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Bioequivalence studies with anti-TNF biosimilars

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ABSTRACT.

Introduction: Biosimilars, as defined by the European Medicines Agency, have been used in Europe since 2006. The landscape was considerably expanded when the first biosimilar of a monoclonal was approved and introduced in the European market. CT-P13 was developed by Celltrion as an infliximab biosimilar in 2013, not without controversy. As these complex molecules cannot be completely identical, some experts, clinicians, and even patients were skeptical regarding the real bioequivalence of the drugs. Currently, several new infliximab and adalimumab biosimilars are available or will reach the market in a few months

Areas covered: Our goal is to review, mainly from a clinical perspective, the available evidence for bioequivalence of anti-TNF biosimilars. We aim to take into account not only preclinical studies, mostly done for regulatory issues, but also data from clinical studies.

Expert Opinion: We can conclude that bioequivalence with originator is well demonstrated in those drugs which have followed European Medicines Agency regulatory pathways. Switching from originator to biosimilar appears safe for all indications. However, there are few data available for switching from one biosimilar to another, or for complete interchangeability. Prospective studies and strict pharmacovigilance are recommended.

Keywords: infliximab, adalimumab, biosimilar, bioequivalence, switching, anti-TNF.

1. INTRODUCTION

Biological medicines ("biologicals") contain active substances from biological source [1, 2]. The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) defined a biosimilar medicine as a medicine "highly similar" to another biological medicine already marketed ("reference medicine") in terms of structure, biological activity, clinical efficacy, safety and immunogenicity profile [1,3].

In 2018, a large wave of biosimilar is just starting, and by 2027, 77% of current biotech spending is expected to be subject to some form of competition. [2]. A large number of biosimilar medicines are in development and can be expected to reach the market in E.U and, may be, the U.S. by 2021 [4]. The introduction of biosimilars increases price competition, which affects not just the price of the respective reference products, but also the price of the whole product class. Price per treatment day (TD) of anti-TNF biosimilars in 2016 compared to price per TD of original products before biosimilar entrance were -13%. The three European countries where the highest price reduction of the total market were achieved in 2016 were Sweden, Norway and Denmark with -39%, -32% and -24% respectively. Biosimilars have the potential to improve patient access of the total market, for example Sweden has increased volume of anti-TNF in 2016 compared before biosimilar entrance to 74% and Slovakia intab 93% [5].

The impact of the introduction of biosimilars for infliximab (IFX) on inflammatory bowel diseases (IBD)-related health care costs has been estimated in the Netherlands. Compared with no introduction of biosimilar, cost savings over a total of 5 years were on average 9,850 € per Crohn´s disease (CD) patient and 2,250 € per ulcerative colitis (UC) patient [6].

A key point in the clinical development of biosimilars is demonstrating bioequivalence [7]. This review focus on anti-TNF biosimilars and bioequivalence studies to reference product. A systematic review of bioequivalence of anti-TNF biosimilars has been published [8], we add our perspective from a clinical point of view and the evidence emerging in the last two years.

2. REGULATORY APPROVAL PROCESS

Biological medicines are made by living organisms, which are naturally variable. Thus, the active substance in the final biological medicine can have an inherent degree of minor variability. This minor variability must fall within the acceptable range to ensure consistent safety and efficacy, and can be present within or between batches of the same biological medicine, particularly when manufacturing processes are modified during the commercial life of

the medicine [1]. EMA has pioneered in the regulation of biosimilars since the approval of the first one in 2006. The requirements for biosimilar approval in the US by FDA are based on the same scientific rationale as in the EU, although specific data requirements may differ between these two regions due to different legal framework [9]. Other international regulators such as Australia, directly apply the principles set out in the EU legislation [10]. The World Health Organisation (WHO) has developed its own guidelines for biosimilars and biosimilar monoclonal antibodies [11,12], with the aim of providing guidance to regulatory agencies worldwide. These WHO guidelines incorporate many of the scientific principles used by EMA. For this reason this review is going to focus on EU´s regulation. Some of our data will not be globally valid, as in some countries regulations are different, and usually less stringent.

Biosimilarity is demonstrated via comparability studies with the reference medicine [7]. Comparability is conceived as a step-wise process that is tailor-made for each product:

- *Comparative quality studies:* in vitro studies compare the protein structure and biological function using sensitive techniques. These studies should be much more sensitive than clinical trials for detecting such differences.
- *Comparative non-clinical studies:* these are pharmacodynamics studies in vitro. Pharmacodynamic studies in vivo (animal models) are only done if no suitable in vitro model exists. In vivo toxicological studies are only required in certain cases.
- *Comparative clinical studies:* these studies are tailored to confirm biosimilarity and to address any questions that may remain form previous analytical or functional studies.

As it has explained before, comparability is not a new concept. In most comparisons with the goal of demonstrating biosimilarity, only detailed analytical and functional in vitro tests are required. However, clinical trials may be needed if any impact on safety and efficacy is anticipated. This is particularly the case with very complex molecules, as monoclonal antibodies, in which is almost impossible to predict all the clinical consequences of a small variation in structure (eg glycosylation).

The goal is to rule out potential product-related differences that could affect pharmacokinetics (PK), efficacy or safety, including immunogenicity. PK studies should be conducted in a homogeneous and sensitive population (healthy volunteers or patients) to detect any possible differences between the biosimilar and its reference medicine. To compare the pharmacological effects, a sensitive endpoint that allows detection of product-specific differences should be chosen. Equivalence margins are set specifically for the indication studied and depend on the endpoint chosen. They should represent the largest difference in efficacy that would not matter

in clinical practice, treatment differences within this range would thus be acceptable because they have no clinical relevance. These margins are not unique to biosimilar testing, they are routinely used in clinical trials.

In EU, for the marketing authorisation procedure of biosimilar, the applicant should present a risk management plan/pharmacovigilance plan and a postmarketing safety monitoring is also required by FDA [1,9].

3. INFLIXIMAB AND ITS APPROVED BIOSIMILARS AGENTS

IFX, marked as Remicade®, was the first anti-TNF used for treating IBD. Its biosimilars, CT-P13 and SB2, were approved by the EMA and FDA for use across all indications of IFX. Other biosimilar products are in development. Due to the large amount of existing data, we will focus on the preclinical and clinical studies of the two-IFX biosimilars approved by EMA and FDA (CT-P13 and SB2). (See Table 1)

3.1 PRECLINICAL EVALUATION OF CT-P13 AND SB2

CT-P13 has been the first biosimilar agent of IFX and has been the first biosimilar monoclonal antibody evaluated by EMA. CT-P13 has the same amino acid sequence, is produced by the same type of cell line and has an identical pharmaceutical form, composition, route of administration and dosing regimen as the reference IFX. It has demonstrated identical primary and higher order structures than IFX. In terms of charge isoform, it has been observed to contain slightly less basic variants than the original product, the difference was shown to be largely due to the presence of C-terminal lysine, but it has shown no effect on the biological potency or safety of CT-P13 [13].

All major physicochemical characteristics and biological activities of CT-P13 were comparable to those of Remicade®. The fermentation, purification of the active substance were adequate. The manufacturing process was satisfactorily validated and quality of the finished product was assured. CT-P13 exhibits a lower level of afucosylated glycans than Remicade®, hence a lower binding affinity to FcγRIIIa and a lower binding affinity towards specific Fc receptors and a lower ex vivo in the most sensitive antibody-dependent cellular cytotoxicity (ADCC). However, no difference could be detected in several experiments that are more representative of pathophysiological conditions, and therefore more relevant clinically. All major physicochemical characteristics and biological activities of CT-P13 were comparable to those of Remicade® [14-16].

The nonclinical studies CT-P13 versus Remicade® included PD, PK and toxicological studies. The nonclinical data consisted in several in vitro primary PD studies (including a human tissue cross reactivity study comparing biosimilar and original molecule), two pivotal toxicological studies (one with toxicokinetics and immunogenicity testing) and one PK study in order to compare the bioactivity profiles. The comparability was shown in the majority of parameters assessed. Some variability was seen in the results were acceptable, as difference observed in FcϒRIIIa binding, this observation does not impact in the biological activity and has no clinically relevant impact of the efficacy and safety of CT-P13 [14,15].

SB-2 is developed and manufactured using Chinese hamster ovary cell (CHO) lines instead of the murine cell line that was used for the production of Remicade®. CHO is widely used for the manufacture of biotherapeutics [17,18]. The characterisation of SB-2 included a comprehensive battery of physicochemical and biological tests using sensitive and qualified analytical methods in order to elucidate the primary, secondary, and higher-order structure, post-translational modifications, glycosylation, charge variants, purity/impurities, and quantity and biological properties.

The relative content of C-terminus with Lys for Flixabi® was much lower than that of Remicade®, this was explained by the use of CHO cells. Heterogeneity of C-terminal residues is a characteristic of therapeutic monoclonal antibodies (mAbs), but C-terminal Lys variation does not impact PK profiles and did not impact on TNF-α binding activity [17].

Minor differences were observed in glycosylation pattern (manose and afucose), there was carried out a thorough investigation to support that these changes do not have any clinical relevant impact. The slightly higher FcγRIIb and FcγRIIIa binding Flixabi® compared to Remicade® did not translate into any difference in the relevant biological activity and is therefore concluded to be without impact on safety/efficacy. Additional biological assays were performed to further justify the observed binding difference of FcγRIIIa using various conditions, and to evaluate the in vitro IBD model in order to support extrapolation of indication. The results of the assays indicate that under these conditions the differences are diminished [17].

Terminal sugars of Fc glycans have been shown to be critical for efficacy because Fc glycans influence FcγRIIIa binding and subsequent ADCC activity. Combined percentages of afucosylated and high mannosylated glycans are positively correlated with FcγRIIIa binding and ADCC in NK92-CD16, while no correlation is observed with the physiologically relevant PBMC (peripheral blood mononuclear cells). Differences in glycosylation could still have some biological impact that might be of interest in later clinical differences [19].

Nonclinical studies included a series of in vitro and in vivo studies to demonstrate PD and PK and immunogenic similarities. Similar PK parameters were observed (rat and mice studies). PD studies supported biosimilarity between SB2 and Remicade® as all results were within the similarity range, with the exception of FcγRIIIa (V/V type), FcγRIIb, and FcRn binding assays. However, the difference was within assay variability for FcγRIIb and FcRn binding assays, and binding activity differences in FcγRIIIa (V/V type) and FcγRIIb were not translated into ADCC activity since the ADCC activity of SB2 was within the similarity range. FcRn is known to internalise antibodies into cellular endosomes to protect antibodies from proteolysis and thus plays a role in prolonging half-life of serum IgG. Nevertheless, despite the small deviations outside the similarity margin in FcRn binding activity, these were not translated into PK differences [17,18,20].

A higher incidence of anti-drug antibody (ADA) in Flixabi® was found compared to Remicade®, so the impact of the differences on the immunogenicity of Flixabi® was discussed in depth. It was concluded that the differences in quality attributes are unlikely to induce higher ADA incidence. Studies showed no differences in epitopes or antibody recognition sites between Flixabi® and Remicade® [17].

3.2 CLINICAL EVALUATION OF CT-P13 AND SB2

CT-P13

Regulatory approval of the IFX biosimilar CT-P13 was based on 2 randomized controlled trials comparing it with its originator product in rheumatic disease: the PLANETAS study in patients with ankylosing spondylitis (AS) [21] and the PLANETRA study in patients with rheumatoid arthritis (RA) [22]. Moreover, PLANETAS and PLANETRA extension studies that evaluate the long-term efficacy and safety of extended CT-P13 treatment over 2 years have recently published [23-25]. See Table 2

The PLANETAS trial, was a phase I randomized, double-blind, parallel-group study that included 250 anti-TNF-naïve patients with active AS [21]. Patients were randomized to receive CT-P13 or IFX dosed at 5 mg/kg at weeks 0, 2 and 6 and then every 8 weeks up to week 30. The primary endpoint of the trial was to demonstrated PK equivalence at steady state [area under the concentration-time curve (AUC) and observed maximum serum concentration (C_{max})] between biosimilar and reference product evaluated between weeks 22 and 30. Steady-state PK was show to be equivalent for CT-P13 and IFX. PLANETAS trial also showed that efficacy, assessed at weeks 14 and 30 and that included several clinical index and clinical criteria, was highly similar between the two groups. The Assessment in Ankylosing Spondylitis Response Criteria (ASAS) 20 and the ASAS40 refer to a 20% and 40% improvement, respectively, in a

set of clinically relevant measures of AS activity. At week 30, the odds ratio (biosimilar/IFX) for the ASAS20 and ASAS40 were 0.91 (95%CI, 0.51 to 1.62) and 1.19 (95%CI 0.70 to 2.00), respectively. Similar findings were obtained at other time points. These efficacy rates were comparable to those reported previously in pivotal trials of IFX in AS. Partial remission rates, adverse events and pharmacokinetics profiles for both products remained equivalent at week 54. In the subsequent open label PLANETAS extension study (n=174), 86 patients treated with IFX were switched to CT-P13 at week 54 and followed for 48 weeks more and 88 patients with CT-P13 continued with biosimilar [23]. Efficacy endpoints at weeks 78 and 102 were all of them equivalent between the maintenance and switch groups. The proportion of treatment-emergent adverse events seemed to be slightly higher in patients switching therapy than in patients continuously treated with CT-P13 (71.4% vs. 48.9%). However, there were no notable differences between the maintenance and switch groups in the incidence of adverse events leading to treatment discontinuation.

Positive results of PLANETAS trial prompted Celltrion to conduct the PLANETRA trial, a phase III randomized, double-blind, parallel-group study that included patients with active RA despite treatment with methotrexate (≥ 3 months) and received a stable dose (12.5-25 mg/week) for ≥ 4 weeks before screening [22]. Patients were randomized to CT-P13 (n=302) or IFX (n=304) with methotrexate and folic acid. The primary endpoint [the American College of Rheumatology 20% (ARC20) response at week 30] was similar for both groups (60.9% for CT-P13 and 58.6% for IFX, 95%CI -6% to 10%). Other clinical disease activity indices, quality of life and all other PK and pharmacodynamics parameters were also highly similar in both groups. Regarding safety, incidence of drug-related adverse events also were equivalent. Of the 606 patients included in PLANETRA study, 455 (CT-P13:233 and IFX:222) were treated up to week 54. In this week, the ACR 20 response rate (CTP-13 74.7% vs IFX 71.3%), remission, pharmacokinetics profile and adverse events rates were also comparable between both groups [24]. Three hundred two patients of 455 who completed the PLANETRA study were enrolled in the open-label, single-arm extension study. All patients received every 8 weeks CT- P13 and concomitant methotrexate from weeks 62 to 102. Of these, 158 had received CT-P13 (maintenance group) and 144 IFX (switch group) previously. At week 102, clinical efficacy and adverse events rate were similar in both groups (maintenance vs switch) [25].

SB2

Regulatory approval of the biosimilar SB2 was based on two pivotal studies published in 2015 that compared it with Remicade®; a phase I randomized, single-blind, three arm, parallel group study in 159 healthy subjects [26] and a phase III, randomised, double-blind, parallel group study in patients with moderate to severe RA despite methotrexate [27].

In the phase I study, all patients received a single dose of 5 mg/kg of one of three IFX study drugs (SB2, EU-IFX or US-IFX) and then were observed for 10 weeks. The primary PK parameters that were studied were AUC from time zero to infinity (AUCinf), AUC from time zero to the last quantifiable concentration (AUClast) and Cmax. Bioequivalence was to be concluded if the 90 % CIs for the ratio of geometric least squares means (LSMeans) of the treatments compared were completely contained within the pre-defined equivalence margin (0.8–1.25). In this clinical study, SB2 showed pharmacokinectic equivalent with its marketed reference products of IFX (EU-IFX and US-IFX). Moreover, no significant difference in terms of safety and immunogenicity profiles was found across the treatment groups [26].

In the phase III study, 584 patients were randomised in a 1:1 ratio to receive SB2 or IFX. In 2017, results of study at week 30 were published [27]. The ACR20 response at week 30 was 64.1% in SB2 vs. 66.0% in IFX. The adjusted rate difference was -1.88% (95% CI -10.26% to 6.51%), which was within the predefined equivalence margin. The adverse event rate was comparable. Also in 2017, study results at week 54 were published [28]. The patient disposition was similar between the both groups: 78.0% of the SB2 group and 76.8% of the IFX group completed the 54 week study. We want to note that starting at week 30, stepwise dose increments by 1.5 mg/kg up to a maximum of 7.5 mg/kg were permitted at each visit if RA symptoms were not well controlled by the existing dose. This study showed that SB2 and IFX maintained comparability up to 54 weeks in all efficacy clinical outcomes measured. Indeed, the equivalence margin for the ACR20 rate difference, which was intended for the primary endpoint at week 30, was met also at week 54. In addition, efficacy related to dose increments, whether regarding frequency or final dose, was comparable between SB2 and IFX. The safety profile was comparable up to 54 weeks, with no particular difference from the 30-week report.

3.3 EXTRAPOLATION

In IBD, after a stringent approval process, the EMA and the FDA authorized the CT-P3 and SB 2 by “extrapolation” for all the therapeutic indications for which Remicade® was previously approved, as we mentioned previously.

Extrapolation refers to the process of extending efficacy and safety data derived from one approved therapeutic indication for which the biosimilar has been demonstrated equivalence with reference medicinal product to other indications for which reference product is approved [7]. The approval of a biosimilar requires clinical data, as we mentioned previously, but clinical trials have a relatively minor role compared to their importance in the development and

approval of new drugs. It is important to know that biosimilar development programs do not want to demonstrate clinical efficacy of the product in a particular clinical indication, since it has been already done with the reference product. An important decision to be taken by de regulatory agencies is if to demand a confirmatory clinical trial for each indication, or to assume that extrapolation of indications is enough guarantee. The EMA state in its most recent published guidelines that "*Extrapolation of clinical efficacy and safety data to other indications of the reference monoclonal antibodies is possible based on the overall evidence of comparability provided from the comparability exercise and with adequate justification", but not as an "automatic or systemic conclusion*" [29]. In anti-TNF drugs, the EMA has included the mode of action of biosimilar in the "*totality of evidence with adequate and relevant justification*".

For biological drugs that have several indications, the question arises as to which disease should be targeted in the pivotal clinical trial. The EMA establishes that the most sensitive disease should be selected for increasing the probability to detect any existing difference between products. But it is difficult to define which the most sensitive disease is. In the case of CT-P13, RA was selected for pivotal trial (PLANETRA study) [22], but it has claimed that IFX has a relatively low efficacy vs. placebo effect in this indication. Other aspects that may difficult extrapolation from AS and RA to IBD are lower IFX doses and the concomitant use of methotrexate in the III phase study. Moreover, RA and IBD have different clearance of IFX and different response to other monoclonal antibodies (for example: rituximab is effective in RA but not in IBD), suggesting the possibility of different mechanisms of inflammation.

Despite the stringent approval process performed by regulatory agencies, extrapolation is one of most controversial issues regarding to biosimilars and finds some resistance in medical community [30-32]. Of course, regulatory agencies rules on pharmacovigilance for biosimilars are very strict because of the two trials required to authorise a biosimilar may not be sufficient to detect differences in the safety related to very infrequent adverse events. Because of that, they require a very detailed risk management plan, even more important if extrapolation is approved.

It is interesting to note that recently (2017), *Kim Y. H, et al.* presented in the 12th Congress of ECCO (European Crohn´s and Colitis Organisation), the first phase III randomised, double blind controlled trial that compares CT-P13 with IFX in patients with IBD (active CD) [33]. They showed that the efficacy of CT-P13 was similar to IFX in terms of CD activity index-70 (CDAI-70) (p-value= 0.5613), CDAI-100 (p-value= 0.7744) and clinical remission (p-value= 0.8329) up to week 6.

3.4 IMMUNOGENICITY

Proteins and other biological medicines have an intrinsic ability to cause an unwanted immune response, which, in rare cases, could cause a serious adverse reaction or reduced efficacy. Formation of immune complexes between antidrug antibody and biologics (reference product and biosimilar) may increase frequency of infusion reactions, increase clearance, reduce serum biologic levels, reduce efficacy, and may have a more direct neutralizing effect on product target binding [32,34-36].

Immunogenicity may be influenced by many factors: product characteristics, treatment-related factors, patient or disease- related factors [32,34]. The proportion of patients who developed treatment-induced ADA varied widely across biologic/biosimilar agents, the incidence of ADA vary considerably across assay methods used and inflammatory disease states [34,36].

FDA mandate at least one clinical trial in which comparative immunogenicity of a biosimilar and its reference product is assessed, EMA has a specific "Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use" [9,37].

The frequency of neutralizing ADA has been similar between biosimilars and their reference products [35]. The proportion of patients positive for ADAs at week 54 in PLANETRA study was similar between the two groups: 41.1 % and 36.0 % with CT-P13 and RP, respectively. [24]. On the open label extension of PLANETRA study, switching CT-P13 in patients previously treated with reference product compared to continuing CT-P13 with AR, the proportion of patients with ADAs was similar between both groups at week 102 (p=0.48) [25]. See table 3

Immunogenicity was also comparable between SB2 and reference product at 54 weeks [28], (p=0,270). At week 54, patients previously receiving IFX were randomised (1:1) to switch to SB2 or continuing SB2, up to week 70 [38], the incidence of ADA was comparable in the different treatments groups. Among patients who were negative for ADA up to week 54, newly developed ADAs were reported in 14.6%, 14.9% and 14.1% of the INF/SB2, INF/INF and SB2/SB2 groups, respectively. See table 3

Patient who develops antibodies to a reference drug with resultant loss of clinical response should not be switched to its biosimilar. ADAs against IFX and CT-P13 in RA and in IBD patients has been shown equivalent immunogenicity with a similar antigenic profile for both IFX versions [39-41]. Findings in Fiorino`s study, in IBD patients, suggest that

immunodominant epitopes in the reference and CT-P13 drugs are equally present in SB2, all antibodies cross-react with any type of infliximab molecule. CT-P13 and SB2 could be interchangeable and will not lead to differences in ADA production [42].

3.5 SWITCHING

Interchangeability and substitution between reference product to biosimilar are an open problem. According to the EMA, interchangeability is to change one medicine for another that is expected to achieve the same clinical result in a given clinical setting and in any patient, with the agreement of the prescribing physician. However, substitution is to dispense one drug instead of another interchangeable drug at pharmacy level, without consulting the prescriber. In general, automatic substitution of biosimilars is not recommended. The FDA determines that a biological product could be considered interchangeable to the referent product only if the biological product is biosimilar and if the expected clinical effects and the safety profile are the same in any given patient and if the risk to switch to biosimilar is not greater than the risk of continue with the originator product [43]. The FDA has the authority to say that a biosimilar is interchangeable and interchangeable product might be substituted for the reference product without the intervention of the prescribing physician [44].

By now, only data regarding switch from infliximab to CT-P13 are available. As we have already mentioned, PLANETAS and PLANETRA extension studies showed similar efficacy and safety after the switch of IFX to CT-P13 and in those who had long-term CT-P13 treatment (102 weeks). Clinical efficacy, safety, and immunogenicity of switching between IFX originator and CT-P13 in IBD were evaluated in several studies [45-70] (see Table 4). Most studies were retrospective, and only one was randomized (NOR-SWITCH trial) [71]. *Gisbert et al.* [43] in their recent systematic review, and after evaluated 24 studies, showed that disease control was confirmed in 1163 of the 1326 included patients. In the sub-analysis in function of type of the disease, the proportion of patients with CD that maintained disease control was 86% and with UC was 93%.

NOR-SWITCH trial deserves special attention, because it is the only controlled and randomized study that evaluates switching [71]. This trial tested the interchangeability from IFX to CT-P13 in patients with different disease: IBD, RA, AS, psoriasic arthritis and chronic plaque psoriasis. Patients included must be on stable treatment with Remicade® for at least 6 months and were randomized 1:1 to either continue IFX or switch to CT-P13. The study was designed as a non-inferiority trial (prespecified non-inferiority margin of 15%). Finally, 481 patients were followed for 52 weeks. The authors did not observe significant increase in disease worsening between originator and biosimilar group. In particular, 155 patients with CD and 93 with UC

were included. Disease worsening was reported in 21.2% vs. 36.5% in originator and biosimilar CD group and in 9.1% vs. 11.9% in originator and CT-P13 UC group. Moreover, there were no differences in safety or immunogenicity. However, this study also has some design limitations and its results cannot yet be generalized to other biologicals medicines and their biosimilars.

Finally, uncertainty remains of multiple switches back-and-forth between a reference medicine and its biosimilar or among multiple biosimilars [72]. We want to note that several ongoing studies will soon provide additional information of the clinical efficacy and safety of switching in patients with IBD (ClinicalTrials.gov :NCT02096861, NCT02998398 and "the SIMILAR Trial'' NCT02452151).

4 ADALIMUMAB AND ITS APPROVED BIOSIMILARS AGENTS

There appear to be several "front runners" in the race to biosimilar adalimumab in Europe and United States. Leading the race are biotech major Amgen and Boehringer Ingelheim Pharmaceuticals. Other biosimilar products are in development (table 5). Due to the large amount of existing data we will focus on the preclinical and clinical studies of the two biosimilars of adalimumab approved by EMA and FDA (ABP 501 or BI 695501).

4.1 PRECLINICAL EVALUATION

ABP 501 is analytically similar, has the same primary amino acid sequence, similar structure and strength as the reference product. Comparative PD, PK and toxicology data demonstrate biosimilarity between ABP 501 and Humira®. [73,74]. A comprehensive assessment between ABP 501, adalimumab (USA) and adalimumab (EU) was conducted to demonstrate similarity in biofunctional activity. This included: testing of binding kinectis to TNFα and relative binding to transmembrane TNFα, the neutralizations of TNFα-induced caspase activation, TNFα- and lymphotoxin-α-induce chemokine production, cytotoxicity, binding to Fc-gamma receptors FcγRIa, FcγRIIa, FcγRIIIa and FcRn, antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity. Data demonstrate that ABP 501 is similar to both adalimumab (US and EU) with respect to biofunctional activities [75].

In a randomised, single-blind, single-dose, three-arm, parallel-group study, healthy subjects were randomised to received ABP 501 (n=67), adalimumab (US) (n=69) or adalimumab (EU) (n=67). The confidence interval (CI) for the geometrical mean ratio (GMR) of AUCinf and Cmax were within the prespecified standard PK equivalence criteria of 0,80 to 1.25 [76].

BI 695501 has demonstrated to be similar to adalimumab (US and EU). A comprehensive biosimilarity exercise has been performed (analysis of primary sequence, secondary and higher order structure, size, charge and hydrophobicity heterogeneity). Functional activity and antibody clearance was also demonstrated to be similar to adalimumab. The presence of foreign particles detected in some pre-filled syringe lots of BI 695501 was studied in depth, and potential safety issues arising from the presence of particles could be ruled out [77].

In 2016, a randomized, double-blind, active comparator phase I clinical study (VOLTAIRE®-PK) in healthy subjects was published. Its aim was to evaluate three-way pharmacokinetic similarity (bioequivalence), safety, and immunogenicity of BI 695501 compared with Humira® in healthy male subjects. *Wynne et al.* included 327 patients who were randomized 1:1:1 to receive one 40-mg dose of BI 695501, US- or EU-approved Humira®. Bioequivalence between the three drugs was demonstrated with the 90% CIs of the ratios of all primary end points: C max, AUCinf and AUC from time zero to the last measurable concentration, being within the prespecified acceptance ranges of 80–125%. [78].

A phase II, 7-week, open-label study (VOLAIRTE® -RL) was conducted to examine administration of BI 695501 using autoinjector, showing a successfully self-administration after training [79].

4.2 CLINICAL EVALUATION OF ABP 501 or BI 695501

At this time, there is no available clinical data regarding the efficacy of ABP 501 or BI 695501 in IBD. See Table 2.

ABP 501.

Comparable efficacy and safety of ABP-501 to US-Humira® was assessed in 2 randomized, double-blind, phase III equivalence studies in patients with moderate to severe RA and in patients with moderate to severe plaque psoriasis.

- The RA trial consisted of 526 patients treated with either ABP 501 (n=264) or US-Humira® (n =262) every 2 weeks with concomitant methotrexate. The primary endpoint, ACR20 response at week 24, safety and immunogenicity were comparable between treatment groups [80].
- In the psoriasis trial was included 350 patients treated with ABP 501 or with originator. 175 patients were randomized to the ABP 501 arm. At week 16, half of the reference group was switched to ABP 501 and followed through week 52. Psoriasis Area and Severity Index percent improvements from baseline were similar across groups for weeks 16, 32 and 50 (range: 85·8-88·2%). Changes from baseline in percentage body

surface area affected were similar across groups and time points. Safety results were also comparable [81]

BI 695501.

VOLTAIRE-RA study was published in 2018. It is a randomised, double-blind, parallel-arm, 58-week equivalence trial that compared efficacy, safety and immunogenicity of BI 695501 and US-sourced Humira® in patients with moderate-to-severe RA on stable methotrexate treatment. Six hundred forty five patients were randomised 1:1 to receive BI 695501 (n=324) or Humira® (n=321) 40 mg subcutaneously for 24 weeks. At week 24, patients originally randomised to Humira® were re-randomised at week 24 to either continue Humira® (n=148) or switch to BI 695501(n=147). There were no differences in the rate of treatment or trial discontinuation between treatment groups. The difference in the proportion of patients achieving an ACR20 response was within the prespecified interval at week 12 and week 24 demonstrating therapeutic equivalence of both drugs. The analysis of the secondary efficacy endpoints supported the findings of the primary efficacy analysis. The mean percentage of patients meeting the ACR20/50/70 response criteria and the mean change from baseline in DAS28-ESR (Disease Activity Score in 28 joints using erythrocyte sedimentation rate) were similar in each treatment group at weeks 12 and 24 and across the switched and the continuous groups after re-randomisation at week 48. BI 695501 and Humira® demonstrated also similar safety and tolerability [82].

5. CONCLUSIONS

Biosimilars are here to stay, and most likely will be very important actors in the fields of rheumatology, dermatology, IBD, ophthalmology and, very specially, oncology. Quality, safety, and efficacy (at least for the clinically tested indications) are clearly warranted for the biosimilars of infliximab (CT-P13 and SB2) and adalimumab (ABP-501 and BI 695501) approved by EMA and FDA.

6. EXPERT OPINION

A. *Biosimilars to antiTNF biologics approved by EMA and/or FDA have demonstrated bioequivalence in all available studies.*

Biologic drugs are complex molecules or even substances. Standard regulations for generics were not adequate, and all regulatory agencies have developed specific rules for approval of *biosimilars*. EMA pioneered in 2006, and the task was apparently well done, as very few relevant incidents have occurred with different biosimilars in Europe. FDA, Australian,

Canadian, Japanese, and other regulatory agencies have released very similar regulations. Although when biosimilars to antiTNF antibodies were finally approved some doubts were raised in scientific societies, and patient's associations, educational efforts and growing evidence have shown that EMA rules do a nice work in practice. Controlled and uncontrolled data from clinical trials and registers have shown that *EMA biosimilarity* nicely translates into *clinical biosimilarity*.

B. *Immunogenicity of biosimilars has not been proven different to originators. In the particular case of CT-P13 immune response to the drug appears identical to originator in a number of very detailed studies*

The most controversial issue is that of immunogenicity, because in the case of monoclonal antibodies the extreme complexity of the molecule, very especially in glycosylation, makes theoretically possible a difference in epitopes. This could be particularly important as clinical experience with originators has demonstrated that immunogenicity is a key determinant of secondary failure to these biologic drugs. In the case of CT-P13, the first released biosimilar to infliximab, there have been done very detailed studies with immunological and chemical techniques that have consistently demonstrated a complete immunologic similarity between the two infliximabs: in fact several serologic methods used in clinic for measuring infliximab levels cannot distinguish both molecules. Clinical comparative trials have not shown any difference in immunogenicity between biosimilars and their reference products, and any immunological unexpected side-effect has been appeared when switching from originator to CT-P13. To date, no relevant differences have been shown between biosimilars and their reference products.

C. *Switching from originator to biosimilars has been found to be safe and effective in several randomized trials and many prospective, observational studies*

Controlled clinical studies are very expensive, and as the differences between originator and biosimilar are expected to be few and difficult to find a high number of subjects needs to be observed to obtain significant statistically and clinically relevant conclusions. However, in all controlled studies biosimilars have shown complete bioequivalence to originators in all cases, according to predetermined criteria. Moreover, a great number of observational studies and data from national or regional registers have confirmed the same type of data. After switching from originator to biosimilar clinical efficacy has not changed and no new safety alert has been detected, in several pathologies and different countries. In fact, thousands of patients have been switched and no consistent problem has been identified to date.

D. *Multiple switching between different biosimilars and originator cannot be recommended with available data*

However, it remains the possibility that as new biosimilars are compared to one originator, some differences (may be even important), could exist between two or more biosimilars. Probably, it would be prudent to avoid several changes in the same patient if there is no a very important reason. As more and more molecules reach the market, potential differences could be important. Multiple switching cannot be recommended with available data. We are expecting results from studies with several crossings of drugs in the same group of patients, but no data are available to date. The wealth of data do not suggest that a really clinically significant problem will be detected in the future, but biology is so complex that we should be prudent.

E. *No unexpected safety issues have appeared after several years of biosimilars use in areas under reliable and strict regulations*

The topic we are considering has very important economic issues. The conflicts of interest can be huge when billions of euros are on the table. This should not be forgotten. So, it is very reassuring for us, as clinicians, that from 2006 the safety record of biosimilars in Europe is excellent. No severe unexpected adverse effect related with a biosimilar has been detected. This record suggests that EMA regulations are very well done, and if pharmacovigilance should remain a priority, we can be confident when prescribing biosimilars to our patients.

F. Personal experience

In our hospital we have been using several biosimilars from 2006, and soon after release we started using CT-P13 (Inflectra ®) for treating our patients with rheumatologic or digestive indications. In fact, we have direct experience in patients with Ulcerative Colitis and Crohn's disease. We have not been able to see any real difference between the biosimilar and the originator. In fact, we have started all new treatments from 2015 with CT-P13, and we are progressively switching and have not noticed any unexpected problem.

In our opinion, biosimilars approved by EMA are a good alternative for our patients, and do contribute to containing costs for the system. Of course, if we think so one reason is we think bioequivalence has been clearly demonstrated by all methods: quality control, preclinical evaluation, controlled clinical trials, and a substantial quantity of observational data.

ARTICLE HIGHLIGHTS BOX

- Biosimilars to antiTNF biologics approved by EMA and/or FDA have demonstrated bioequivalence in all available studies.
- Immunogenicity of biosimilars has not been proven different to originators.
- Switching from originator to biosimilars has been found to be safe and effective in several studies
- Multiple switching between different biosimilars and originator cannot be recommended with available data
- No unexpected safety issues have appeared after several years of biosimilars use
- Biosimilars approved by EMA are a good alternative and do contribute to containing costs for the system

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Declaration of Interests

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Reviewer Disclosures

Peer reviewers on this manuscript have no relevant financial relationships or otherwise to disclose.

TABLES

Table 1. Biosimilars and original product of infliximab authorised by EMA and FDA

INFLIXIMAB	EMA	FDA

	Tradename	***Company***	***Date of authorisation***	***Tradename***	***Company***	***Date of authorisation***
Original product	*Remicade*®	Janssen	August 1999	*Remicade*®	Centocor	August 1998
CT-P13	*Inflectra*® *Remsima*®	Hospira-Pfizer Celltrion	September 2013 September 2013	*Inflectra*®	Celltrion	April 2016
SB2	*Flixabi*® *Zessly*®	Samsung Bioepis Sandoz	May 2016 May 2018	*Renflexis*®	Samsung Bioepis	April 2017
PF-06438179				*Ixifi*®	Pfizer	December 2017

Table 2: Efficacy of infliximab and adalimumab biosimilar compared with reference products. Randomized controlled trials

IFX BIOSIMILARS				ADALIMUMAB BIOSIMILARS	
CTP13 vs.Reference IFX				ABP 501 vs. reference adalimumab	
PLANETRA TRIAL (RA) (ITT population) [25]	***ACR20***	***ACR50***	***ACR70***	***RA trial [81]***	***ACR20***
At week 30				*At week 24*	
CTP-13 (n=302)	60.9	5.1	16.6	ABP501 (n=260)	74.6
Reference IFX (n=304)	58.6	34.2	15.5	Reference adalimumab (n=261)	72.4
Tmt difference (%) [95 % CI]	2 (-6 to 10)	NR	NR	RR of ACR20 (90% CI)	1.04 (0.95-1.13)
At week 54					
CTP-13 (n=302)	57.0	33.1	16.2		
Reference IFX (n=304)	52.0	31.6	15.2		
PLANETAS TRIAL (AS) [23,24]	***ASAS20***	***ASAS40***		***Phase II Psoriasis trial [82]***	***PASI % IMPROVEMENT***
At week 14				*At week 16*	
CTP-13 (n=115)	62.6	41.7		ABP501 (n=260)	80.9
Reference IFX (n=122)	64.8	45.9		Reference adalimumab (n=261)	83.1
OR (95%CI)	0.91 (0.53–1.54)	0.85 (0.51–1.42)		least-square mean difference (95%CI)	-2.18 (-7.39 to 3.02)
At week 30					
CTP-13 (n=112)	70.5	51.8			
Reference IFX (n=116)	72.4	47.4			
OR (95%CI)	0.91 (0.51–1.62)	1.19 (0.70–2.00)			
At week 54					
CTP-13 (n=106)	67.0	54.7			
Reference IFX (n=108)	69.4	49.1			

OR (95%CI)	0.89 (0.50–1.59)	1.26 (0.73–2.15)			
SB2 vs.Reference IFX				BI695501 vs. reference adalimumab	
Phase III SB2 (RA) (Full analysis set) [27,28]	***ACR20***	***ACR50***	***ACR70***	***VOLTAIRE –RA trial. RA trial (Full analysis set) [83]***	***ACR20***
At week 30				*At week 12*	
SB2 (n=290)	55.5	30.7	15.5	BI695501 (n=321)	67.0
Reference IFX (n=293)	59.0	33.8	17.1	Reference adalimumab (n=318)	61.1
Tmt difference (%) [95 % CI]	-2.95 (-10.8 to 4.9)	-2.53 (-10.07 to 5)	-1.06 (-7.06 to 4.9)	Difference in proportions (BI 695501 – Humira, %) 90%CI	5.9 (-0.9 to 12.7)
At week 54				*At week 24*	
SB2 (n=302)	64.5	40.8	23.2	BI695501 (n=321)	69.0
Reference IFX (n=304)	68.4	38.7	23.1	Reference adalimumab (n=318)	64.5
Tmt difference (%) [95 % CI	-3.34 (-11.8 to 5.1)	NR	NR	Difference in proportions (BI 695501 – Humira, %) 90%CI	4.5 (-3.4 to 12.5)

IFX: infliximab. RA: rheumatoid arthritis. ITT: intention to treat. ACR20: American College of Rheumatology 20%. ACR50: American College of Rheumatology 50%. ACR70: American College of Rheumatology 70%. AS: ankylosing spondylitis. ASAS: Ankylosing Spondylitis Response Criteria. PASI: Psoriasis Area and Severity Index. CI: confidence interval.

Table 3. Clinical trials evaluating antidrug antibody detected in patients in treatment with infliximab originator and biosimilars CT-P13 and SB2

First author	Study	Disease	Week	Proportion of patients positive for ADA		
				RP group	BS group	
Yoo DH [24]	Double blind. Compare RP to CT-P13	RA in combination to MTX	54	36.0 %	41.1 %	
Smolen JS [28]	Double blind. Compare RP to SB2	RA in combination to MTX	54	57.5 %	62.4 %	
				Switch group	BS group	
Yoo DH [25]	Open-label extension. Compare switching from RP to CT-P13 to CT-P13	RA in combination to MTX	Switch group received RP for 54 weeks and BS until 102 weeks. BS group received CT-P13 for 102 weeks	44.8 %	40.3 %	
				RP group	Switch group	BS group
Smolen JS [38]	Double blind. Compare switching from RP to SB2, to to RP to SB2	RA in combination to MTX	Switch group received RP for 54 weeks and BS until 78 weeks. RP and BS groups received RP and BS for 78 weeks	50.5 % (after week 54 14.9%)	45.7% (after week 54 14.6%)	53.6% (after week 54 14.1%)

RP: Reference Product; ADA: antidrug antibody; BS: Biosimilar; RA: rheumatoid arthritits; MTX: metotrexate

Table 4. Studies evaluating switching between infliximab originator and CT-P13.

First Author	Study design	Sample size (number of patients)	Disease Control (no disease worsening after switching)
Arguelles-Arias [45,46]	Prospective	74	86% at 6 months 73% at 1 year
Bettey [47]	Prospective	134	93%
Buer[48]	Prospective	125	95%
Díaz Hernández and Rodríguez Glez[49,50]	Retrospective	72	100% at 6 months 93% at 1 year
Eberl [51]	Prospective	62	100%
Fiorino [52]	Prospective	97	100%
Guerrero Puente [53]	Prospective	36	86%
Hamanaka [54]	Retrospective	3	100%
Hlavaty [55]	Retrospective	12	100% at 6 months 75% at 1 year
Jahnsen [56]	Prospective	56	100%
Jarzebicka [57]	Retrospective	5	100%
Jones [58]	Prospective	71	76%
Jung [59]	Retrospective	36	86%
Kang [60]	Retrospective	9	89%
Kang [61]	Prospective	27	93%
Kolar [62]	Prospective	74	99% at 6 months 100% at 1 year
Nugent [63]	Prospective	33	85%
Park [64]	Retrospective	46	87%
Razanskaite [65]	Prospective	143	80% at 6 months 73% at 1 year
Soret [66]	Prospective	63	95%
Sieczkowska [67]	Prospective	22	100%
Smits [68]	Prospective	51	82% at 4 months
Strik [69]	Prospective	44	86%
Suk [70]	Retrospective	42	81%

Table 5 Biosimilars and original product of adalimumab authorised by EMA and FDA

ADALIMUMAB	EMA			FDA		
	Tradename	***Company***	***Date of authorisation***	***Tradename***	***Company***	***Date of authorisation***
Original product	*Humira*	Abbvie	September 2003	*Humira*	Abbvie	December 2002
ABP 501	*Amgevita* *Solymbic*	Amgen Amgen	March 2017 March 2017	*Amjevita*	Amgen	September 2016
BI 695501	*Cyltezo*	Boehringer Ingelheim	November 2017	*Cyltezo*	Boehringer Ingelheim	August 2017
SB5	*Imraldi*	Samsung Bioepis	August 2017			
GP2017	*Halimatoz* *Hefiya* *Hyrimoz*	Sandoz Sandoz Sandoz	July 2018 July 2018 July 2018			
Others molecules in vias of authorisation: M923, FKB327, TUR01, ZRC-3197, MSB11022						

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