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REVIEW

The biosimilars journey: current status and ongoing challenges

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Abstract

Biosimilar products are already approved and marketed in several countries. The Food and Drug Administration has approved ten different biosimilars, and the European Medicines Agency has approved 40. Even though this scenario has provided important experience with biosimilar products, there are still challenges and unanswered questions. Up to now, a good amount of knowledge has been gathered in order to support the importance of the totality of evidence and the construction of a biosimilarity exercise for regulatory approval. In addition, the extrapolation of indications has been proved viable when a careful analysis is performed. The models for clinical trials and the use of the most sensible populations have been extensively discussed, and there is apparent homogeneity in manufacturer choices for study designs. However, some challenges remain. The lack of regulatory harmony, especially concerning naming, the marketed intended copies, the interchangeability, and the biosimilars in orphan diseases are some of those and are the focus of discussion in this review.

Keywords: biologics, biosimilars, extrapolation of indications, immunogenicity, interchangeability, rare diseases, switching.

Citation

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Background

Biologic drugs are large and complex pharmaceuticals whose structure, physicochemical and biochemical characteristics, and manufacturing process have direct influences on their organic activity.[1] Since the introduction of insulin in the treatment of diabetes, the production and analytical processes behind biologics have undergone extensive improvement, which allowed the development of more complex and specific molecules such as monoclonal antibodies (mAbs).[2] Even though the use of biologics has represented a great advance in the treatment of several diseases, their high cost has had a direct impact on healthcare budgets around the world, and in many countries, they are one of the leading costs related to healthcare expenditure.[3] However, the expiration of the biologics' patents has provided one possible solution for these economic challenges: the production of similar biologic products.[2]

In contrast to small molecules, the production of biologics normally involves live organisms, and due to their complexity, one proposed 'similar biologic' is never identical to its reference product (RP). Even different batches of the RP can present minimal differences through time. These minimal changes could have a direct impact on pharmacokinetics (PK) and pharmacodynamics (PD), as well on efficacy and safety. Therefore, regulatory agencies have defined specific comparability pathways to define whether the RP and the new similar molecule offer sufficient similarity in terms of structure, purity, and pharmacological and clinical characteristics. This process is now known as a biosimilarity exercise.[4] When all the features in this exercise are matched, the approved product can be defined as a biosimilar.[5] When a product claims to have high similarity to a given RP but has not provided sufficient evidence, according to the regulatory pathway for biosimilars, it is called an intended copy. However, the terms 'biomimic' and 'nonregulated biologic' have been used as well.[6]

As a result of this high complexity, biosimilar drugs have a series of unique features, which have been the focus of several debates and discussions.[2] Some of these characteristics, such as the extrapolation of indications, have already gathered a reasonable level of evidence to support them.[7] On the other hand, topics such as interchangeability, naming, and pharmacovigilance are still controversial and have not achieved consensus among the different regulatory agencies.[6,8]

The experience gathered so far and the current challenges are the main topics of this review and will be discussed later.

Biosimilars approval and regulation – where do we stand now?

Some biosimilars are already approved and marketed in several countries. The European Medicines Agency (EMA) has approved 40 biosimilars (Table 1).[9] Some of these approvals actually represent the same molecule, for example, the rituximab biosimilar, CT-P10, which is authorized under four different marketing names, each with a different set of indications.

The same has happened for the rituximab biosimilar, GP2013, which is under two different names, and the infliximab biosimilar, CT-P13 that is also under two different names. Therefore, the number of authorized molecules is smaller. The United States Food and Drug Administration (FDA) has approved and authorized ten biosimilars (Table 1), eight of which are mAbs or fusion proteins, one is a filgrastim biosimilar, and one is an erythropoietin biosimilar.[10] Both the FDA and EMA have updated and abbreviated regulatory pathways for

Table 1. Biosimilars approved by the EMA and FDA.

Marketing name	Common name	Manufacturer/marketing authorization holder	Authorization date
Approved by EMA			
Abasaglar (previously Abasria)	Insulin glargine	Eli Lilly Nederland B.V.	09/09/2014
Abseamed, Epoetin Alfa Hexal, Binocrit	Epoetin alfa	Medice Arzneimittel Pütter GmbH & Co. KG	28/08/2007
Accofil	Filgrastim	Accord Healthcare Ltd	18/09/2014
Amgevita, Solymbic	Adalimumab	Amgen Europe B.V.	22/03/2017
Bemfola	Follitropin alfa	Gedeon Richter Plc.	27/03/2014
Benepali	Etanercept	Samsung Bioepis UK Ltd	14/01/2016
Blitzima, Ritemvia Rituzena (previously Tuxella), Truxima	Rituximab	Celltrion Healthcare Hungary Kft. Celltrion Healthcare Hungary Kft.	13/07/2017 17/02/2017
Cyltezo	Adalimumab	Boehringer Ingelheim International GmbH	10/11/2017
Erelzi	Etanercept	Sandoz GmbH	23/06/2017
Filgrastim Hexal, Zarzio	Filgrastim	Hexal AG	06/02/2009
Flixabi	Infliximab	Samsung Bioepis UK Ltd (SBUK)	26/05/2016
Grastofil	Filgrastim	Apotex Europe BV	18/10/2013
Imraldi	Adalimumab	Samsung Bioepis UK Ltd	24/08/2017
Inflectra Remsima	Infliximab	Pfizer Europe MA EEIG Celltrion Healthcare Hungary Kft.	10/09/2013
Inhixa, Thorinane	Enoxaparin sodium	Techdow Europe AB	15/09/2016
Insulin lispro Sanofi	Insulin lispro	Sanofi-Aventis Groupe	19/07/2017
Lusduna	Insulin glargine	Merck Sharp & Dohme B.V.	04/01/2017
Movymia	Teriparatide	STADA Arzneimittel AG	11/01/2017
Terrosa	Teriparatide	Gedeon Richter Plc.	04/01/2017
Mvasi	Bevacizumab	Amgen Europe B.V.	15/01/2018
Nivestim	Filgrastim	Hospira UK Ltd	08/06/2010
Omnitrope	Somatropin	Sandoz GmbH	12/04/2006
Ontruzant	Trastuzumab	Samsung Bioepis UK Ltd (SBUK)	15/11/2017
Ovaleap	Follitropin alfa	Teva Pharma B.V.	27/09/2013
Ratiograstim	Filgrastim	Ratiopharm GmbH	15/09/2008
Retacrit, Silapo	Epoetin zeta	Hospira UK Ltd	18/12/2007
Rixathon, Riximyo	Rituximab	Celltrion Healthcare Hungary Kft.	15/06/2017
Tevagrastim	Filgrastim	Teva GmbH	15/09/2008
Herzuma	Trastuzumab	Celltrion Healthcare Hungary Kft.	09/02/2018

(Continued)

Table 1. (*Continued*)

Approved by FDA			
	Name with suffix		
Zarxio	Filgrastim-sndz	Sandoz	March 2015
Inflectra	Infliximab-dyyb	Celltrion Inc.	April 2016
Erelzi	Etanercept-szzs	Sandoz	August 2016
Amjevita	Adalimumab-atto	Amgen Inc.	September 2016
Renflexis	Infliximab-abda	Samsung Bioepsis Co., Ltd	May 2017
Cyltezo	Adalimumab-adbm	Boehringer Ingelheim	August 2017
Mvasi	Bevacizumab-awwb	Amgen Inc.	September 2017
Ogivri	Trastuzumab-dkst	Mylan GMBH	December 2017
Ixifi	Infliximab-qbtx	Pfizer Inc.	December 2017
Retacrit	Epoetin alfa-epbx	Hospira Inc.	May 2018

EMA, European Medicines Agency; FDS, Food and Drug Administration.

biosimilars.[11,12] However, many others still have regulatory gaps, which allow for the approval of intended copies. There is still a third scenario, in which intended copies were approved before the improvement or implementation of more specific laws for biosimilars.[13–15] The regulatory agencies have not yet made official requests or announcements, which raises questions about the future of these biologics.[13–15] India, China, Colombia, and Mexico have marketed intended copies of etanercept (ETN), and some Latin American countries and India have approved and marketed an intended copy from rituximab.[16–19] These products have not gone through a complete biosimilarity exercise, known as totality of evidence, and might indicate different efficacy and safety profiles to what has already been verified in some cases.[20] Moreover, the marketing of intended copies could also represent an important challenge for pharmacovigilance.

However, since the approval of the first biosimilar mAb, CT-P13, a great deal of experience has been accumulated, which has helped to answer important questions, especially regarding the importance of preclinical essays, extrapolation of indications, and establishing the clinical trial (CT) models and the most sensitive populations.

Where do we stand regarding the extrapolation of indications?

The extrapolation of indications is an important regulatory advantage with direct impact on costs. It consists of extrapolating the efficacy and safety data from one already studied condition to the other indications of the RP, for which the biosimilar was not directly tested. This implies a cost reduction as a result of transitioning from conducting several phase III trials, as is the norm, to possibly only conducting one trial. The extrapolation of indications was already supported by the World Health Organization (WHO) under the following conditions: (1) A sensitive clinical test model is used to detect potential differences between both products; (2) The mechanisms of action and/or the involved receptor in the studied pathology and the extrapolated one are the same; (3) Safety and immunogenicity of the biosimilar have been sufficiently characterized, and there are no unique/additional safety issues expected for the extrapolated indication; (4) Convincing arguments that the efficacy findings from the CT can be extrapolated to the other indications.[21] Even with these specifications, in some cases the extrapolation can be controversial. That was the case of CT-P13, which was the first mAb biosimilar to receive approval worldwide. At first, the Canadian agency did not approve the extrapolation of indications for inflammatory bowel disease (IBD). The rationale behind this decision was based on differences in the fucosylation profile between CT-P13 and the RP, which was related to a diminished binding capacity with FcγRIIIa. This receptor is related to the antibody-dependent cell-mediated cytotoxicity (ADCC), which is an immune response important in IBD pathophysiology. When analyzed through very sensitive *in vitro* models using isolated natural killer cells from the patients with Crohn's disease, this biosimilar showed a reduced ADCC. However, in less-sensitive models with mononuclear cells from peripheral blood or total blood, this difference was no longer significant. In 2016, the Canadian agency allowed for the extrapolation of the indication for IBD, based on good postmarketing results and additional physicochemical analysis.[22]

The FDA states that, for establishing the extrapolation of indications, the manufacturer must use the most sensitive population in CTs to detect clinically meaningful differences in not only efficacy but also safety and immunogenicity.[12] The most sensitive population is the clinical condition in which the difference of the effect between the RP and the placebo

is highest (the placebo-adjusted efficacy).[23] In the CT-P13 clinical studies, the population used for the phase III trials was composed of rheumatoid arthritis and ankylosing spondylitis patients, even though the most sensitive population in the case of infliximab is psoriasis patients.[23] Nevertheless, the current accumulated safety and efficacy data have shown that the molecule appears to be equally safe and efficient in all the treated indications.[24] In addition, both of the other infliximab biosimilars approved by the FDA, SB2 and PF 06438179, have had RA patients included in their phase III trials. The ETN biosimilar, GP2015, and the adalimumab biosimilar, ABP 501, have presented equivalence trials in psoriasis.[25,26] The bevacizumab biosimilar, ABP 215, which was approved both by the EMA and FDA, has been tested by an equivalence phase III trial with non-small-cell lung cancer patients, who were considered suitably sensitive to allow detection of differences between products.[27] These trials have allowed the extrapolation of indications for other oncological conditions (Table 2) with some differences between the USA and Europe. For trastuzumab, some experts affirm that the total pathologic complete response would occur in early breast cancer with HER2 positivity and would be the most sensitive endpoint and population for equivalence trials.[28] This was the case for the molecule, CT-P6, which was approved by the EMA.[29] MYL-1401O previously was tested in metastatic breast cancer with overall response as an endpoint.[30] It was approved by the FDA and was granted extrapolation for metastatic gastric cancer. This choice of indication and endpoint was discussed with the FDA and EMA and was considered adequate.[31] The SB3 molecule, which has included early breast cancer patients in its study, was used with event-free survival and overall survival as endpoints and also granted extrapolation of indications.[32] In the case of the rituximab biosimilars approved by EMA, CT-P10 and GP2013, the extrapolation of indications for oncological conditions was granted based on follicular lymphoma trials, and the approval for rheumatoid arthritis was granted based on the results of the trials for the specific condition since the pathological mechanisms differ widely. All the approved indications are listed in Table 2.[33–35]

In summary, the extrapolation of indications has been authorized based on the totality of evidence, and so far, the evidence gathered through prospective and retrospective studies indicates good outcomes in terms of safety and efficacy for all indications approved.[36–39]

Where do we stand regarding CTs, and what are the best models for testing and approving biosimilars?

In contrast to originator biologics, the (CTs for biosimilars do not compose the most fundamental step of drug development and come only after extensive physicochemical characterization.[40] However, regulatory agencies still require CTs to approve a biosimilar. For example, the FDA considers the realization of phase I trials in a relevant population fundamental to demonstrating comparability in PK and PD between the RP and the biosimilar.[12] PK and PD are generally more sensitive than clinical efficacy endpoints to assess the similarity of the two products. Phase III trials would be of use to resolve remaining uncertainties involving efficacy and safety. However, in the case of a manufacturer that chooses not to present phase I and III trials, the sponsor should provide a scientific justification if it believes that a comparative phase III clinical study is not necessary. The agency also expects the assessment of comparable immunogenicity in at least one CT, which could be collected from either phase I or III studies.

Generally, to prove comparable efficacy and safety, the FDA expects a clinical study or studies designed to establish statistical evidence that the proposed product is neither inferior to the RP by more than a specified margin nor superior to the RP by more than a (possibly different) specified margin. Typically, an equivalence design with symmetric inferiority and superiority margins would be used. If a product shows efficacy results above the superiority margin, it is considered a biobetter and not a biosimilar. Therefore, in this case the biosimilarity exercise is not fulfilled. In some cases, a noninferiority study design with a single inferiority margin could be used. This would be especially applicable to accessing immunogenicity or safety and provided that lower events would have no influence in efficacy.[40] In most cases, use of an asymmetric interval would generally allow for a smaller sample size than needed with symmetric margins.[41] However, if there is a demonstration of clear superiority, then further consideration should be given to whether the proposed product can be considered a biosimilar to the RP. However, proving noninferiority does not guarantee equivalence. Therefore, this design may not be ideal for biosimilar trials.[12] Until now, all the mAbs or Cepts biosimilars approved by the FDA used in the treatment of inflammatory disorders have presented equivalence studies[25,26,35,42–45] with the exception of the rituximab biosimilar, GP2013, which has been tested in equivalence studies of follicular lymphoma, but only one phase I noninferiority trial for rheumatoid arthritis has been published so far.[33,35] Indications studied in phase III trials and study designs from all FDA and EMA approved mAbs and Cepts are described in Table 2. Considering the reduced number of CTs performed for biosimilars, it is also fundamental that the study population is properly selected. As mentioned earlier, using the most sensitive population may be the most appropriate for these designs.

Ongoing challenges

Lack of consensus in naming systems

A product's name has a direct influence on the physician's ability to prescribe an intended biologic medicine.[46] Moreover, it has a strong impact on the product's pharmacovigilance and traceability, and in the case of biosimilars, on interchangeability.[47]

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Table 2. Biosimilars approved by the EMA and/or FDA, the design of phase III trials, and approved indications.

Molecule	mAb	Approved by	Marketing name	Conditions used in phase III trials	Study design	Indications
CT-P13	Infliximab	FDA EMA	Inflectra Remsima	RA[66] AS[67]	Equivalence[66] Equivalence[67]	Psoriatic arthritis, rheumatoid arthritis, ulcerative colitis, Crohn's disease, psoriasis, ankylosing spondylitis
GP2015	Etanercept	FDA EMA	Erelzi	Psoriasis[26]	Equivalence[26]	Ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, psoriasis, juvenile rheumatoid arthritis
ABP 501	Adalimumab	FDA EMA	Amjevita Amgevita	RA[45] Psoriasis[25]	Equivalence[45] Equivalence[25]	Ankylosing spondylitis, rheumatoid arthritis, ulcerative colitis, psoriatic arthritis, Crohn's disease, psoriasis, juvenile rheumatoid arthritis
SB2	Infliximab	FDA EMA	Renflexis Flixabi	RA[44]	Equivalence[44]	Psoriatic arthritis, rheumatoid arthritis, ulcerative colitis, Crohn's disease, psoriasis, ankylosing spondylitis
BI 695501	Adalimumab	FDA EMA	Cyltezo	RA[68]	Equivalence[68]	Ankylosing spondylitis, uveitis[x], rheumatoid arthritis, hidradenitis suppurativa[x], ulcerative colitis, psoriatic arthritis, Crohn's disease, psoriasis, juvenile rheumatoid arthritis

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Table 2. (*Continued*)

Molecule	mAb	Approved by	Marketing name	Conditions used in phase III trials	Study design	Indications
SB5	Adalimumab	EMA	Imraldi	RA[43]	Equivalence[43]	Ankylosing spondylitis, arthritis, uveitis, rheumatoid arthritis, hidradenitis suppurativa, ulcerative colitis, psoriatic arthritis, Crohn's disease, psoriasis
ABP 215	Bevacizumab	FDA	Mvasi	Advanced NSCLC[69]	Equivalence[69]	Metastatic colon carcinoma, non-small-cell lung carcinoma, glioblastoma, metastatic renal cell carcinoma, cervical cancer
		EMA				Fallopian tube neoplasms, non-small-cell lung carcinoma, renal cell carcinoma, ovarian neoplasms, peritoneal neoplasms, breast neoplasms, cervical cancer, metastatic colon carcinoma
MYL-1401O	Trastuzumab	FDA	Ogivri	Metastatic breast cancer[30]	Equivalence[30]	Breast cancer, metastatic gastric cancer
CT-P6	Trastuzumab	EMA	Herzuma	Nonmetastatic breast cancer[29]	Equivalence[29]	Breast cancer, metastatic gastric cancer
SB3	Trastuzumab	EMA	Ontruzant	Early breast cancer[32]	Equivalence[32]	Breast cancer, metastatic gastric cancer
GP1111	Infliximab	FDA	Ixifi	RA[32]	Equivalence[32]	Ankylosing spondylitis, rheumatoid arthritis, ulcerative colitis, psoriatic arthritis, Crohn's disease, psoriasis

(Continued)

Table 2. (*Continued*)

Molecule	mAb	Approved by	Marketing name	Conditions used in phase III trials	Study design	Indications
CT-P10	Rituximab	EMA	Truxima	Follicular lymphoma[34] Rheumatoid arthritis[70]	Noninferiority[34] Equivalence[70]	Rheumatoid arthritis, chronic B-cell lymphocytic leukemia, non-Hodgkin lymphoma, microscopic polyangiitis, Wegener granulomatosis
			Blitzima			Non-Hodgkin lymphoma, chronic B-cell lymphocytic leukemia
			Ritemvia			Wegener granulomatosis, microscopic polyangiitis, non-Hodgkin lymphoma
			Rituzena (previously Tuxella)			Chronic B-cell lymphocytic leukemia, non-Hodgkin lymphoma, microscopic polyangiitis, Wegener granulomatosis
GP2013	Rituximab	EMA	Rixathon	Follicular lymphoma[35] RA[33]	Equivalence[35] Noninferiority$^{\alpha 33}$	Rheumatoid arthritis, chronic B-cell lymphocytic leukemia, non-Hodgkin lymphoma, microscopic polyangiitis, Wegener granulomatosis
			Riximyo			Rheumatoid arthritis, non-Hodgkin lymphoma, microscopic polyangiitis, Wegener granulomatosis

X: Indications approved only by the EMA.
AR, Rheumatoid arthritis; AS, Ankylosing spondylitis; EMA, European Medicines Agency; FDS, Food and Drug Administration; NSCLC, Non-small cell lung cancer.

Given that a biosimilar is not identical to the RP, it is questionable whether both drugs should be equally named. Both the WHO and the FDA have provided recommendations regarding the subject in recent publications. The WHO proposes the use of a unique identification code, called the biological qualifier (BQ), to differentiate drugs under the same International Nonproprietary Name (INN). The BQ complements the INN with the addition of four random consonants to identify the manufacturer of the active substance that would be applied to all drug substances of biological medicines, including biosimilars, innovator products, nonglycosylated and glycosylated proteins, and impure mixtures and complex biologically extracted products, such as heparin or pancreatin, with the exception of vaccines.[48] The FDA made a similar decision using the suffix strategy.[49] According to their decision, the proposed suffix should be unique; devoid of meaning; composed of four lowercase letters, of which at least three are distinct; nonproprietary; attached to the core name with a hyphen; and free of legal barriers that would restrict its usage. Table 1 shows the already approved biosimilars and their suffixes. However, the EMA uses identical INNs and lists the prescription by brand to distinguish the products and allow pharmacovigilance.[50] In Latin America, naming policies are heterogeneous.[14,51] Despite a trend toward establishing differentiation between RPs and biosimilars through naming, globally, there is still lack of consensus. This lack of harmonization could have direct implications on pharmacovigilance data, monitoring interchangeability, automatic substitution, and even in reimbursement processes.[52,53]

The interchangeability question

Interchangeability is a characteristic between two or more products that indicates switching these products back and forth represents no prejudice in terms of their efficacy or safety when compared to the products alone.[19,54] The interchangeability of biologics is a concern for doctors and patients due to the uncertainty of their impacts on immunogenicity safety and efficacy.[55] To establish the interchangeability of biosimilar drugs, the 2009 United States Biologics Price Competition and Innovation Act requires the following conditions to be met: (a) the biological product is biosimilar to the RP; (b) the clinical results are similar to those obtained for the RP and are expected for any patient; and (c) alternation or exchange between the biosimilar and its RP should not generate risks related to safety or a decrease in efficiency that are higher than those expected from the use of the RP without alternation or exchange of the products. The FDA has recently published a draft requiring clinical data supporting interchangeability.[54] It includes evidence from at least one prospective clinically controlled study with a sufficient lead-in-period of treatment with the RP, followed by a randomized two-arm period (switching versus nonswitching). The switching arm should have a minimum of three switches with each one crossing over to the alternative product.[54]

According to this document, proved interchangeability would also allow automatic substitution. The European guidelines do not provide recommendations on interchangeability, which leaves decisions concerning access to the European national regulatory authorities.[20] Currently, more than 50 studies have evaluated the efficacy, safety, and immunogenicity consequences of switching between the RP and the biosimilar.[56] The majority of these studies concern infliximab biosimilars, and more specifically, CT-P13.[24,56] Apparently, there is no prejudice in clinical features after the single switch is on. However, none of these studies has directly evaluated interchangeability following more suitable models, such as required by the FDA, in which there is the alternation of drugs between groups.[57]

The adalimumab biosimilar, BI 695501, is already registered in a CT under the number NCT03210259, which plans to demonstrate interchangeability with the RP. The primary objective is to assess the PK similarity between patients receiving RP continuously compared with those who alternate between BI 695501 and the RP in patients with moderate-to-severe chronic plaque psoriasis. The study plans to enroll 240 patients and it is currently recruiting.[58] The ETN biosimilar, GP2015, was recently involved in a crossover study. In this recently published study, patients who had achieved at least a 50% improvement in Psoriasis Area Severity Index (PASI 50) from baseline at week 12 were re-randomized to either continue the same treatment on a once weekly dosing schedule or to undergo a sequence of three treatment switches between GP2015 and ETN at six weekly intervals until week 30. Switching treatments did not impact efficacy, safety, or immunogenicity.[59]

Moreover, in some countries, such as the USA and many European countries, there is already more than one approved biosimilar from the same RP. The assessment of efficacy and safety equivalence and the switching data were all obtained from comparison with the RP. Could these data also be extrapolated to the biosimilars when examined among themselves? Could these products be switched?

One recently published paper could add some insights about this matter. This retrospective study evaluated the antidrug antibodies (ADAs) of 34 IBD patients under antitumor necrosis factor treatment. The therapy could be reference infliximab alone, CT-P13 alone, or switching between both. All the analyzed ADA antireference infliximab had cross-reaction with both SB2 and CT-P13. Similarly, the cross-reactivity between ADA anti-CT-P13 with SB2 and reference infliximab was 100%. That means all antibodies cross-reacted with any type of infliximab molecule analyzed. The authors suggest that the slight differences in charged glycans observed between these products would not be sufficient to affect their immunogenicity.[60]

Despite growing evidence, additional data are still needed in order to investigate whether interchangeability is a viable process.

Consensuses regarding use of biosimilars have been published for some patient groups.[61] In general, they recognize biosimilars as an opportunity to increase access to expensive therapies and would accept receiving biosimilar treatment once it was prescribed, respecting a shared decision between the physician and the patient. The rationale involved in participating in CTs for biosimilars is probably also related to the possibility of gathering evidence that would increase access to treatment, rather than individual benefit. According to this consensus, patients have positioned themselves against automatic substitution, once this decision does not follow this shared process. Furthermore, the patients considered nonethical the act of exchanging a product purely for economic reasons, once their condition is adequately controlled and stable with a specific drug.[61] Medical societies in general also agree that the decision to switch products should be based on a shared decision between patient and physician.[13,55,62]

Biosimilars in rare diseases

Orphan drugs are medicines used in the treatment of rare diseases, which are often associated with high treatment costs.[63] These drugs present a series of challenges regarding the development of biosimilars, including (a) the high costs of obtaining the RP for manufacturing purposes; (b) a reduced number of batches in order to determine batch-to-batch variability and to build extensive comparability data; (c) difficulties in obtaining a large enough population size for phase I and III trials; and (d) a heterogeneous population with the condition.[64] There are already some biosimilar orphans in development, ABP 959 and BOW080, which are two eculizumab-intended biosimilars. ABP 959 already has a registered ongoing phase III randomized controlled trial of paroxysmal nocturnal hemoglobinuria to compare the efficacy and safety with the RP and is planned to include 40 subjects.[65] As mentioned earlier, CTs are still required by the regulatory agencies to demonstrate biosimilarity. The FDA states that the nature and scope of the clinical study or studies will depend on the nature and extent of residual uncertainty regarding biosimilarity after conducting structural and functional characterization and, where relevant, animal studies.[12] In theory, these studies could not be presented if there is scientific justification that supports it.[12] Even though the initial and most essential step in demonstrating biosimilarity is the preclinical one, until now, all the biosimilar approvals were based on the totality of evidence including CTs.

Conclusions

In the last several years, the evidence supporting the use of biosimilars has grown significantly. Their approval and marketing in many countries around the globe have provided important clinical experience for physicians, patients, and health systems and the possibility to answer doubts or to reinforce theoretical concepts. In contrast, in some countries, there are still intended copies that are marketed that potentially result in unknown differences in efficacy and safety. Some issues, such as the extrapolation of indications, were reinforced by positive postmarketing data gathered to date. Others, such as interchangeability, remain without practical answers and represent an important challenge. Moreover, residual uncertainty remains regarding orphan biosimilars and the possibility of approval without comparative CTs. The lack of harmony between agencies, especially regarding naming, is still present and represents a possible barrier toward effective pharmacovigilance among countries.

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