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Review

The future landscape of biosimilars in rheumatology: Where we are where we are going

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A B S T R A C T

Introduction: The upcoming of biosimilars in rheumatic diseases have generated considerable interest throughout the past five years among pharmaceutical industries and regulatory agencies, their development is associated with considerable variation and heterogeneity on the variable requirements for license and marketing throughout the various continents.
Aim: In this article we reviewed the contents of the conference presented on the last XI International Conference in Autoimmunity in Lisbon.
Evidence: Truly biosimilars that followed requirements from stringent agencies are now available and licensed for infliximab, etanercept, adalimumab and rituximab but several compounds from the same mechanism of action are also being developed and are reviewed and the strengths of their evidence analized and discussed. The use of intended copies (biomimics) and its presence in less regulated markets are also reviewed and the risks of their use without proper monitoring is also evaluated.
Place in therapy: Biosimilars for rheumatic diseases is expected to change the access of patients to high costs biologics and gradually more and more patients are being switched to biosimilars either by the rheumatologist prescription or mandatory national indications. The economic impact is expected to be huge in the coming years. Second generation biosimilars are also being developed and clinical trials are underway for license in the near future.

1. Introduction

Biological therapies had great impact on the standard of care of systemic immune mediated inflammatory disorders. During the past few years expiration of patents protecting the use of the innovator medications has provided the opportunity to commercialize highly similar versions generally known as biosimilars, although in some countries other terminologies were also applied, such as similar biotherapeutic products, biocomparables, and follow on biologics among other terms. Biosimilars are approved by regulatory agencies via pathways that require well powered head to head comparisons with the originator compound. The introduction of biosimilars in the market has the potential to provide savings to healthcare authorities and expand access to the group of therapies where high cost can be a limiting issue. It is fortunate that the scientific committee of the XI International Congress in Autoimmunity included this topic for discussion since in various countries in Asia and in Latin America there is inequitable access to biologic therapy and heterogeneity on the regulatory aspects that led to the use of compounds known as intended copies, such medications already available in some markets were not properly compared with the originator biologic compound [1]. In this manuscript we exclusively review the present and immediate future landscape of truly biosimilars in the treatment of autoimmune diseases.

2. Etanercept

Etanercept commercially known as Enbrel is a protein comprised of the extracellular domains of two TNF receptors (tumor necrosis factor) attached to a portion of an IgG immunoglobulin and acts primarily to bind and neutralize TNF. Preclinical and clinical studies were started in 1993 and in 1998 were approved for the treatment of patients with moderate to severe rheumatoid arthritis. Key clinical studies were followed by evaluating early patients with RA (The Tempo and ERA trials), with Psoriasis (Global Psoriasis Pivotal Trial), and in patients with Ankylosing Spondylitis and Juvenile Arthritis [2].

The main patent for the use of Enbrel in the USA was to be expired in October 2012 but Amgen announced in the end of 2011 that it was granted a new patent protecting it from competition by other biosimilars until 2028 [3].

There over ten companies developing etanercept biosimilars, although the most important and advanced clinical development are with four of them mentioned below.

In Europe however, the patent expired in 2015. In 2016 the joint venture between Biogen and Samsung Biologicals were granted approval of the first etanercept biosimilar SB4 (Benepali) for the treatment of RA, Psoriatic Arthrtitis non radiographic Spondyloarthritis and plaque Psoriasis. Although EMA considered Benepali highly similar to Enbrel some structural and side effects of the biosimilar are now being

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considered and receiving additional attention. [4,5,6] Switching from etanercept to Benepali did not result in any increase in immunogenicity. Data published confirming switching and maintaining efficacy from etanercept to SB4 was reported by Emery and coworkers [7] SB4 was approved In Canada and also in Brazil with a different trade name Brenzys.

There are four Enbrel biosimilars with phase 3 trials finished and licensed or close to license requirements request by their respective companies. Coherus Biosciences reported that CHS-0214 is equivalent to the innovator etanercept in patients with RA with respect to efficacy as measured as a primary end point. No meaning full differences in regard to safety and immunogenicity. This program was partnered with Daiichi Sankyo and Baxter and included 644 patients from 13 different countries. The development plan for approval was finalized and were approved in the of last year CHS-2014 was also evaluated by comparing it with commercial European source of etanercept in patients with Psoriasis including patients with Psoriatic Arthritis. PASI results were similar in patients with psoriasis and psoriatic arthritis [8,9].

The other Enbrel biosimilar and licensed derived from Sandoz, the generics division of Novartis. The phase III study known as Egality evaluated efficacy, safety and immunogenicity of GP2015 compared to Enbrel in patients with moderate to severe chronic plaque psoriasis. The positive results showed the biosimilar to have results in the same magnitude that Enbrel. FDA approved the biosimilar with the trade name Erelzi in September of 2016. The trial known as Egality was a randomized double blind trial involving 531 patients and carried out in 74 dermatology clinics in 11 European countries and South Africa. The primary end point was PASI responses after the first twelve weeks. Key secondary end points were percent change from baseline safety and immunogenicity [10] A few additional comments for its marketing. It is approved for all indications of the reference drug but not as an interchangeable medication, which means it may not be substituted for the reference product by a pharmacist without knowledge of the prescriber. Also it will take a while until American patients may have access to Erelzi since litigation is underway between Amgen and Sandoz on the infringement of patents. Sandoz Enbrel biosimilar has been also accepted for review and approved also by EMA. [8] The fourth Enbrel biosimilar comes also from Asia with the results of a phase III multicentre trial of LBEC0101 developed by LG Chem in Korea against the reference etanercept in terms of efficacy and safety in patients with active rheumatoid arthritis inadequately responding to methotrexate, 374 patients were randomized half in each group efficacy and safety were comparable between the two compounds. It is already licensed in South Korea and in Japan in partnership with Mochida Pharmaeceuticals with the trade name Eucept.This is the second Enbrel biosimilar launched in Korea three years after Samsung Bioepis was approved in 2015. [11]

Sandoz Enbrel biosimilar has been also accepted for review by EMA [8]. In this chapter we elected not to comment on etanercept biosimilars already on the market or soon to be marketed in some countries that are purported to be enbrel biosimilars but relevant data to confirm biosimilarity is missing. This aspect is being extensively reviewed in two articles one touching on the risks of biocopies that are being used in some Latin America countries and in another just published looking on the extensive analytical variability of the various biocopies copies currently in use Latin America [11,12,13,14,15]. Finally, one truly biosimilar of etanercept was developed in South Korea and approved for use with the name Davictrel by Hanwha Chemical (HD203) and although expected to be a future biosimilar the company dissolved its biomedicine production facilities and no future landscape expected for this product [16].

SB4 (Benepali) is already in the market in Europe also in Brazil and on hold in the USA due to patent litigation. In Canada and Korea SB4 is marketed as Brenzys although not available yet and partneship with Merck Sharp Dohme will allow distribution in certain countries in Latin America…GP2015(Erelzi) will be in the market in Europe shortly being approved by EMA with indications in inflammatory arthritis and psoriasis. CHS-2014 is not expected to be in the market until 2018 according to the manufacturers. (Table 1).

Table 1
Etanercept biosimilars.

Truly etanercept biosimilars released 2018–2019
SB4(Samsung-Bioepis)
CHS -0214 (Coherus –Baxter)
GP 2013 (Sandoz)
LBEC0101(LG Chem)

3. Rituximab

Rituximab is a chimeric monoclonal antibody against the protein CD20 and is being used for the treatment of many lymphomas, transplant rejection, rheumatoid arthritis and other autoimmune disorders. [17,18,19,20,21,22] The originator product was initially approved by the FDA for the treatment of Rheumatoid Arthritis in November 1977 and by EMA in June 1998. With patent expiration a large number of companies started the development of biosimilars [23].The number of companies developing Rituximab were over 15 two years ago, some companies that were active in their other biosimilar programs like Boehringer Ingelheim and Samsung halted their development, CT-P10 Celltrion and. TEVA Pharmaceutical had their application for a biosimilar of Rituximab approved by EMA with all indications and their submission to the FDA was accepted for review and approved [24]. It is marketed with the commercial name of Truxima by EMA. This is the brand name aprroved by EMA in february 2017, after this three more brand names of the same product were approved for different indications in the EU Market.

Although marketing strategy in Europe appears with some confusion with different brand names. (Truxella, Ritemvia, Blitzima). It is the first biosimilar of the reference anti CD20 antibody Rituximab and besides the lymphoma indications was approved for all rheumatologic indications rheumatoid arthritis granulomatosis polyangiitis and microscopic polyangiitis. [25] Merck suspended their phase trials (TL011, MK-8808) in this case related to readequate safety requirements from more strict regulatory agencies. Archigen Biotech a joint venture between AstraZeneca UK and Samsung BioLogics, has applied for FDA approval to begin Phase I clinical trials for its rituximab biosimilar, SAIT101.It is not expected that completion of their phase three trials finish recruitment before the end of 2018.

On the table below we list what we believe will be the truly rituximab biosimilars that are expected to reach the market on the 2018 including GP 2013, PF-05280586 and ABP 798 although the state of clinical trial of the latter is not available yet. [26,27,28] GP 2013 is the second rituximab biosimilar approved and it is expected to be marketed as Rixathon or Riximyo. (Table 2).

Some less stringent markets approved intended copies of biosimilars and are already on the market and some were withdrawn for various safety related issues.This is the case of Biocad version approved in Russia (Acellbia), Dr. Reddy(Reditux)in several Latin American countries and at least three intended copies are available in India (Maball,

Table 2
Rituximab biosimilars.

Truly Rituximab biosimilars to be released in 2018–2019
Celltrion South Korea CT-P10
Sandoz Switzerland GP-2013 trials in RA
Pfizer USA PF-05280586 trials in RA
Amgen USA ABP 798 trials in RA and Lymphoma
RXTM83 trial in Lymphoma.
Boehringer Ingelheim, BI 695500 trial in RA.

Mabtas, Toritz) besides Dr. Reddy version mentioned above… Kikuzabam with local technology from a Mexican pharma was removed from the market in 2014.An Argentinian company Elea was able to approve for use a Rituximab copy (RTXM83-Mabscience) for use in lymphoma although the regulatory agency in Argentina follows closely WHO recommendations for approval and a trial for efficacy is still underway, therefore our impression is that the medication is available in the Argentinian market without proper data. Two additional comments are pertinent in this section One relates to the fact that besides the four truly listed above the copies approved in Russia, India and Argentina will likely not reach the markets where high standards of comparability against the innovator are requested [29,30,31] The introduction of a new monoclonal antibody engineered antibody that attaches to CD20 on certain B cells (Obitunuzumab) maybe a future biologic that will compete with the truly biosimilars of Rituximab and will share the rheumatology market for use in autoimmune diseases such as RA and Anca positive vasculitis [32]. The giant biotechnology Poland company Mabion plans to license a Rituximab biosimilar in more regulated markets through an agreement with the giant generic company Mylan but no data on their trials are available.

4. Adalimumab

Adalimumab is a TNF-inhibiting, anti-inflammatory, biologic medication. It binds to tumor necrosis factor-alpha (TNFα), which normally binds to TNFα receptors, leading to the inflammatory response of autoimmune diseases. By binding to TNFα, adalimumab reduces the inflammatory response. It was approved in rheumatoid arthritis and by additional trials approved in psoriasis, psoriatic arthritis, juvenile arthritis, ankylosing spondylitis, inflammatory Bowell disease uveitis and more recently hidroadenitis suppurative [33,34,35,36,37]. Patent expiration was expected by the end of 2016 but the manufacturer have applied for extension with seventy additional patents protecting the brand Humira from biosimilar entry until 2022.It was expected a prolonged litigation process which may delay the introducing of future biosimilars in the market.

Amgen performed a randomized, double-blind, active-controlled study (study number 20120262)and evaluated safety, efficacy and immunogenicity of ABP 501 compared to adalimumab in adult patients with moderate-to-severe rheumatoid arthritis who had an inadequate response to methotrexate. The study consisted of a screening period of four weeks and a treatment period of 22 weeks. Patients were randomized to receive either 40 mg ABP 501 subcutaneous injection (SC) every two weeks (n = 264) or 40 mg SC adalimumab every two weeks (n = 262) until week 22. The study completed at week 24, followed by a safety follow-up period through to week 26.FDA approved Amgen biosimilar based on the review of evidence that included analytical animal study pharmacokinetics and clinical effectiveness that demonstrates that Amgen commercial name Amjevita is a biosimilar from Abbvie adalimumab brand however it was not characterized as interchangeable [32,33,34] Patent expiration was expected by the end of 2016 but the manufacturer have applied for extension with seventy additional patents protecting the brand Humira from biosimilar entry until 2022 [32]. However, Amgen in Ocotber 2017 announced that it has reached a global settlement with Abbvie to resolve all pending litigation regarding the launching of AMJEVITA/AMGEVITA their biosimilar of Humira. It is expected to be on the market in Europe by the end of 2018 and in the USA by the year 2023 [38,39].

www.amgenbiosimilars.com < http://www.amgenbiosimilars.com > < http://www.amgenbiosimilars.com/ < http://www.amgenbiosimilars.com/

Copycats versions of adalimumab were or are being developed by five different companies,Amgen,Sandoz, Pfizer, Boehringer Ingellheim and Coherus Biosciences and are expecting to finish recruiting or submitted for licensing by 2018 [40–47]. Coherus BioSciences, Inc. reported topline results from an ongoing Phase 3 clinical study of CHS-1420, an adalimumab (Humira®) biosimilar candidate. This study met its primary endpoint demonstrating similarity between CHS-1420 and Humira with respect to percentage of subjects achieving 75% improvement in psoriasis area and severity index (PASI-75) at Week 12. The 95% confidence intervals for the difference between treatment groups fell well within the prespecified margin. Both CHS-1420 and Humira were similarly well tolerated with similar safety profiles in this study. Submission for approval has not been reported by the company. [40]

Boehringer Ingelheim today announced top-line results from the pivotal Phase III clinical study of BI 695501, a biosimilar candidate to U.S.-licensed Humira® and EU approved Humira® (adalimumab)*. BI 695501 met the clinical study primary efficacy endpoint to establish equivalence with Humira® in patients with active rheumatoid arthritis (RA). The secondary endpoints for efficacy, safety and immunogenicity of BI 695501 vs. Humira®, were also met. The study included 645 patients diagnosed with moderate to severe rheumatoid arthritis. [36] The European agency EMA and the FDA accepted the licensing of Boehringer biosimilar with a commercial name Cytelzo.

The Marketing Authorization Application (MAA) for SB5, an adalimumab biosimilar candidate referencing Humira®1, has been accepted for review by the European Medicines Agency (EMA).In their phase 1189 patients were randomized to receive 40 mg of SB5, Adalimumab from Europe and USA Adalimumab in a three arm study. SB5 is the third biosimilar candidate to that was submitted to the EMA by Samsung Bioepis, the joint venture between Samsung BioLogics and Biogen, previously the European Commission approved BENEPALI® (etanercept), a biosimilar referencing Enbrel®2, and FLIXABI® (infliximab), a biosimilar referencing Remicade.It is already on the market in South Korea and in countries such as Turkey with the brand name Imraldi. [37,38]. Although in the USA this biosimilar will not be available until 2023 Biogen and Samsung Bioepis have agreed a licensing deal with the owner of the innovator molecule Abbvie in Europe on a country by country basis to end the patent dispute.

Pfizer is developing a biosimilar of adalimumab, designated PF 06410293, a comparability trial finished recruitment.Pfizer completes a phase I comparative pharmacokinetics trial in healthy subjects in USA (https://clinicaltrials.gov/ct2/show/NCT02237729).

Pfizer also reported that in July 2015, it began evaluating patients in a multinational phase III clinical trial of PF-06410293, a potential biosimilar to Humira (adalimumab). The phase III clinical trial evaluated the efficacy, safety and immunogenicity of PF-06410293 plus methotrexate and adalimumab sourced from the EU plus methotrexate in subjects with moderately to severely active rheumatoid arthritis who have had an inadequate response to methotrexate monotherapy Pfizer reported in Eular 2018 the results of their trial., it began dosing patients in a multinational phase III clinical trial of PF-06410293, a potential biosimilar to Humira (adalimumab) with 597 patients stratified to receive the innovator or the biosimilar. The phase III clinical trial evaluated the efficacy, safety and immunogenicity of PF-06410293 plus methotrexate and adalimumab sourced from the EU plus methotrexate in subjects with moderately to severely active rheumatoid arthritis that have had an inadequate response to methotrexate monotherapy. The results were of similar by the week 26 and now patients were bindly randomized to continue Adalimumab of a European source or transition to PF-06410293 [39].

Sandoz a Novartis division evaluated GP2017 a biosimilar of the reference Adalimumab in adult patients with moderate to severe plaque psoriasis, in a 51 week double blind phase 3 study ran studies assigning patients to G02017(231 patients) or ref-ADMB 80 mg subcutaneously at week 0 then 40 mg biweekly until week 17 [40].

Zydus Biovation a division of Cadila Health Care Ltd. has developed a biosimilar of TNF-alpha blocker, adalimumab which is a fully human monoclonal immunoglobulin G1(IgG1) by produced by recombinant techniques from Chinese hamster ovary(CHO) cells with 1330 amino acids with a molecular weight of 148 kDa. Extensive analytical

Table 3
Adalimumab bisosimilars.

Truly Adalimumab biosimilars to be relased 2018–2019
ABP 501 (Amgen)
CT-P17 (Celltrion)
CHS-1420 (Coherus)
MSB 11022 (Merck)
M923(Momenta)
PF-06410293 (Pfizer)
SB5 (Samsung-Bioepis)
GP 2017 (Sandoz)
FKB327 (Fujifilm Kyowa Kirin Biologicals)
ONS 3010 (Oncobiologics)

physicochemical and biological comparability appears to point to be highly similar to the reference adalimumab. The study was performed in India and the sample size was rather small 59 patients on the innovator and 60 on the drug to be tested. After 12 weeks that patients treated every other week with adalimumab reference and the proposed biosimilar had statistically response rates with mean changes of DAS 28 of 2.1 with both preparations of adalimumab well tolerated by the patients included in the study. There were no references on the estimated equivalence margin proposed for the study although the results fall within the equivalence margin accepted by other studies. Immunogenicity evaluation for the short period of the study was reported to be similar with both compounds with anti-drug antibodies in two patients on the biosimilar and in one patient with adalimumab. The overall results of this short study suggests that reference Adalimumab (Humira) and the proposed biosimilar(Exemptia) have high degree of biosimilarity. It is not expected that such short trials with small number of patients will be accepted for review by more stringent agencies [41]. In India also on the mid part of 2018 the India based generics company Hetero launched its similar biologic of adalimumab Mabura but no data is available on their comparability trials, so no comments on their standards of quality safety and efficacy [47].

Momenta PharmacEuticals announced a positive phase 3 results for a proposed biosimilar of Adalimumab M923 in patients with moderate to severe chronic plaque psoriasis. The proportion of subjects that achieved PASI 75 following 16 weeks of treatment were equivalent between M923 and Adalimumab. Patients that extended to 48weks of treatment alternated M923 and the reference adalimumab.It is expected that Momenta Adalimumab will be marketed under an agreement with Baxter International although development strategy also exists between Momenta and the giant generic Mylan… [48].Merck biosimilars a division of the Merck group have published pharmacokinetics and immunogenicity of MSB 11022 a biosimilar of adalimumab but their phase III results are not available [49,50,51].Finally, EMA accepted application for adalimumab biosimilar from Fujifilm Kyowa Kirin Biologics a japanese based biosimilar developer. The reported pharmacokinetics of this compound was similar with Adalimumab from Europe and USA.Efficacy results were not available until the writing of the manuscript [52]. The same comments apply to a adalimumab biosimilar being developed by Oncobiologics a biotech company from Cranbury New Jersey [53].(Table 3).

5. Infliximab

Biosimilar of Infliximab was the first to be licensed and marketed in Europe and are still being developed. The South Korean developer Celltrion launched with the two trade names Inflectra and Remsima [54–56]. Amgen ABP 710 and PF -064381779 have finished development but with Hospira acquisition is not expected that Pfizer infliximab would be pursued intensively by the company The pharmacokinetics and safety attributes of Pfizer infliximab have been confirmed in successive publications. Novartis group Sandoz acquired the rights to Pfizer Infliximab that will be extended to the 28 countries that form the European market. Sandoz intends to complete the phase III program and submit to EMA.

Table 4
Infliximab biosimilars.

Truly Infliximab biosimilars to be released −2018-2019
PF -064381779(Pfizer-Sandoz)
ABP 710 (Amgen)
BOWO15 (Epirus)
STI-002 (Sorrento Therapeutics)
BCD-055 (Biocad)

Infliximab BOW015 was investigated in a comparative safety/efficacy equivalence study in patients with RA (n = 189). BOW15 global phase III trial was expected to be finished in 2017 but the parent company Epirus has ceased operations and no information is available of stage of the development. Infimab is being pursued in India by Ranbaxy Laboratories. [41] Samsung Celltrion Remsima/Inflectra and Samsung Flixabi are already available in the market approved in both major markets EMA and FDA. SB2 (Flixabi ®; Samsung Bioepis) SB2 has been studied in a comparative safety/efficacy study to demonstrate equivalence of efficacy, safety, immunogenicity, and pharmacokinetic outcomes versus infliximab in patients with moderate to severe RA (n = 584) A positive phase III from Sorrento Therapeutics Infliximab was reported but no information on licensing is available [57–60] (Table 4).

6. Conclusions

The continuing rise in health care costs created the opportunity that cheaper biologics knowns as biosimilars may replace the more expensive ones creating wider access and benefit for patients with autoimmune diseases. Regulatory requirements limits the widespread use of not so well evaluated biocopies in Europe USA and in some countries in Asia and Latin America. The effect of health care costs is not yet clear but there is estimation that in the next decade savings could reach 50 billions US dollars. Also in the next five years second generation biosimilars are expected to reach the market as newers anti cytokine therapies are being sought. [61–65] In addition new data presented at the Annual European Congress of Rheumatology(EULA2018) show data on SC CT-P13 a subcutaneous formulation of the biosimilar CT-P13 with acceptable efficacy, however, the innovator did not have this presentation which makes the new formulation not a real biosimilar but an alternative formulation of the original biosimilar. Similar results were also presented for SC CT-P13 in patients with inflammatory bowel disease. After almost a decade of experience in trials and practice the decision to prescribe a biosimilar still raise concerns in regard to immunogenicity switching and how the decision to switch is performed and in this article we are able to show the increased number of biosimilars that are expected to be available for the clinician specialized in treating patients with autoimmune diseases [65].

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