the administration of a subsequent dose
Peak-trough fluctuation	PTF	Variation between maximum and minimum drug concentration
Time until maximum drug concentration	tmax	Time after drug administration when maximum concentration is reached
Volume of distribution	VD	Relates the amount of drug in the body to the concentration of drug in blood or plasma, measuring the apparent space available to contain the drug in the body

RESULTS

RESULTS OF THE SEARCH

Of 280 articles that were screened, 121 studies were excluded for wrong study population, 144 studies were excluded for wrong study type and 3 studies were excluded for wrong language. After exclusion of duplicates, 5 studies out of the 12 remaining were included in the review (online supplementary appendix A). Two of these trials concerned an infliximab biosimilar candidate[9, 10], two trials concerned etanercept biosimilar candidates[11, 12] and the last trial concerned a rituximab biosimilar candidate[13]. The characteristics of the 5 included trials are summarized in Table II.

INFLIXIMAB BIOSIMILAR CANDIDATE

Two 2013 trials were found with pharmacological assessment of an infliximab biosimilar candidate, CT-P13 The first one is the PLANETAS trial[9], a phase 1 randomised, double-blind, prospective study in which 250 patients with active ankylosing spondylitis according to 1984 modified New York criteria were treated with either CT-P13 or original infliximab at 5 mg/kg intravenously every 8 weeks, for 30 weeks. The primary endpoint was demonstration of PK equivalence assessed between weeks 22 and 30 (AUC and Cmax at steady state) and secondary endpoints included additional PK parameters, efficacy, immunogenicity and safety. Baseline demographics were similar in both groups. Mean AUC and Cmax at steady state were similar between CT-P13 and original infliximab, with a ratio of geometric means of 104.5% and 101.5% (90% CI), respectively. A subgroup analysis of the patients for whom anti-drug antibodies (ADA) were negative revealed higher mean values of AUC and Cmax for both CT-P13 and infliximab, when compared to the overall population. However, the ratios of geometric means remained near 100% for both measures. Secondary PK measures, including Cmax, Cmin and tmax for each drug administration, as well as average concentration at steady state, total clearance (CL) at steady state, volume of distribution (VD) at steady state and t1/2 were also highly similar between CT-P13 and original infliximab. No significant difference was found between the two drugs in terms of clinical response or safety assessment.

The second CT-P13 study, the PLANETRA trial[10], was a phase 3, randomized, double-blind, prospective study in which 606 patients with rheumatoid arthritis according to the 1987 American College of Rheumatology criteria, and with active disease despite methotrexate (12.5-25 mg for ≥ 3 months) were treated with either CT-P13 or original infliximab at 3 mg/kg intravenously every 8 weeks, for 30 weeks. Since

TABLE II. CHARACTERISTICS OF THE TRIALS INCLUDED IN THE REVIEW

Study	Type of study	Intervention	Population	Trial duration	Primary outcomes	Secondary outcomes	Bioequivalence of primary outcomes
Park 2013	Randomized controlled trial	CT-P13 vs original infliximab, 5 mg/kg iv., q8 weeks	250 patients with active AS (125 in each arm)	30 weeks	AUC ss: 32765.8 vs 31359.3 µgh/mL C_{max} ss: 147 vs 144.8 µg/mL	Comparable secondary PK outcomes (C_{max}, C_{min}, t_{max}, Comparable clinical efficacy and safety	AUC ss: 104.5% C_{max} ss: 101.5%
Yoo 2013	Randomized controlled trial	CT-P13 vs original infliximab, 3 mg/kg iv., q8 weeks	606 patients with active RA (302 vs 304)	30 weeks	ACR20 at week 30: 60.9% vs 58.6% (95% CI:-6%, 10%; ITT)	Comparable efficacy outcomes Comparable safety outcomes Comparable PK outcomes (C_{max}, C_{min}, t_{max}, C_{avss}, PTF) Comparable PD outcomes (CRP, ESR) Not comparable PD outcomes: ACCP at week 30 and IgG RF at week 14	Yes (95% CI within ± 15%)
Gu 2011	Randomized, open-label, single-dose, crossover trial	TuNEX vs original etanercept, 25 mg sc. once, crossover after 1 week washout	25 healthy male volunteers, crossover after 1 week washout	28 days (dosing at day 0 and day 7, plus 21 days follow-up)	AUC_{0-t}: 231.53 vs 244.23 µgh/mL $AUC_{0-\infty}$: 246.61 vs 259.04 µgh/mL C_{max} : 1.26 vs 1.28 µg/mL	Comparable secondary PK outcomes (t_{max}, CL, VD, $t_{1/2}$) Comparable tolerability	AUC_{0-t}: 95% $AUC_{0-\infty}$: 95% C_{max} : 99%
Yi 2012	Randomized, double-blind, single-dose, crossover trial	HD203 vs original etanercept, 25 mg sc. once, crossover after 1 month washout	42 healthy male volunteers, crossover after 1 month washout	49 days (dosing at day 0 and day 28, plus 21 days follow-up)	AUC_{0-t}: 315.8 vs 283.2 µgh/mL $AUC_{0-\infty}$: 353.8 vs 319.3 µgh/mL C_{max} : 1.35 vs 1.25 µg/mL	Comparable secondary PK outcomes (t_{max}, CL, $t_{1/2}$) Less total AE with HD203 (25 vs 38)	AUC_{0-t}: 112.7% $AUC_{0-\infty}$: 109.9% C_{max} : 107.6%

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TABLE II. CONTINUATION

Study	Type of study	Intervention	Population	Trial duration	Primary outcomes	Secondary outcomes	Bioequivalence of primary outcomes
da Silva 2013	Preclinical animal study	GP2013 vs original rituximab (5 mg/kg once, 20 mg/kg weekly or 100 mg/kg weekly)	14 cynomolgus monkeys 5 mg/kg dosage, 16 cynomolgus monkeys 20 mg/kg dosage, 16 cynomolgus monkeys 100 mg/kg dosage	30 weeks	(no primary//secondary outcome separation) Comparable AUC (PK) and AUEC (PD) for the three groups of monkeys (showed in graphics) Other results reported: similiar α-fucosilated glycans and *in vitro* ADCC; similar inhibition of tumor growth in mouse xenograft models.		PK and PD bioequivalence stated (values not shown in the article)

ACCP: anti-cyclic citrullinated peptide, ADCC: antibody dependent cellular citotoxicity, AE: adverse events, AUC: area under the curve, AUEC: area under the effect curve, Cav,ss: average drug concentration at steady state, CI: confidence interval, CL: total drug clearance, Cmax: maximum drug concentration, Cmin: minimum drug concentration, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, ITT: intention to treat population, PD: pharmacodynamic, PK: pharmacokinetic, PTF: peak-trough fluctuation, RA: rheumatoid arthritis, RF: rheumatoid factor, ss: steady state, t1/2: drug half-life, tmax: time to maximum drug concentration, VD: volume of distribution.

PK bioequivalence was demonstrated in the PLANETAS trial, this study intended to prove clinical and safety similarity between the two biotechnologicals. However, PK and PD parameters were included as secondary endpoints and were submitted to a comparability exercise. Baseline demographics were similar in both groups. Highly similar values were obtained for CT-P13 and original infliximab concerning PK outcomes, namely mean Cmax, Cmin and tmax for each drug administration, and average concentration at steady state and peak-trough fluctuation between weeks 22 and 30. Markers chosen to assess PD were C-reactive protein, erythrocyte sedimentation rate, anti-cyclic citrullinated peptide (ACCP) and rheumatoid factor (RF), measured at weeks 14 and 30. All the results were highly similar for CT-P13 and original infliximab, except for ACCP at week 30 (189.8 vs 174.6 IU/mL) and IgG RF at week 14 (40.5 vs 33.4 IU/mL). Regarding primary endpoints, equivalence of efficacy and safety was demonstrated.

Both PLANETAS and PLANETRA trials assessed the proportion of patients with ADA at the end of follow-up, and once again the percentages were highly similar for CT-P13 (27.4% and 48.4%, respectively) and original infliximab (22.5% and 48.2%, respectively).

ETANERCEPT BIOSIMILAR CANDIDATES

Two trials with pharmacological assessment of etanercept biosimilar candidates were retrieved. The first one was published in 2011 and evaluated PK and tolerability of the biosimilar candidate TuNEX[11]. This was a phase 1 randomized, open-label, single-dose, crossover trial in which 25 healthy male volunteers were administered subcutaneously with 25 mg of TuNEX or original etanercept and, after a one-week washout, they would receive the other drug. Baseline demographics were similar in both groups. PK bioequivalence was demonstrated between TuNEX and original etanercept with highly comparable Cmax, AUC0-t and AUC0-∞ mean values yielding geometric ratios of 99%, 95% and 95% (90% CI), respectively. Other PK outcomes such as tmax, CL, VD, and t1/2, as well as tolerability outcomes were also similar between the two groups.

The second trial was published in 2012 and evaluated PK and tolerability of the biosimilar candidate HD203[12]. Study design was very similar to the TuNEX trial, except for the number of participants (42 instead of 25), the double-blinding method and the washout period (one month instead of one week). Once again,

comparable Cmax, AUC0-t and AUC0-∞ results produced bioequivalent geometric mean ratios of 107.6%, 112.7% and 109.9% (90% CI), respectively. Other PK outcomes such as tmax, CL, and t1/2 were also similar between the two groups. Although in each group a similar number of patients reported adverse events, a significantly higher number of total adverse events was found in the original etanercept group (25 vs 38), being the most frequently reported rhinorrhea, cough and headache.

RITUXIMAB BIOSIMILAR CANDIDATE

Only one pharmacology trial of a rituximab biosimilar candidate was found. This 2013 study evaluated post-translational modifications, *in vitro* biological activity and pharmacological properties of the GP2013 molecule[13]. PK and PD were assessed in three groups of cynomolgus monkeys: 14 monkeys were equally distributed and administered intravenously with single-dose of 5 mg/kg GP2013 or original rituximab; 16 monkeys were equally distributed and administered intravenously with weekly 20 mg/kg of GP2013 or original rituximab, for 4 weeks; and 16 monkeys were equally distributed and administered intravenously with weekly 100 mg/kg of GP2013 or original rituximab, also for 4 weeks. Comparable AUCs were observed within each group of monkeys for GP2013 and original rituximab. The 90% CI fell between the standard bioequivalence range of 80-125%. Regarding Cmax, geometric mean was 13% lower with GP2013 when compared with original rituximab in the single-dose group. This difference was not considered relevant and was attributed by the authors to serum sampling heterogeneity. PD was assessed through B-cell depletion and once again bioequivalence was demonstrated by 95% CIs of the area-under-the-effect curves falling between 80 and 125%.

DISCUSSION

The present literature review aimed to ascertain the pharmacology of biosimilar candidates to be used in rheumatology. In the five included trials, biosimilar candidates to infliximab (CT-P13), etanercept (TuNEX and HD203) and rituximab (GP2013) showed comparable pharmacological properties to their reference products. Furthermore, all four drugs demonstrated PK bioequivalence since ratios of geometric means for AUC and Cmax fell between the established range of 80-125%. PK values obtained for infliximab and etanercept biosimilar candidates were also similar to those reported in previous infliximab and etanercept studies that used identical populations and dosing patterns[9,14]. It must be pointed out, however, that PK bioequivalence for GP2013 was assessed only in non-human primates.

The demonstration of pharmacology, efficacy and safety bioequivalence in the PLANETAS and PLANETRA trials has granted the biosimilar candidate CT-P13 the authorization for use in the European Union from September 2013 as branded names Inflectra®[15] and Remsima®[16]. This is the first biosimilar approved for use in rheumatology and others will naturally follow. A phase 3 trial to assess the efficacy and safety of TuNEX is currently recruiting patients with rheumatoid arthritis and is expected to be completed by the end of 2015[17]. The current status of efficacy and safety testing of HD203 in patients with rheumatoid arthritis is unknown since neither *Clinicaltrials.gov* nor the pharmaceutical companie's websites are updated with this information[18]. GP2013 PK bioequivalence demonstration in cynomolgus monkeys does not guarantee PK similarity of GP2013 and original rituximab in humans, although it supports progression of candidate drug to human trials[19]. A phase 1 trial is currently underway to assess the pharmacology and safety of GP2013 in patients with rheumatoid arthritis[20].

Immunogenicity assessment is addressed in both the European and North-American biosimilar guidelines since protein aggregation in biosimilar candidates, or even original antibodies, can lead to increased production of ADA with meaningful loss of efficacy and severe adverse events. The type of bioanalytical assay to use, relevant parameters to evaluate and acceptable margin of equivalence are still a matter of debate[21]. The proportion of ADA-positive patients in the PLANETAS and PLANETRA trials was comparable for CT-P13 and original infliximab. This proportion was higher than observed in earlier studies but similar to more recent ones, which might be explained by the increased sensitivity of newly-developed analytical methods[10]. Neither the TuNEX nor the HD203 trials assessed Immunogenicity. Reasons stated were that etanercept usually causes no relevant immunogenic response and that the study design was inadequate to accurately evaluate ADA. The authors emphasize the need for this type of appraisal in multiple-dosing studies[12]. This also applies for future trials of GP2013.

This is a non-systematic review. It should also be

noted that some pharmaceutical companies do not publish the results of non-clinical and clinical testing of biosimilars in scientific journals, hence other biosimilars that were not captured by this review are in development.

CONCLUSION

Published data concerning pharmacological assessment of biosimilar candidates to be used in rheumatology has shown highly similar results to the original molecules. Nevertheless, it is of the utmost importance that regulatory agencies maintain a stringent approval policy with a comprehensive non-clinical and clinical evaluation, followed by an active pharmacovigilance plan, for the sake of patient benefit and biosimilar success.

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ONLINE SUPPLEMENTARY APPENDIX A

PUBMED SEARCH TERMS (INCEPTION TO AUGUST 31, 2013) AND REASONS FOR EXCLUSION

			Total	Wrong population	Wrong study type	Wrong language	Detailed review
Biosimilar OR biogeneric	AND	Pharmacology	204	95	105	1	3
		Pharmacodynamic	17	12	3	1	1
		Pharmacokinetic	35	14	17	1	3
		Infliximab	7	0	5	0	2
		Etanercept	6	0	4	0	2
		Adalimumab	3	0	3	0	0
		Golimumab	0	0	0	0	0
		Certolizumab	0	0	0	0	0
		Rituximab	8	0	7	0	1
		Abatacept	0	0	0	0	0
		Anakinra	0	0	0	0	0
		Tocilizumab	0	0	0	0	0