Chapter

Rheumatic Diseases and Biosimilars: Evidence about Switch from Originators to Biosimilars in the Real Life

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Abstract

Biosimilars are broadly available for the treatment of several diseases including inflammatory arthritis. Thanks to biosimilars it has been possible to treat a greater number of rheumatic patients who previously were undertreated due to the high cost of originators, in several countries. There are a lot of data from double blind, randomized, controlled clinical trials, especially on TNF inhibitors (TNFi), concerning the maintenance of clinical efficacy after switching from originators to biosimilars; therefore, such a transition is increasingly encouraged both in the US and Europe mainly for economic reasons. However, despite the considerable saving, such shifts to biosimilar drugs are still being debated, principally over their ethical implications. Since the drugs are similar but not identical, the main issues are related to the possibility to compare the adverse events and/or the lack of efficacy and, to date, the variability in effectiveness for a single patient remains an unpredictable datum before effecting the switch. Despite encouraging data about the maintenance of efficacy and safety after the switch, there are many reports of discontinuation due both lack of efficacy or and adverse events. In this chapter we aim at showing the disease activity trend and the safety after the transition to TNF-i biosimilars in patients with rheumatic diseases in real life..

Keywords: Infliximab, Etanercept, Adalimumab, real-life, originator, biosimilar, switch

1. Introduction

As previously stated, a biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing approved reference product (RF). Before they are approved, biosimilars are requested to undergo a precise development process in order to establish biosimilarity when compared to their originator. The European Medicines Agency's (EMA) Scientific Committees evaluate biosimilars according to the same standards that apply to all biological medicines; in fact, every new biosimilar is required to produce studies that show to what extent it is similar to the RF originator and that there are no clinically

meaningful differences between them in terms of safety, quality and efficacy. This element allows avoiding the repetition of clinical trials already carried out with the originator in the first place; in fact, rule no. EMA/CHMP/BWP/3354/1999 clearly states that "(...) biologic drugs are required to undergo proper studies for each registration and disease of pertinence" [1]. In order to get the approval, each biosimilar must give a coherent justification as to why the indication in question makes use of extrapolation instead of carrying out a comparative study in each case [2]; in this context, the extrapolation allows the indication of a biosimilar to be transferred to another indication where only the originator was tested without performing additional clinical studies with the biosimilar in the other indication due to their aforementioned similarity which is given by the definition itself. However, there are concerns that these differences may impact on efficacy or safety in certain indications, which extrapolations cannot establish properly.

Nevertheless, given the efforts inferred by the development and the analysis of the studies requested to approve the originators, biosimilars can only be authorized once the period of data exclusivity on the 'reference' biological medicine has expired; in general, this timelasts for at least eight years from the marketing authorization [3].

Despite the approval given by the European League Against Rheumatism (EULAR) to insert the possibility to use biosimilars in the guide lines, it is quite manifest that, to date, both a certain struggle and a severe mistrust in the usage of such biosimilars are still very present among clinicians and patients [4]. These problems origin from various concerns; one of the main complications in the usage of biosimilars comes from double-blind randomized controlled trials (RCTs) concerning the maintenance of clinical efficacy after switching from originators. To date, many studies have been showing conflicting results on the topic, which has led physicians to mistrust the clinical effectiveness of the switch for patients in therapy with originators [5]. Contrariwise, more and more studies and societies are gathering data confirming that comparable efficacy and tolerability were observed in patients who switched since data support the long-term efficacy of biosimilars in patients with rheumatic diseases [6]. In fact, in the majority of studies, efficacy endpoints were maintained in the switch group as well as the number of patients with remission as per ACR/EULAR criteria.

One of the most important studies, NOR-SWITCH, was published in 2017 on Lancet; its main purposes were to evaluate the switch from originator infliximab (IFX) to biosimilar CT-P13 and to compare its effectiveness with the maintained treatment with IFX. In order to achieve this goal, a 52-week, randomized, double-blind, non-inferiority trial was performed gathering data from 40 Norwegian study centres. Only patients on stable treatment with the originator for at least 6 months before randomization were included. Two hundred and fourty one out of 481 patients were on continued treatment and 240 were switched from the originator to CT-P13. The frequency of adverse events was similar between groups, and switching was not shown to affect clinical endpoints. The results of this study strongly revealed that switching from the originator to the biosimilar TNF-i does not result in worse outcomes than continued therapy with the originator with the assumed non-inferiority margin of 15%. Similar results were obtained from other important studies in patients with Rheumatoid Arthritis such as PLANETRA (71.8% and 71.8%, respectively, for ACR20, 48% and 51.4%, respectively, for ACR50, and 24.3% and 26.1%, respectively, for ACR70) as well as from registries like DANBIO; these two elements predominantly focused on IFX.

Another valuable aspect has to be considered whilst discussing the shift to biosimilars: Health technology assessment (or HTA). The rationale for a biosimilar is to promote competition among manufacturers to lower prices and potentially increase access to affordable therapies.

A Canadian study concerning biosimilars and their impact on health-related budget showed that in a two-year period of time, approximately one billion dollars in savings could have been realized through exclusive purchasing of biosimilar drugs for IFX, filgrastim, and insulin glargine as opposed to the originator products [7]. However, to date, in the US this phenomenon is not as frequent as it appears to be in Europe since a report compiled in 2018 indicated that only 3% of biologic spending (which is equivalent to US$3.2 billion)is subject to competition from biosimilar products [8].

Nonetheless, despite the considerable saving, such shifts to biosimilar drugs are still being debated, principally over their ethical implications. Since the drugs are similar but not identical, the main issues are related to the possibility to compare the adverse events and/or the lack of efficacy and, to date, the variability in effectiveness for a single patient remains an unpredictable datum before effecting the switch. Despite data about the maintenance of efficacy and safety after the switch, there are many reports of discontinuation in real life data due both lack of efficacy or adverse events.

The European Medicines Agency (EMA) was the first regulatory body to develop a specific regulatory pathway for the approval of biosimilars when it published 'Guidelines on similar biological medicinal products' in 2005 [9]. Since then, many biosimilar agents have been approved by regulatory agencies in Europe and North America. The first biosimilars were the somatropin analogs, introduced in Europe. Erythropoietin biosimilars followed in 2007.

The TNF-i biosimilars approved in Rheumatology are biosimilars of 3 molecules, IFX, ETA and Adalimumab (ADA).

2. Immunogenicity

Immunogenicity is by definition the property of a substance to induce an immune response usually mediated by the adaptive immune system [10]. When applied to the pharmacological field, immunogenicity may represent both a desired (e.g., with the use of vaccines) or undesired (e.g., during a treatment with biological agents) event. Big molecules, like monoclonal antibodies (moAbs) or their derivates are high inductors of immunogenicity. Besides the size, many other factors can influence drugs' immunogenicity, including variables related to the recipient (demographic characteristics, genetics, underlying disease, concomitant immunosuppressive drugs) or to the drug itself (impurities, posttranslational modifications, doses, route and intervals between two consecutive administrations) [11]. In modern times, manufacturing techniques for the production of moAbs have evolved in order to restrain the degree of unwanted immunogenicity. One example is the process of humanization of moAbs, aiming at the replacement of primitive mouse domains with human ones [12].

The class of TNF-i agents used for rheumatic diseases includes antibodies with different molecular structures. Three of them (IFX, ADA and golimumab) are full-length moAbs belonging to the human isotype class IgG1. IFX is a chimerical antibody, retaining 25% of the original murine structure, while ADA and golimumab are fully human moAbs. Etanercept (ETA) is a fusion protein consisting of two identical tumor necrosis factor receptor-2 (TNFR2) regions linked to the fragment crystallizable (Fc) of a human IgG1. Finally, certolizumab-pegol is a monovalent Fab fragment of a humanized anti-TNFα antibody conjugated to two molecules of polyethylene glycol (PEG) [13]. Though each of them works by neutralizing the pro-inflammatory cytokine TNF-α, differences in their molecular structures likely account for separate mechanisms of action and immunogenicity rates. Chimerical and human full-length moAbs are able to bind either soluble or transmembrane

TNF-α in a more efficient way than other TNF-i, eliciting complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC) and reverse signaling effects, including apoptosis, in transmembran TNFα-bearing cells [14]. In addition, TNF-i agents having the Fc can mediate other biological effects in FcγR-bearing cells like monocyte–macrophages, which may result either in the potentiation of immunetolerance or in the release of pro-inflammatory cytokines. This dual effect likely depends on the interaction of the drugs with different types of FcR, which may intracellularly transduce an inhibitory or activating signal.

This premise on the molecular characteristics and mechanisms of action of the licensed TNF-i is essential for clarifying many aspects related to the immunogenicity of these drugs. Immunogenicity rates, in terms of anti-drug antibody (ADAb) formation, are in fact highly variable among patients undergoing TNF-i therapy [15]. Studies reported higher ADAb titers in rheumatoid arthritis (RA) patients treated with ADA and IFX and lower ADAb titers in patients treated with ETA, certolizumab pegol and golimumab [16]. The production of ADAbs in IFX-treated patients may be attributed to the chimerical structure of the drug. Similarly, ADAbs synthesized in ADA-treated individuals may recognize murine epitopes located in the complementarity-determining regions of ADA combinatory sites [17]. Moreover, full-length moAbs, like IFX and ADA, may be captured by dendritic cells by means of a Fc-dependent phagocytosis and antigenic fragments of the drugs may be presented to T helper (Th)2 lymphocytes, with the following stimulation of a humoral immune response leading to ADAb production [12]. The latter mechanism could be particularly pronounced in rheumatic patients having a constitutional hyper-activation of the B cell compartment, like those suffering from RA.

Serum ADAbs can be measured by means of several assays that display some sensitivity and specificity limits. They include the enzyme-linked immunosorbent assay (ELISA) and the electrochemiluminescence (ECL) assay, both based on bridging formats, the radioimmunoassay (RIA) and other antigen-binding tests (ABT) [15]. ELISA and ECL may underestimate the presence of monovalent ADAs, like those having an IgG4 isotype, while ABT seem to have higher sensitivity.

ADAb titers can widely vary according to sampling time and antibodies may belong to distinct isotype classes, have different affinity for the ligand or a variable degree of ligand neutralization [15]. ADAb belonging to the IgM, IgG, IgA and IgE isotypes have been reported in patients undergoing TNFi treatments [18, 19]. These antibodies can already be detected in the serum of IFX-treated patients between the second and the third infusion, whereas they may appear after 6 months of treatment in patients assuming ETA or ADA. Crucial is also the identification of neutralizing and non-neutralizing antibodies. The first may have a noteworthy impact on the efficacy of TNF-i treatment, whilst the second can play a major role in immunogenicity and immunogenicity-related adverse events, such as anaphylaxis, infusion reactions or cross-reactivity phenomena to endogenous proteins [11].

Recently, the introduction of drug-tolerant assays has allowed the possibility to detect immunocomplexes of ADAbs bound to TNF-i drugs, providing very relevant information in selected cases. The formation of immunocomplexes may in fact be at basis, on the one hand, of the development of a therapeutic non-response due to a higher clearance of opsonized drug by the reticuloendothelial system, while, on the other hand, it may explain the occurrence of some safety issues, like serum sickness-like reactions [20].

Post-translational modifications can have an additional impact on the biological effects of MoAbs and further influence their immunogenicity. For instance, a reduction in the content of fucose and an increase in the content of galactose and sialic acid of moAbs have shown to potentiate ADCC and CDC, indirectly favoring the clearance of the drug and its phagocytosis by antigen presenting cells (APC) [21].

Finally, immunogenicity may occur as the hyper-activation of immunological axes other than the humoral branch. Our previous studies showed that RA patients experiencing a reduced efficacy or adverse events during the treatment with IFX may have an aberrant expansion of Th1, Th17 and Th9 lymphocytes to the detriment of T regulatory subsets following the in vitro exposure to the drug [22, 23]. However, other authors showed that IFX may also favor the differentiation of IL-10-producing T cells having an immunoregulatory phenotype [24].

Immunogenicity is a matter of crucial importance when it comes to biosimilars. Biosimilars may in fact differ from originators in terms of structural characterization, glycan profile and purity/impurity content, which may altogether contribute to slight changes in the mechanism of action (neutralization of transmembrane of soluble TNFα, CDC or ADCC) compared to the originator counterparts [25, 26]. Despite the homology in the primary amino acid sequence, biosimilars may display substantial differences in the secondary (α-helices and β-strands), ternary (disulfide bonds) and quaternary (subunit arrangement and folding) structure as well as in post-translational modifications (glycosylation, oxidation, deamidation, methylation, acetylation, truncated isoforms) [25]. Intentional or unintentional changes to the original molecular structure may take place as a consequence of different manufacturing techniques, cell lines, culture media, purification, ultrafiltration or diafiltration processes.

Several divergences from reference products (RF) have been reported among the class of TNF-i biosimilars. The biosimilar IFX CT-P13 was shown to differ from its originator in terms of charged isoforms and carbohydrate chains, in turn associated with slight differences in the content rate of C-terminal lysine [27, 28]. Furthermore, it was reported an increased amount of fucosylated glycans in CT-P13 compared to the RF [29]. Fucosylation seems to predominantly occur in the Fc domain of CT-P13 and to significantly impair the binding of FcγIIIa receptors on monocyte–macrophage cells, thus influencing ADCC and, possibly, immunogenicity by preventing the internalization of the drug into APC [30, 23].

Similarly, the biosimilar ETA SB84 also showed slight differences in the amount of acidic variants, afucosylated and neutral galactosylated glycan content and O-glycan occupancy compared to the RF, despite no effects on its biological activity were reported in vitro. Interestingly, a lower particle concentration, aggregate content and product-related impurities were observed in SB4, which may account for reduced immunogenicity rates [31]. In another comparative exercise study, the in vitro characterization of the ETA biosimilar GP2015 did not evidence any significant differences with the originator according to the binding affinities to TNF-α, C1q and FcR [32]. When compared to its originator, the ADA biosimilar SB5 was reported to have a slightly higher content in free sulfhydryl groups and acidic variants that were however judged not clinically meaningful. The latter feature likely depends on lysine C-terminus content and degree of sialyation, although they were not associated with changes in SB5 biological activities [33]. Another study aiming to assess the physicochemical properties of the ADA biosimilar HLX03 reported a slightly lower percentage of high mannosylated glycans in the biosimilar drug, although this did not result in impaired FcγRIII binding and ADCC in human peripheral blood mononuclear cells [34].

In line with these preclinical considerations, results from clinical trials or registry data collection reported similar immunogenicity rates with the use of biosimilar and branded TNF-i so that current guidelines and regulatory agencies recommend the use of biosimilars as an effective and safe alternative to originators [5].

The immunogenicity rates between branded and biosimilar IFX emerged from the two randomized controlled trials (RCTs) PLANETRA and PLANETAS enrolling RA and ankylosing spondylitis (AS) patients and from the NOR-SWITCH and

DANBIO registries collecting the data of 482 patients with inflammatory bowel diseases (IBD), psoriasis (PsO) and psoriatic arthritis (PsA) and 802 patients with RA, spondyloarthritis (SpA) and PsA, respectively, appear similar [35]. Patients who were switched from originator to biosimilar IFX did not experience variations in ADAb serum concentration compared to patients who were not switched.

Similar results were obtained with ADA biosimilars. Pharmacokinetics studies conducted on healthy volunteers showed that the production of ADAbs, measured through ECL, may occur in up to 70% subjects following a single injection of ADA, being associated with a high proportion of neutralizing antibodies [36]. Although higher ADAb activity was associated with lower serum concentrations of ADA, the proportion of patients developing ADAbs was similar among biosimilar and originator treatment arms and ADAbs appeared cross-reacting. These data are in line with those of an ex-vivo study analyzing the sera of RA and IBD patients, which showed the presence of shared immune-dominant epitopes between biosimilar and branded ADA [37]. Taken together, these results may also explain the lack of meaningful differences in ADAb titers in patients switched from originator to biosimilar ADA [38]. Phase III RCTs on the use of biosimilar ADA in patients with autoimmune diseases indicate similar or lower percentages of total and neutralizing ADAbs, being consistent between the experimental and the traditional arm of treatment. ADAb production has been however associated with a faster elimination of ADA and lower changes in disease activity scores from baseline [39–41].

RCTs conducted on RA and PsO patients treated with ETA biosimilar have shown a reduced percentage of ADAb production in the experimental arm with no detection of neutralizing antibodies [42, 43]. Following the switch from reference ETA to its biosimilar no immunogenicity issue was observed in another RCT on RA patients after 24 weeks [44].

Based on these data and in consideration of the pharmacoeconomic advantages derived from the use of biosimilar rather than branded drugs, it would be natural to incentive the use of biosimilars not only as the first prescription but also as part of a switching strategy. Reassuring efficacy and safety data have in fact emerged from RCTs [39–47], which also reported non-significant variations in ADAb titers following the switch.

Nevertheless, lack of efficacy and reduced retention rates have been observed among rheumatic patients switched from originator to biosimilar TNF-i drugs in real-life. Data from registries on ETA- and IFX-treated RA, PsA and axial SpA patients followed-up for up to one year indicate a lower retention rate in switcher patients compared to historic cohorts, which seems mostly dependent on patients' characteristics, including the underlying rheumatic disease and the disease activity at the time of the switch [48–50]. Since immunogenicity studies are usually not carried out as a part of clinical and laboratory routine, it is unfair whether these results might mirror a real immunogenicity issue or rather represent a nocebo effect [51].

3. Biosimilars in real life

3.1 Etanercept

ETA is a fully soluble human dimeric fusion protein, which competes with soluble human TNF- α for binding cell-surfaced TNF receptors, precluding the activation of the inflammatory cascade. It is the only fusion receptor TNF-i available, as it differs from other biologics directed against TNF-α which are monoclonal antibodies. This difference may explain its minimal to none efficacy in granulomatous diseases, including inflammatory bowel diseases. uveitis, and ANCA-related

vasculitis; on the other hand, ETA showed a better retention rate and a lower impact on the reactivation risk of tuberculosis infection [52].

ETA was the first TNFi approved in the United States (US) and Europe.

In1998 and in2000 respectively, ETA was approved by FDA (Food and Drug Administration) and EMA for the treatment of RA; shortly after this authorization, new indications were approved, including polyarticular juvenile idiopathic arthritis (JIA), PsA, AS, PsO and pediatric-PsO.

To date, three biosimilars of the originator ETA (Enbrel®)are available. On January 2016, SB4 (known as Benepali® in Europe) received the authorization from EMA for the same indications of its originator, whist FDA approved its use in the US on April 2019 (Eticovo®). GP2015(Erelzi®)was approved by EMA on June 2017 whileYLB113- (Nepexto®) on May 2020. All of these biologics have demonstrated the bioequivalence with the RF in clinical trials [42, 53–56] for at least one of the approved indications given to the originator and, based on the same mechanism of action, indications have been extrapolated for all approved indications (**Table 1**) [57]. Other biosimilars of ETA, approved neither by EMA nor by FDA, are available in the rest of the world [58].

Due to disputes about these extrapolations and the unrequested need to confirm the safety and efficacy of biosimilars in real life in rheumatic diseases, numerous real-life studies have been published in the last years. The vast majority of real-life data are focused on SB4, while more data derive from registries. One of the first established registries to compare SB4 with reference ETA was the nationwide observational Denmark DANBIO registry that included patients treated with ETA originator (2061) switched to SB4 (1621–79%) affected by RA, AxSpA and PsA (77%, 77% and 86%, respectively). The switched patients had a low disease activity and stable disease during the 3 months before the switch and received DMARDs less frequently than non-switchers. After one year of observation, authors found a lower retention-rate in SB4 population compared with the retention rate of a historic ETA originator cohort. They also found a higher withdrawal rate among non-switchers - 32.9% (145/440) - vs. switchers 18.4% (299/1621); however, disease activity was found to be higher in this group. During the follow-up, among the 299 withdrew switchers to SB4, 120 patients needed to be switched back to the originator due to lack of efficacy. A sub-analysis of this group showed that the main reason SB4 failed was attributable to the patient perception of the disease (PGS - patient global score) rather than CRP or tender/swollen joints. The authors concluded that reasons to withdraw treatment were more frequently related with patients'

Indications	**IFX**	**ETA**	**ADA**
Rheumatoid Arthritis	√	√	√
Juvenile idiopathic arthritis	—	√	√
Psoriatic arthritis	√	√	√
Ankylosing Spondylitis	√	√	√
Crohn's disease	√	—	√
Ulcerative colitis	√	—	√
Plaque psoriasis	√	√	√
Pediatric Crohn's disease	√	—	—
Pediatric ulcerative colitis	√	—	—

Table 1.
TNF-inhibitors approved indications.

factors, such as being in remission or not and with subjective perception rather than objective evidence of poor disease activity control. No major adverse events were observed after the switch [48].

To date, data on SB4 from spontaneous studies are available.

A review published in 2019 focused on real world evidence about SB4, identifying 13,552 patients that used this biosimilar in Europe; among these patients, 11,053 switched from the reference ETA while 768 (6.9%) switched back to the originator. The majority of patients included were affected by RA, PsA and SpA; there were also a small percentage of psoriatic patients without arthritis (2.5%) and a negligible proportion of patient affected by other inflammatory related diseases (Juvenile Arthritis and IBD, 0.1%). Outcomes included the effectiveness of SB4 evaluated with a comparison between pre-switch and post-switch disease activity, retention rates, reasons for discontinuations, the evaluation of back-switchers, acceptance of the switch. In general, the results of this extensive review confirmed the efficacy of SB4 without statistically significant changes in laboratory or clinical parameters of inflammation and disease activity. No meaningful differences in the number of adverse events were observed before and after the switch, confirming its safety. However, a proportion of patients ranging between 3 to and 7.5 % switched back to the RF. Data about small studies showed that disease flares documented by ultrasound, CRP values or clinical examination represent the main reasons to switch. On the other hand, data about from DANBIO registry highlight the subjective factors (such as tender but not swollen joint count with, no differences in CRP serum levels) as the main reason to be switched back to the RF. The percentage of switching back was comparable to the smaller studies (7%). Retention rates of the included studies were at least 75% at 12 months of follow-up. By comparing results of two large registries (Spanish BIO-SPAN [59] and Danish DANBIO [48] authors found that the obligatory nature of the switch was not necessarily related with a higher acceptance rate; Spanish, Danish and Swedish [60] registries shared a higher concomitant use of methotrexate in the switchers. Other variables, such as the duration of usage of the originator and disease activity at the time of the switch were variably related with the degree of acceptance. A proper communication with the patient seemed to improve the acceptance rate of the switch as some authors found out that the older the patient or the longer the disease duration, the less accepted was the switch. Globally, acceptance rates ranged between 51.6% and 99.0%.The RABBIT registry confirmed the data of the registration study reporting lower rates of site reaction in patients treated with SB4 vs. the originator [61]. Differences in treatment practices, lack of clinician confidence with the drug andnocebo effects could have influenced this report [62].

More recently, two independent Italian groups published results from their SB4 switch cohort from originator.

Both studies included patients affected by RA, PsA and AxSpA, treated with ETA originator who switched to ETA SB4.

The former is a single center studyincluding 80 patients in low disease activity. The aim was to evaluate the disease activity trend after the switch, comparing the trend during the 12 months before the switch with the trend at 12 months after switchthrough the analysis of disease activity parameters currently used for each diagnosis. Data analysis did not show significant differences in any of evaluated parameters after the switch from originator to biosimilar. A percentage of 12.6% (11 out of 85 patients) interrupted the treatment with the biosimilar due to lack of efficacy (7/11) or subjective features (2/11) or adverse events (2/11) which have been classified as not serious [63]. No correlation with demographic data, concomitant therapy or disease duration was found.

The second study included 220 patients in stable clinical conditions, from 2 Italian University Hospital, in treatment with originator for at least 6 months; the period of observation was at least 6 months. Among them, 165 patients were observed up to 12 months while 65 patients were observed up to 18 months. Treatment persistence was observed to be 99.1%, 88.6% and 64.6% at 6, 12 and 18 months, respectively. The interruption was due to lack of efficacy in the majority of cases (19 patients), whileit was discontinued due to safety issues in 11 patients. No interactions with other demographic or disease factors were found in this study as well [64].

In the overall data available about back-switching, the main reason was lack of efficacy, strictly followed by adverse events. However, the former was reported to be subjective by many authors.

3.2 Infliximab

IFX is a chimeric human-murine IgG1 monoclonal antibody produced in murine hybridoma cells by using recombinant DNA technology; it is approved for RA, AS, PsA, Crohn Disease (CD), Crohn Disease (CD), Ulcerative Colitis (UC) and PsO [65].

The originator product, Johnson & Johnson and Merck's Remicade (IFX), was approved by the FDA in August 1998 and by the EMA in August 1999 [66].

The patents of reference IFX expired in the US in September 2018 and in Europe in February 2015. Some of the IFX biosimilars are presented in **Table 2**.

The NOR-SWITCH extension trial aimed to assess efficacy, safety and immunogenicity in patients who used IFX CT-P13 throughout the 78-week study period (maintenance group) versus patients who switched to IFX CT-P13 at week 52 (switch group).

Three hundred and eighty patients were recruited (197 in the maintenance group with the RF and 183 in the switch group). In the full analysis set, 127 (33%) had CD, 80 (21%) UC, 67 (18%) SpA, 55 (15%) RA, 20 (5%) PsA and 31 (8%) PsO. The primary outcome was disease worsening during follow-up based on disease-specific evaluation parameters. The NOR-SWITCH extension showed no difference in safety and efficacy between patients who maintained CT-P13 and patients who switched from originator IFX to CT-P13, supporting the assertion that switching from originator IFX to CT-P13 is both safe and effective [69].

Other interesting data come from a French study published in 2018 by Avouac and coworkers [70], in which no change in objective disease activity measures nor in IFX levels were observed in 260 patients with chronic inflammatory diseases who were receiving maintenance therapy with innovator IFX and systematically shifted to biosimilar IFX CT-P13; 31 of them (11.9%) had RA and 131 (50.4%) had axSpA while the others had other inflammatory diseases (IBD above all). The retention rate was observed to be 85% (221 out of 260 patients) at the time of the third biosimilar infusion. From the beginning of the switch to the last visit (mean follow-up of 34 weeks), 59 patients (23%) discontinued biosimilar IFX, mainly due to lack of efficacy (47, 80%). However, no clinical or biological factors were associated with biosimilar discontinuation. No serious adverse events occurred. No change in disease activity parameters or IFX levels was detected. However, a significant increase of BASDAI (2.94 ± 2.20 vs. 3.18 ± 2.21, P ¼ 0.046, before vs. after switch, respectively) was observed in patients with axSpA. Sensitivity analyses for effectiveness included changes of disease activity parameters and IFX levels between baseline and the last visit as well as the occurrence of adverse events leading to drug discontinuation. No changes in IFX levels or objective parameters were observed after the systematic switch to biosimilar IFX in a real clinical practice setting.

Company name	Product name	Stage of development
Amgen, USA	Avsola (ABP 710)	Approved by FDA in December 2019
Biocad, Russia	BCD-055	Non-originator biologicalapproved in Russia in Feb 2018
Celltrion/Hospira (Pfizer), South Korea/USA	Remsima/Inflectra (CT-P13)	Intravenous version approved in EU in September 2013. Subcoutaneous version approved in September 2019. Approved by FDA in April 2016.
	Ixifi (PF-06438179)	Pfizer received FDA approval for Ixifi in December 2017.
EpirusBiopharmaceuticals, USA	Infimab	'Similar biologic' approved in India in September 2014
MabTech/Sorrento Therapeutics, China*/USA	STI-002	Positive phase III trial for copy biological in China reported in January 2016
Mabpharm/Sorrento Therapeutics, China*/USA	CMAB008	Copy biological submitted to China's NMPA for approval in January 2020
Nichi-Iko Pharmaceutical, Japan	NI-071	Phase III trial in rheumatoid arthritis expected to be completed in March 2015. Approved in Japan in September 2017. US phase III trial in rheumatoid arthritis expected to be completed February 2019.
NipponKayaku, Japan	IFX BS	Approved in Japan in November 2014
Ranbaxy Laboratories/Epirus Biopharmaceuticals, India*/USA	BOW015	'Similar biologic' approved in India in December 2014. Global phase III trial expected to be completed in July 2017.
Samsung Bioepis (Biogen/Samsung/ Merck), South Korea/USA	Flixabi (EU)/Renflexis (US) (SB2)	Approved in EU in May 2016. Approved by FDA in April 2017.
Sandoz, Switzerland	Zessly (PF-06438179)	Sandoz acquired EEA rights from Pfizer in February 2016. Approved in May 2018
Shanghai BiomabsPharmaceuticals, China	Baimaibo	Phase III trial in RA in China started March 2018

EC: European Commission; EEA: European Economic Area, this area includes the 28 EU Member States, plus Iceland, Liechtenstein and Norway; EMA: European Medicines Agency; EU: European Union; FDA: US Food and Drug Administration; NMPA: National Medical Products Administration. Adapted by https://www.gabionline.net/Biosimilars/General/Biosimilars-of-IFX [67, 68].

Table 2.
Biosimilars and non-originator biologicals of IFX.

Patient-reported outcomes were the only to be observed; a possible explaination could be, again, the nocebo effect rather than proper pharmacological differences, as demonstrated by the stability of objective measures (i.e. swollen joint count), CRP values and plasma levels of the drug.

Data from registries including DANBIO [49], also support the safety and efficacy of changing from a bio-originator to its biosimilar. The DANBIO registry evaluated 802 patients affected by RA, PsA and axial spondyloarthritis (AxSpA) who switched from originator IFX (IFX, Remicade) to biosimilar IFX CT-P13. The average follow-up was 413 (339–442) days. Disease activities 3 months before and after the switch as well as the changes over time were calculated. 1-year CT-P13 retention rate was similar to the historic IFX cohort (84.1 vs. 86.2) and did not differ

significantly from the bio-originator. Results showed that 132 patients discontinued biosimilar IFX due to lack of effect (71/132 = 54%), followed by adverse events (37/132 = 28%). Authors found that patients with previous IFX treatment with a duration of >5 years had longer CT-P13 retention.

Smaller 'real-world' observational studies also confirmed comparable efficacy and safety of transitioning from originator to biosimilar IFX CT-P13 to that of continuing treatment with biooriginator IFX [71, 72].

In a single centre in Finland, Nikiphorou and colleagues observed similar patient-reported disease activity and symptoms after transitioning to biosimilar IFX CT-P13. Thirty-nine consecutive patients with RA (38%), AS (36%), PsA (18%), juvenile idiopathic arthritis (JIA) (5%), chronic reactive arthritis (3%), were switched to biosimilar after a mean (SD) of 4.1 (2.3) years on IFX. Thirty-one patients were on concomitant methotrexate.

At a median (range) of 11 (7.5–13) months following the first administration of IFX-biosimilar-CT-P13, disease activity and patient reported outcomes (PROs) were similar for IFX-originator and IFX-biosimilar-CT-P13. Eleven patients (28.2%) discontinued biosimilar-CT-P13, due to anti-IFX originator antibodies (n = 3), subjective reasons with no objective deterioration of disease (n = 6) or other causes (latent tuberculosis, n = 1, new-onset neurofibromatosis, n = 1); the clinical effectiveness of IFX biosimilar in both PROs and disease-activity measures was comparable to IFX originator during the first year of switching. Authors did postulate that subjective reasons (negative expectations) may play a role among discontinuations of biosimilars [73].

Similar results were obtained by German and colleagues [74], that aimed to assess the long-term retention rate of CT-P13 after switching from originator IFX, wich appeared to be identical to a historical cohort, confirming the safety, efficacy and acceptability of the switch in the long term (median follow-up of 120 weeks; range 6–145). Among the 39 withdrawals, 25 (64%) patients discontinued CT-P13 during the first period of follow-up. Reasons for stopping CTP-13 belatedly included an objective clinical worsening in 5/14 patients, non-serious safety issues in 6/14 patients (psoriatic lesions, digestive disorders, asthenia and subjective neurological symptoms with negative extensiveinvestigations and stable remission in 3/14 patients). No case of subjective clinical worsening was observed during the second period of the follow-up. The weight of patients' acceptance was also taken into account in a cohort of 89 patients (63 AS, 12 PsA and 14 RA) that agreed to switch from the originator to CTP-13 [75]. After a median follow-up of 33 weeks, 72% of patients were still treated with CT-P13. This rate of maintenance was significantly lower than the one found in the historical control cohorts and prospective study cohorts: 88% and 90% respectively (p = 0.0002). Among patients requesting a return to the originator, 13/25 (52%) showed clinical activity for their disease, one patient presented with serum sickness and 11 (44%) did not exhibit objective activity. An analysis excluding these 11 patients eliminated the difference in retention rate between the 3 cohorts (p = 0.453) suggesting patient reluctance to switch and negative perception of the biosimilar.

After returning to the originator, patients without objective clinical activity all returned to their previous state.

In a cohort of 222 patients treated with originator, 192 agreed to switch to CT-P13 as they were included in a Dutch multicenter prospective cohort study (BIO-SWITCH) [76]. Patients with a clinical diagnosis of either RA, PsA, or AS who agreed (transition group) or did not agree (control group) to transition to CT-P13 were both eligible for inclusion in the study. During 6 months follow-up, 24% of the patients (n = 47) discontinued CT-P13. 37 patients restarted originator, 7 switched to another biologic drug, and 3 continued without a biologic drug.

The DAS28-CRP remained stable from baseline to month 6. The BASDAI slightly increased (difference of +0.5 [95% CI 0.1, 0.9]); CRP, IFX levels and anti-IFX antibody levels did not change. Just before CT-P13 discontinuation, DAS28-CRP components tender joint count and patient's global assessment of disease activity, as well as BASDAI, were increased when compared to baseline. The most frequently reported AEs were arthralgia, fatigue, pruritus, and myalgia. One-fourth of patients discontinued CT-P13 during 6 months of follow-up, mainly due to an increase in the subjective features of the tender joints count and the patient's global assessment of disease activity and/or subjective symptoms, possibly explained by nocebo effects and/or incorrect causal attribution effects.

Boone and colleagues [77], aimed to investigate the role of the nocebo effect in a cohort of 125 patients enrolled in the study (73 CD, 28 UC, 9 RA, 10 PsA and 5 AS). As expected they have shown no statistically significant changes in effectiveness and safety in any of the indications after a median of 4 infusions in 9 months but they hilighted the nocebo response of 12.8% was found among the patients during a minimal observation period of 6 months after the transition to biosimilar IFX without differences between the indications.

For SB2 the real-life data available are fewer and they are related to Inflammatory Bowel diseases and PSO [78]. In the work of Fautrel [78], only Four SAEs were reported: one considered related to SB2 (infected cyst) and three unrelated (two RA disease flares and one overdose of vitamin K antagonists).

There is less evidence regarding the cross-switch from different IFX biosimilars.

Gisondi et al. [79] investigated the effectiveness and safety of cross-switching from CT-P13 to SB2 in 24 patients with PsO and they concluded that it was not associated with a significant change in PASI score or additional adverse events.

Same result were obtained by Bazzani et al. [80]. The Authors retrospectively evaluated the efficacy and safety of the sequential use of 2 biosimilars of IFX in 50 patients already being treated with Remicade® for AS (25 patients), RA (15 patients) and PSA (10 patients) ant they did not found significant alterations in the clinical response. The safety profile was also not modified by this therapeutic model.

3.3 Adalimumab

In 2002 Humira, the originator ADA, became the third TNFi to be approved in the USA after IFX and ETA. ADA has shown excellent efficacy and safety and it is widely used in clinical treatment for RA [81]. It is the best-selling drug worldwide, with global sales worth $18 billion in 2017 alone [82]. It is also one of the most versatile drugs, seeing as it has been approved SpA, PSO, PsA, CD, UC, polyarticular juvenile idiopathic arthritis (JIA), hidradenitis suppurativa (HS) and noninfectious uveitis [83].

Currently, seven ADA biosimilars are approved either in the EU and/or the USA: ABP 501, BI 695501, FKB327, GP2017, MSB11022, PF-06410293 and SB5, all of which have been proven to be similar in terms of safety and efficacy to the licensed RF (RP). ADA is a recombinant, fully human, IgG1 monoclonal antibody that is structurally and functionally indistinguishable from naturally occurring human IgG1. It was engineered through phage display technology and it is produced in a Chinese hamster ovary cell line [84]. ADA is administered by subcutaneous injection and its peak plasma concentration is reached after approximately 131 h. It possesses a widely distribution which includes the synovium. Similar to naturally occurring human IgG, its elimination half-life is roughly 10 to 14 days. ADA specifically binds to TNF-alpha (both soluble and membrane-bound) and blocks the interaction with p55 and p75 cell-surfaced TNF receptors [85]. Despite being a

fully human antibody, up to 30% of RA patients develop ADAb again ADA. ADA can prevent the drug from binding to its target and/or forming immune complexes; such phenomena decrease serum drug levels and increase markers of inflammation in RA patients [86]. Amgen's ABP 501 was the first ADA biosimilar to be approved by FDA in 2016 (Amjevita®) and by EMA in 2017 (as Amgevita/Solymbic®). Boehringer Ingelheim's BI 695501 (Cyltezo®) was approved by the EMA and FDA in 2017. Samsung Bioepis's SB5 (Imraldi®) was approved by the EMA in 2017 and by the FDA in 2019. FKB327 (Hulio®) was approved by the EMA and FDA in 2018 and 2020, respectively while GP2017 (Hyrimoz®/Hefya®/Halimatoz®) was approved by the FDA and EMA in 2018, finally MSB11022 (Hidacio®) was approved by the EMA in 2019. PF-06410293 (Abrilada®, Amsparity®) was approved by the FDA and EMA in 2019 and 2020, respectively.

Unlike biosimilar IFX and ETA [87] there are not many open label extension or pharmacovigilance studies for biosimilar ADA.

Despite a lot of data from registration studies, including single switch, multiple switch and switch-back strategies from RF, proving the safety and efficacy of ADA biosimilars, no data on real life switch from ADA-RF to ADA biosimilars are available.

4. Final considerations

Real-life data confirm both efficacy and safety of biosimilars based on large-scale studies.

In clinical practice, the switch from the RF to a biosimilar must be based on a shared decision between the patient and the prescribing physician. It is worth noticing that if a biosimilar gets the "interchangeability" designation allowed by the FDA, it could be automatically substituted at the pharmacy level without consulting the prescribing physician [88]. This designation can be applied only if the manufacturer is able to provide sufficient evidence that "the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product (biosimilar) and the RF is not greater than the risk of using the RF without such alternation or switch." "To date none of the biosimilars have received such designation. Despite controversies regarding the non-medical switch, biosimilars are becoming substitutes of branded biological agents for their lower cost, for the reassuring data on adverse events and serious adverse events not only from registration studies but from real-life studies. Furthermore, biosimilars have the opportunity to make biologic treatment for rheumatic diseases more widely available.

Regarding immunogenicity there are several possible factors that may confound the results. Firstly, concomitant medications might affect the incidence of ADAbs and nAbs. In the phase III trials of all biosimilars, patients used MTX while being treated with biologics, but the combination of MTX therapeutic protein-drug interactions, which can then reduce the incidence of ADAbs and improve efficacy [89] . Secondly, most of the trials allowed patients to be treated with <2 biologic therapies prior to the start of the trial, which may have a potential impact on the incidence of ADAbs and nAbs. Moreover, the incidence of ADAbs and nAbs increased with the duration of treatment [90]. Based on the real-life analysis all of biosimilars showed comparable efficacy, safety, and immunogenicity to the RP. Subtle differences are considered to be present due to methodological bias rather than the properties of biosimilars.

The results of studies about the switch from RP to biosimilars, confirmed in most real-life reports, have shown that switching from RP to a biosimilar does not have a significant impact on efficacy, safety, and immunogenicity. Most of the data

regarding the switch-back or the withdrawal treatment showed that the nocebo effect plays a not negligible role, even if objective disease flares can occur.

To conclude, biosimilars will offer exciting opportunities in improving treatment access and increasing treatment options worldwide in the next years. They have the potential to cause an unprecedented impact on the utilization of biologic medications and will continue to challenge originator biologic therapies.

Similar to TNFi biosimilars already on the market, real-world data and pharmacovigilance studies are critical to developing long-term evidence to provide assurances on efficacy as well as safety. These biosimilars will offer exciting opportunities in improving treatment access and increasing treatment options worldwide.

Conflict of interest

The authors declare no conflict of interest.

Notes/thanks/other declarations

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