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Calleja-Hernández, Miguel Ángel; Martínez-Sesmero, José Manuel; Santiago-Josefat, Belén

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REVIEW
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Biosimilars of monoclonal antibodies in inflammatory diseases and cancer: current situation, challenges, and opportunities

Biosimilares de anticuerpos monoclonales en enfermedades inflamatorias y cáncer: situación actual, retos y oportunidades

Miguel Ángel Calleja-Hernández[1], José Manuel Martínez-Sesmero[2], Belén Santiago-Josefat[3]

[1]Pharmacy department, Hospital Universitario Virgen Macarena, Seville, Spain. [2]Pharmacy department, Hospital Clínico Universitario San Carlos, Madrid, Spain. [3]Amgen S.A., Barcelona, Spain.

Author of correspondence
Miguel Ángel Calleja Hernández
Servicio de Farmacia
Hospital Universitario Virgen Macarena.
Calle Dr. Fedriani, 3
41009 Sevilla, Spain.

Email:
mangel.calleja.sspa@juntadeandalucia.es

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Abstract

The approval pathway for biosimilars of monoclonal antibodies in the European Union is aimed at ruling out the presence of significant differences with the original biological in quality attributes, efficacy, immunogenicity and safety. It also provides the rationale for extrapolating the evidence obtained with a biosimilar in at least one indication to the rest of the approved indications of its original biological, thus simplifying the development programme of biosimilars. Biosimilars of monoclonal antibodies available in the European Union for the treatment of inflammatory diseases and cancer have fulfilled all the requirements for approval, and many of them have additional evidence available. Moreover, real world data confirms the safety and efficacy of these drugs in the indications they are being used for. In Spain, many scientific societies endorse the regulatory pathway of biosimilars and acknowledge their role in the efficiency of the healthcare system. Even so, some barriers remain that limit their use. The implementation of different measures at the patient, prescriber, institutional, and national levels might increase the penetration of biosimilars, freeing up resources that may be invested in other therapies and, potentially, boost innovation.

Resumen

El proceso de aprobación de los biosimilares de anticuerpos monoclonales en la Unión Europea está dirigido a descartar la presencia de diferencias significativas con el biológico original en los atributos de calidad, eficacia, inmunogenicidad y seguridad. Proporciona además la justificación para extrapolar la evidencia obtenida con un biosimilar en al menos una indicación al resto de indicaciones aprobadas para su biológico original, simplificando el programa de desarrollo de los biosimilares. Los biosimilares de anticuerpos monoclonales disponibles en la Unión Europea para el tratamiento de enfermedades inflamatorias y del cáncer han cumplido todos los requerimientos establecidos para la aprobación, y en muchos casos disponen de evidencia adicional. Además, los datos de uso en la vida real están confirmando la seguridad y eficacia de estos fármacos en las distintas patologías en las que se están utilizando. En España, varias sociedades médicas avalan el proceso regulatorio de los biosimilares y reconocen su papel en la eficiencia del sistema sanitario. No obstante, todavía existen algunas barreras que limitan su uso. La aplicación de diferentes medidas a nivel de paciente, prescriptor, institucional y nacional podría aumentar la penetración de los biosimilares, liberando recursos que podrían invertirse en otras terapias y, potencialmente, favorecer la innovación.

KEYWORDS
Biosimilars; Extrapolation; Interchangeability; Efficiency; Nocebo; Inflammatory diseases; Cancer; Spain.

PALABRAS CLAVE
Biosimilares; Extrapolación; Intercambiabilidad; Eficiencia; Nocebo; Enfermedades inflamatorias; Cáncer; España.

Introduction

A biosimilar is a drug that contains a version of the active ingredient from an original biological drug (also called "reference product")[1]. The production process of biological drugs is complex and subject to many variables, as it involves living organisms and often, recombinant DNA technology. As a result, original biologicals themselves show variability between different manufacturing batches and even within the same batch, which has to be maintained within acceptable ranges to avoid an impact on clinical performance. Pharmaceutical companies engaged in developing biosimilars, in addition, do not have access to the manufacturing specifications of the original biologicals, which are proprietary. So, these companies must design their own manufacturing procedures, and improve them until the critical attributes of their biosimilars (those that can affect pharmacokinetics [PK], efficacy, and safety) are within an acceptable variability range[2]. In practice this means that, while a biosimilar can never be an exact copy of the original biological, it must be highly similar in terms of critical attributes. Once this has been achieved, the biosimilar must undergo a specific approval pathway in order to confirm the absence of clinically meaningful differences compared to the original biological.

The present work aims at describing the current status of biosimilar monoclonal antibodies (mAbs) in the European Union (EU) and in Spain. First, we review the regulatory pathway of biosimilar drugs in the EU, with a special emphasis on the particularities of mAbs, due to their complexity. This pathway gives the rationale for extrapolation and switch, two of the most controversial aspects of biosimilars, which are further discussed. Subsequently, we describe the biosimilar mAbs currently available in the EU in two therapeutic areas in which they are extensively used (inflammatory diseases and oncology). We briefly analyse the design of the pivotal trials that have led to their approval, the aspects supporting extrapolation, and the evidence available regarding other relevant aspects (long-term data, switch). Finally, we focus on the current status and future perspectives of biosimilars in Spain, also extensive to biosimilar mAbs, and explain the measures that could favour the use of these drugs, contributing to the efficiency of the health system.

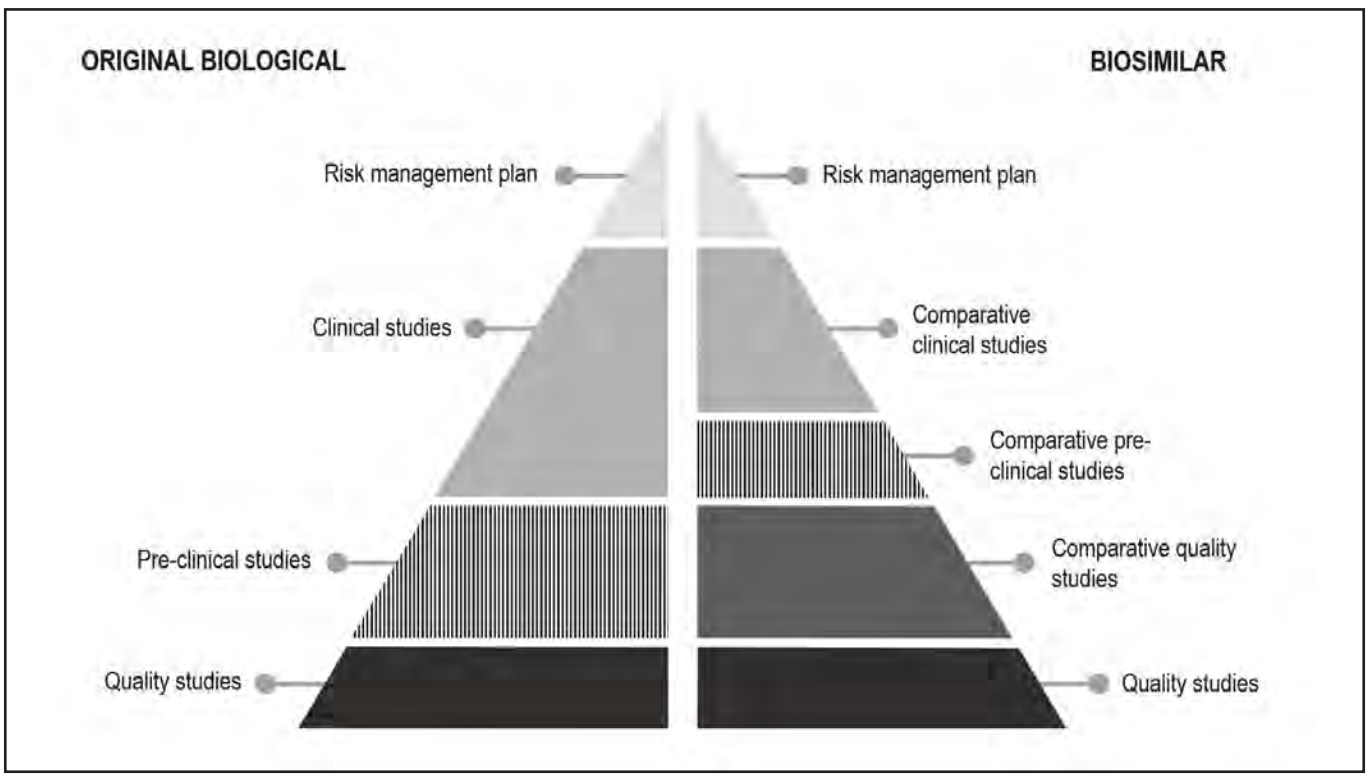
Regulation of biosimilars in the European Union

Biological drugs (including mAbs) must go through a centralised approval process before they can be marketed in the EU. The specific pathway for biosimilars was established in 2004, and its goal is to confirm the absence of clinically meaningful differences compared to the original biological. This is achieved through comparability studies which are carried out in stages, with the results in each phase determining the studies needed in the next[3]. Figure 1 shows the relative weight of each type of evidence in the approval process of biological drugs and their biosimilars.

The first stage consists of quality studies, as they are considered much more sensitive than clinical studies in detecting minor differences that can have an impact on safety, efficacy, or immunogenicity. Quality studies may involve 20 to 40 analytical tests[4], which compare the primary structures, post-translational modifications, variants, higher-order structures, and biological activities of the biosimilar and the original biological. In the case of mAbs, which have multiple functional domains, characterising the biological activity involves not only determining the mechanism of action, but also the function of the antigen-binding (Fab) and crystallisable (Fc) fragments, both separately and bound. Finally, impurities, formulation, potency, and stability are analysed[2].

The next stage involves pre-clinical studies that, in the case of mAbs, should always include *in vitro* pharmacodynamic (PD) studies. These compare the binding of the Fab and Fc fragments of both products (biosimilar and original) to their target molecules, and the functions mediated by this binding. If quality studies have shown relevant differences with respect to the original biological, if the original biological mediates effects that cannot be completely explained by *in vitro* studies (as is the case with several mAbs), or if any other doubts persist, *in vivo* studies (PK, PD, and/or safety) are required before proceeding with clinical trials. *In vivo* studies should be performed in a relevant species (usually primates, due to the specificity of mAbs) and/or model (e.g., transgenic mice, xenograft models). If these are unavailable, the developer of the biosimilar can proceed directly to the clinical phase, provided measures are taken to mitigate the potential risks[5].

Figure 1. *Requirements for approval: differences between original biological and biosimilar drugs.*



Since the original biological has already demonstrated efficacy, safety, and a positive benefit/risk profile, the main objective of the biosimilar's clinical phase is solely to demonstrate comparability with the original biological. The type of studies required will depend on the complexity of the molecule. In general, PK/PD and immunogenicity studies are required for all biosimilars[3]. PD studies should only be performed if there is a valid surrogate marker of efficacy, which is not always the case for mAbs. Clinical PK data, on the other hand, are especially relevant. If the biosimilar demonstrates an exposure similar to that of the original biological, coupled with favourable analytical and functional data, the developer can proceed directly to phase III clinical studies at the same dose approved for the original mAb, without the need for phase II studies[2].

For some biosimilars, if valid clinical markers of PD are available, no further clinical studies are necessary beyond phase I. MAbs, however, are particularly complex molecules. So, at least one phase III study of equivalence in efficacy (and that evaluates safety) is required, no matter how robust the evidence collected in the PK/PD studies is[3]. In these phase III studies, the populations and variables chosen must be sensitive enough to detect differences between the original biological and the biosimilar, if they exist. These variables are not always the most commonly used in the chosen indication/therapeutic area. For example, in the oncology setting, response rate is considered a suitable variable for evaluating the equivalence between a biosimilar and its original biological, if it is sufficiently sensitive to the action of drugs and is not influenced by external factors[5]. The Spanish Society of Medical Oncology's (SEOM's) position statement on biosimilar antibodies is in agreement with this. However, it also points out that the inclusion of traditional efficacy variables in clinical studies carried out with biosimilars, such as progression-free survival or overall survival, would be desirable[6].

The issue of immunogenicity deserves special consideration. All biological products have an intrinsic ability to trigger unwanted immune reactions, and mAbs are no exception. Since they are not replacement therapies, mAbs do not usually elicit the production of neutralizing antibodies against endogenous molecules (as for example may occur with recombinant erythropoietins)[7]. Still, an immune response to the mAb can reduce or eliminate the clinical response, or trigger serious adverse reactions[8]. Therefore, to be approved in the EU, biosimilar mAbs must demonstrate that they do not present significant differences in immunogenicity as compared to their original biologicals.

The first step in determining the immunogenicity of a biosimilar is to characterize by analytical techniques the drug-related factors that are involved in the development of anti-drug antibodies (amino acid sequence, glycosylation, formulation, impurities) and compare them with those of the original biological[3,8,9]. Nevertheless, the development of antibodies also depends on patient-related (e.g., age, immune system status), disease-related (e.g., comorbidities, concomitant treatments), and study treatment-related (e.g., exposure) factors[1,3]. Moreover, in the case of mAbs, it is particularly difficult to predict potential immunological reactions in humans based solely on differences at the product level. Animal studies are not particularly sensitive in this regard, either. Therefore, approval of a biosimilar mAb will always require clinical immunogenicity data, which can be obtained either during PK or efficacy/safety studies, or in stand-alone studies. When choosing the study population, it is important to bear in mind that healthy patients (usually participating in PK studies) may have the greatest sensitivity for detecting differences in immunogenicity due to their stronger, faster-acting immune response[1,3].

Once all the data described above has been obtained, the last step in applying for approval of a biosimilar is the same as in original biologics, namely, to present a risk management plan[3]. This includes a pharmacovigilance plan and risk minimisation measures, and is based on the experience gained with the original biological[3]. As part of the risk management plan, during the first five years after approval, the summary of product characteristics and the package leaflet must include an inverted black triangle, together with a statement asking healthcare professionals and patients to report any adverse reactions that may occur, to indicate that the drug is undergoing particularly intensive monitoring. This black triangle requirement applies to all biologics (not only biosimilars) that have been approved after demonstrating a favourable risk/benefit profile. The aim of this follow-up is to collect information that could not be obtained during development (for example, long-term effects) and to ensure that the safety profile remains favourable[10]. Under European—and by extension Spanish—law, to facilitate traceability, each notification of an adverse reaction involving a biosimilar must include the trade name (unambiguous, as opposed to the active ingredient name) and the batch number[11,12]. However, the introduction of this legislation has not increased the inclusion of trade names in safety reports involving biologics, and batch reporting continues to be very poor (5-21%)[13].

For biologics in general (including biosimilar mAbs) it can be difficult to assess long-term safety purely on the basis of spontaneous reports of adverse reactions, so the European Medicines Agency (EMA) can request the inclusion of patients in registries to promote the comprehensive and consistent capture of safety data[1,3]. They can also request additional post-marketing safety studies. These studies facilitate the detection of rare adverse reactions that are only observed when the drug is used in larger populations and for longer periods than in registry studies[3].

In summary, the safety of biosimilar mAbs is monitored more thoroughly than that of most chemical synthesis drugs (given their complexity), but there are no special pharmacovigilance requirements for biosimilars aside from those applied to the original biologics. The evidence acquired since 2006 supports the strategy of the EMA: so far, no relevant safety differences have been detected between approved biosimilars and their original biologics, and no biosimilars have been withdrawn for safety reasons[3].

Extrapolation

Once the biosimilar has shown similarity with the original biological in terms of quality, pre-clinical data, and PK/PD, and has demonstrated an equivalent efficacy and similar safety in at least one of its approved indications, the EMA allows to extend the totality of evidence of the biosimilar to the other indications approved for the original biological, on the basis of the experience gained with the product. This avoids unnecessary repetitions of phase III clinical trials, with their inherent ethical and economic implications. The only aspect that cannot be extrapolated directly is immunogenicity which, as already mentioned, is influenced by factors not related to the product[1,3].

Under EMA regulations, the following conditions must be met in order to allow extrapolation: (a) The mechanism of action should be mediated by the same target molecule in both indications; (b) The biosimilar must have demonstrated equivalence with the original biological in comparative studies conducted in a sufficiently sensitive population to detect differences between the two, if any; (c) If the indications fall within different therapeutic areas, and the mechanism of action, posology and/or PK of the biosimilar differ from those of the original biological, additional studies may be necessary; (d) The biosimilar must have demonstrated a safety profile comparable to that of the original biological in the evaluated indication; and (e) The biosimilar should undergo additional immunogenicity studies[1,3]. This strategy is supported by the safety and efficacy data obtained since the first biosimilar was approved in the EU in 2006[3].

It is important to remember that extrapolation is not an entirely new concept; it is similar to the comparability exercise that is routinely applied to original biologics when major changes are made in their manufacturing process. In these cases, the EMA also relies on quality and *in vitro* pre-clinical studies to apply the evidence obtained with the pre-change biological to the biological obtained using the new process, and does not require repeated clinical trials for each approved indication[3].

Interchangeability, substitution, and switch

Biosimilars approved for a given indication are expected to have the same clinical effect as the original biological. So, it is possible to exchange the original biological for its biosimilar (or vice versa), or one biosimilar for another, through switching (prescriber) or substitution (pharmacist). The EMA does not provide recommendations on interchangeability with the original biological: although it advises involving prescribers in the final decision, the joint position of the EMA and the European Commission (EC) is that member states must decide whether biologics and their respective biosimilars can be interchangeable[3].

Under European law, switch studies are not mandatory for biosimilars. However, all biosimilar mAbs targeting inflammatory diseases[14-17] and one

used to treat cancer[17] have included single or, less frequently, multiple switches in their phase III clinical trials. A systematic review of the literature up to June 2017, that also considered post-authorization studies, identified 50 studies in the area of inflammation with switches from original mAbs to biosimilars. The authors concluded that in the vast majority of these studies, no differences were reported in terms of efficacy, safety, and immunogenicity after the switch. It should be noted that nearly all of the studies identified in this review involved a single switch from the original biological to a biosimilar. Also, the authors could not identify any study reporting a switch between biosimilars of a given original biological[18]. A second systematic review of pre- and post-authorization studies up to November 2017, only identified two switch studies in cancer indications, which according to the authors was probably due to technical and ethical difficulties[19]. It has to be noted that, unlike inflammatory diseases, the acute nature of many cancer indications involve a short-term use of therapeutic mAbs which hinders switch assessments. The number of switch studies in these less frequently explored scenarios (oncology, multiple switch) is likely to increase in parallel with the growing availability of biosimilar mAbs. However, the increase in treatment options will also make it difficult to cover all the situations that prescribers will face in clinical practice. In this regard, post-marketing monitoring, patient records and databases, and real world evidence studies can provide valuable additional information on different switch patterns and their outcomes. This, together with the strict requirements established by the EMA for the approval of biosimilar mAbs, will build on the evidence obtained in clinical studies on the safety of interchanging drugs with the same biological active ingredient[20].

Biosimilars monoclonal antibodies currently available in the European Union

We retrieved the list of biosimilars approved in the EU (up to February 2019) from the EMA webpage (https://www.ema.europa.eu/en/medicines), by combining the filters "categories=human", "medicine=European public assessment reports (EPAR)", "authorisation status = authorised" and "medicine type=biosimilar". Approval status was double-checked with the Union Register of Medicinal Products (https://ec.europa.eu/health/documents/community-register/html/index_en.htm). We later conducted a manual review to limit the results to mAbs indicated in the therapeutic areas of interest. To complete the information provided by the EMA EPARs, we conducted a search in PubMed and the main inflammation/oncology meetings, to find relevant data published post-authorization.

Inflammatory diseases

The nine biosimilars of mAbs approved in the EU for the treatment of inflammatory diseases (including rheumatology, dermatology and gastroenterology) focus on three molecules: adalimumab, infliximab, and rituximab. Although they are not antibodies, as their structure only includes a portion of antibody (human IgG constant region), the two biosimilars approved for etanercept, a TNF-alpha inhibitor, have been also included due to their complexity[15,16]. Table 1 shows relevant data on these biosimilars.

All of the rituximab and infliximab biosimilars, and half of the adalimumab (FKB-327, SB5) and etanercept (SB4) biosimilars have been approved for their use in inflammatory diseases on the basis of a single phase III trial in rheumatoid arthritis, a population sensitive enough to detect differences, although the immunosuppressants that these patients receive could prevent the evaluation of immunogenicity differences[15,17]. To obtain further information, GP2017 and ABP501 (both adalimumab) underwent an additional phase III trial in patients with psoriasis[17]. Meanwhile, GP2015 (etanercept) was first evaluated in patients with psoriasis[16], and the results of an additional phase III trial in rheumatoid arthritis have been published afterwards[21,22]. In several of their biosimilar evaluations, the Committee for Medicinal Products for Human Use (CHMP) has expressed its preference for continuous variables (e.g., change in the Disease Activity Score 28 [DAS28] or the Psoriasis Area and Severity Index [PASI]) over categorical variables (e.g.: *American College of Rheumatology* 20 [ACR20] or PASI75), and for early response measurement (before the response curve reaches its plateau) over delayed ones, considering these to be more sensitive to potential differences. For this reason, most studies have included continuous efficacy variables (either primary or secondary), and have evaluated them at different time points[16,17]. Of the biosimilars considered here, those with longer-term treatment in patients with rheumatoid arthritis are SB4 (etanercept), FKB-327 and ABP501 (both adalimumab) with >90 weeks. The duration of treatment in psoriasis studies was comparable across the different biosimilars (51-52 weeks)[16,17]. As already mentioned, the development programmes of all mAb/etanercept biosimilars approved for inflammatory diseases have evaluated the effects of switch (in psoriasis, ABP501, GP2017 [both adalimumab] and GP2015 [etanercept]), although evidence on multiple switch is only available for GP2017 (adalimumab), and GP2015 (etanercept)[16,17]. In all the studies performed, efficacy, safety, and immunogenicity were reported to be equivalent after single or multiple switches. In the post-marketing period, the vast majority of switch studies have been performed with CT-P13 (infliximab)[18].

Oncology

The EC has approved nine biosimilars of mAbs for oncology indications, including trastuzumab, rituximab, and bevacizumab. Relevant data is shown in Table 2.

CT-P10 and GP2013, biosimilars of rituximab, have been evaluated in patients with advanced follicular lymphoma, this being the most commonly approved indication for rituximab in cancer and sensitive enough to detect potential differences between the biosimilar and the original biological. The primary variable chosen in both cases was the overall response rate (ORR), which is relevant in this indication, according to the CHMP[17].

All phase III studies of trastuzumab biosimilars have been performed in patients with breast cancer, because the mechanism of action described for early and metastatic HER2+ breast cancer, and for metastatic HER2+ gastric cancer, is similar. The population of patients with early HER2+ breast cancer receiving neoadjuvant and adjuvant chemotherapy included in SB3, ABP980, and CT-P6 confirmatory studies is considered more sensitive for evaluating potential differences than the population with metastatic cancer included in the phase III study of MYL-1401O and in the main phase III study of PF-05280014, though the later has also a supportive phase III study in the neoadjuvant setting. The CHMP, however, has validated both approaches. Similarly, the CHMP has endorsed the sensitivity of the main variable chosen for CT-P6 and ABP980 (total pathological complete response [PCR], absence of invasive cancer in both the breast and axillary lymph nodes), but the main variable chosen in the SB3 trial (PCR in the breast alone) has also been consideredd acceptable[17]. The effects of switching have only been evaluated for ABP980[17,19], and data suggest that the switch from the original biological to the biosimilar did not affect efficacy, safety, or immunogenicity.

The pathology chosen for the phase III studies of the bevacizumab biosimilars ABP215 and PF-06439535 (non-small cell lung cancer) was also endorsed by the CHMP as sufficiently sensitive, and the main variable assessed (ORR) is considered the most sensitive to detect potential differences between the original biological and its biosimilars[17].

Current status and future perspectives of biosimilars in Spain

The contribution of biosimilars to the efficiency of the health system has been recognised by several Spanish medical and pharmaceutical societies[6,32-34]. On the one hand, the savings can be directly attributed to the acquisition of biosimilars instead of the original biologics. The abbreviated approval pathway of biosimilars eliminates parts of the registration dossier which are required for original biologicals (e.g. phase II studies, many phase III studies). As a result, launch prices for biosimilars in Spain are on average 30% below that of the original biologicals[35]. On the other hand, biosimilars can lead to indirect savings for the health system, driven by legal requirements and competition. In Spain, specifically, when the first biosimilar of an original biological is marketed (always at a reduced price as compared to the reference product), the price of the original biological must be lowered to, at least, match the price of the biosimilar[36]. This, in theory, blurs the price advantage that would represent an incentive for the use of the biosimilar. However, it must be considered that manufacturers are allowed to offer additional discounts through later negotiations and public tenders. Also, as more biosimilars become marketed for a given original biological, competition increases, pushing prices even lower. A usual way of promoting competition is, again, public tenders, especially those in which procurement contracts are of short duration and/or are granted to several providers at the same time[37].

Table 1. Main characteristics of biosimilars of monoclonal antibodies approved in the European Union in the area of inflammatory diseases up to February 2019

Drug substance	Brand name	Molecule	Marketing authorisation holder in the EU	Year approved in the EU	Development programme				Approved indications										
					Indication/s assessed in phase III	Primary endpoint	Maximum treatment duration (weeks)[a]	Switch sequence (maximum no. switch/arm)	Psoriasis (includ. pediatric)	Psoriatic arthritis	Rheumatoid arthritis	Axial spondyloarthritis	Crohn's disease (includ. pediatric)	Ulcerative colitis	JIA	Hidradenitis suppurativa	Non-infectious uveitis (includ. pediatric)	Microscopic polyangiitis	Wegener's granulomatosis
ADALIMUMAB[b]	**Humira®[23]**	---	**Abbvie**	**2003**	---	---	---	---	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		
	Hulio®	FKB-327[17]	Mylan	2018	RA	ACR20 week 24	98	B-O O-B (1)	X	X	X	X	X	X	X	X	X		
	AMGEVITA®	ABP501[17,24]	Amgen	2017	Ps RA	Improvement in PASI week 16[c] ACR20 week 24[d]	52[c] 92[d]	O-B (1)[c]	X	X	X	X	X	X	X	X	X[e]		
	Imraldi®	SB5[17]	Samsung Bioepis	2017	RA	ACR20 week 24	52	O-B (1)	X	X	X	X	X	X	X	X	X[e]		
	Hyrimoz®	GP-2017[17,25]	Sandoz	2018	Ps RA	PASI75 week 16[c] Change DAS28 week 12[d]	51[c] 24[d]	B-O-B-O-B O-B-O-B-O (4)[c]	X	X	X	X	X	X	X	X	X		
ETANERCEPT	**Enbrel®[17]**	---	**Pfizer**	**2000**	---	---	---	---	**X**	**X**	**X**	**X**			**X**				
	Benepali®	SB4[14,15]	Samsung Bioepis	2016	RA	ACR20 week 24	100	O-B (1)	X	X	X	X			X				
	Erelzi®	GP2015[16,21,22]	Sandoz	2017	Ps RA	PASI75 week 12[c] Change DAS28 week 24[d]	52[c] 48[d]	O-B-O B-O-B (2)[c] O-B (1)[d]	X	X	X	X			X				
INFLIXIMAB	**Remicade®[23]**	---	**Janssen**	**1999**		---	---	---	**X**[e]	**X**	**X**	**X**	**X**	**X**[f]					
	Inflectra® Remsima®	CT-P13[17,26]	Pfizer Celltrion	2013	RA	ACR20 week 30	54	O-B (1)	X[e] X[e]	X X	X X	X X	X X	X[f] X[f]					
	Flixabi®	SB2[17,27]	Samsung Bioepis	2016	RA	ACR20 week 30	70	O-B (1)	X[e]	X	X	X	X	X[f]					
	Zessly®	GP1111[17,27]	Sandoz	2018	RA	ACR20 week 14	70	O-B (1)	X[e]	X	X	X	X	X[f]					
RITUXIMAB	**MabThera®[23]**	---	**Roche**	**1998**	---	---	---	---			**X**							**X**	**X**
	Ritemvia® Rituzena® Truxima®	CT-P10[17]	Celltrion	2017	RA	Change DAS28 week 24	48	O-B (1)			X							X X X	X X X
	Rixathon® Riximyo®	GP2013[17,29]	Sandoz	2017	RA	Change DAS28 week 24	52	O-B (1)[g]			X X							X X	X X

The original biological drug is shown in bold. ACR20: 20% improvement in criteria established by the *American College of Rheumatology*; B: biosimilar; DAS28: *Disease Activity Score* 28; EU: European Union; JIA: juvenile idiopathic arthritis; O: original drug; PASI: *Psoriasis Area and Severity Index*; PASI75: ≥ 75% improvement in PASI; Ps: psoriasis; RA: rheumatoid arthritis. [a]Considering duration of treatment in the phase III study ± extension study, with data available to February 2019. [b]Idacio® (adalimumab) and Kromeya® (adalimumab), both from Fresenius Kabi, gained the positive opinion of the CHMP on January 2019. As of 1st March 2019, the EC decision had not been published[30,31]. [c]In patients with psoriasis. [d]In patients with rheumatoid arthritis. [e]In adult patients only. [f]Also in pediatric patients. [g]The effects of the switch were not evaluated within the 52-week phase III study, but in another 24-week study conducted by the market authorisation holder.

Table 2. Main characteristics of biosimilars of monoclonal antibodies approved in the European Union in the area of cancer up to February 2019

Drug substance	Brand name	Molecule	Marketing authorisation holder in the EU	Year approved in the EU	Development programme			Approved indications										
					Indication/s assessed in phase III	Primary endpoint	Switch sequence (maximum no. switch/arm)	NHL[a]	CLL[b]	Metastatic gastric cancer HER2+	Early breast cancer HER2+	Metastatic breast cancer HER2+	Metastatic breast cancer	NSCLC[c]	Ovarian, fallopian tubes, or peritoneal cancer[d]	Metastatic CRC	Renal cell carcinoma[e]	Cervical cancer[f]
RITUXIMAB	**MabThera®**[23]	---	**Roche**	**1998**	---	---	---	**X**	**X**									
	Blitzima®	CT-P10[17]	Celltrion	2017	AFL	ORR in cycle 8	---[g]	X	X									
	Ritemvia®							X										
	Rituzena®							X	X									
	Truxima®							X	X									
	Rixathon®	GP2013[17]	Sandoz	2017	AFL	ORR in cycle 8	---[g]	X	X									
	Riximyo®							X										
TRASTUZUMAB	**Herceptin®**[23]	---	**Roche**	**2000**	---	---	---			**X**	**X**	**X**						
	Ontruzant®	SB3[23]	Samsung Bioepis	2017	Stage 1 HER2 + or locally advanced breast cancer	PCR breast in cycle 8	---			X	X	X						
	KANJINTI®	ABP980[17]	Amgen	2018	Stage 1 HER2 + breast cancer	Total PCR in cycle 8	O-B (1)			X	X	X						
	Herzuma®	CT-P6[17]	Celltrion	2018	Stage 1 HER2 + or locally advanced breast cancer	Total PCR in cycle 8	---			X	X	X						
	Trazimera®	PF-05280014[17]	Pfizer	2018	Metastatic HER2+ breast cancer[h]	ORR in cycle 8	---			X	X	X						
	Ogivri®	MYL-1401O[17]	Mylan	2018	Locally recurrent or metastatic HER2+ breast cancer	ORR in cycle 8	---			X	X	X						
BEVACIZUMAB	**Avastin®**[23]	---	**Roche**	**2005**	---	---	---						**X**	**X**[i]	**X**	**X**	**X**	**X**
	MVASI®	ABP215[17]	Amgen	2018	NSCLC	RR of ORR during study (6 cycles)	---						X	X	X	X	X	X
	Zirabev®	PF-06439535[23]	Pfizer	2019	NSCLC	ORR during study (6 cycles)	---						X	X[i]		X	X	X

The original biological drug is shown in bold. AFL: advanced follicular lymphoma; CLL: chronic lymphocytic leukaemia; CRC: colorectal cancer; EU: European Union; HER2+: human epidermal growth factor receptor 2 positive; NHL: non-Hodgkin's Lymphoma; NSCLC: non-small cell lung cancer; O-B: from the original drug to the biosimilar; ORR: overall response rate; PCR: pathological complete response; RR: risk ratio. [a]Includes follicular lymphoma responding to induction therapy, chemoresistant or relapsed/refractory grade III-IV follicular lymphoma, and diffuse large B cell lymphoma. [b]Without previous treatment or relapsed/refractory. [c]Advanced non-resectable, recurrent or metastatic, and with predominance of non-squamous histology. [d]Either advanced in first-line of treatment, platinum-sensitive in first recurrence, or platinum-resistant and recurrent. [e]Advanced and/or metastatic. [f]Persistent, recurrent or metastatic. [g]Switch data only available in rheumatology. [h]A second support study evaluated breast PCR and ORR as secondary endpoints in patients with operable HER2+ breast cancer. [i]While MVASI and Zirabev are only indicated in combination with paclitaxel, Avastin is also indicated in combination with capecitabine in patients in whom treatment with taxanes or anthracyclines is not considered appropriate. [i]Unlike Avastin and MVASI, Zirabev is only indicated for the treatment of NSCLC without activating mutations of the epidermal growth factor receptor (EGFR).

The contribution of each of these scenarios to savings in health costs depends on the degree of market penetration of biosimilars in the system. For example, a retrospective analysis of Spanish data estimated the savings derived from the introduction of biosimilars at €479 million between 2009 and 2016. Over half (65%) of this saving occurred between 2015-2016, and was mainly due to biosimilars of infliximab and insulin glargine driving down the price of the original drug, and not to direct acquisition of biosimilars. The same analysis estimates savings of €1,965 million between 2017 and 2020, due to the launch of biosimilars for the treatment of pathologies that are highly prevalent and/or are currently treated with original high-price biologics[35]. Direct and indirect savings derived from biosimilars free up resources that can be invested in new original treatments and health technologies. The use of these therapies not only provides an immediate benefit to the patient, but also drives innovation in the pharmaceutical industry, which in turn leads to additional benefits for patients in the long term. The effect of biosimilars on innovation is further strengthened by the provision of new administration devices associated with some biosimilars, and of additional clinical trials and real world evidence.

The latter is especially relevant as prescribers' decision-making process relies mainly on scientific evidence. In this sense, it is important to note that the abbreviated approval pathway of biosimilars (justified by the totality of evidence available) has not undermined their efficacy and safety, as shown by the data collected by the EMA so far. As previously commented, biosimilars' phase III studies have included populations and variables that meet the requirements of the CHMP and, in some cases, companies have conducted supportive studies in indications historically demanded by medical societies, such as psoriasis[32]. Likewise, development programs have included characteristics not initially required by the EMA to demonstrate biosimilarity, but which may be of interest to prescribers, such as switch studies. Stepping up effective efforts to communicate this evidence to prescribers will most likely help overcome any remaining qualms about biosimilars, and help increase their market share without necessarily having to impose prescription targets.

Another factor that can help increase the use of biosimilars, due to its influence on prescribers, is a favourable (or at least neutral) position of medical societies and the explicit mention of biosimilars in treatment guidelines. On the first point, much progress has been made, and currently several Spanish scientific societies endorse the evidence generation pathway established by EMA for biosimilars. As an example, the Spanish Hospital Pharmacy Society (SEFH), Society of Digestive Pathology (SEPD), Society of Rheumatology (SER), SEOM, and the Academy of Dermatology and Venereology (AEDV) currently accept extrapolation, provided EMA requirements are met[6,32-34,38]. With regard to the mention of biosimilars in clinical guidelines, although it is still a pending issue, some advances have also been made. An example are the SER recommendations for the use of biologics in patients with axial spondyloarthritis[39].

Confidence in the safety profile of biosimilars is another key aspect. Long-term safety data is already available from clinical trials, and all biosimilars have a risk management plan and must fulfil the same post-marketing pharmacovigilance requirements as the original biologics. In addition, data from clinical practice in larger and more diverse populations than those included in clinical trials will be generated during the post-marketing period. Traceability will become increasingly important as new biosimilars are released and therapeutic options for the same active ingredient increase. The unique identifier printed on all prescription medication packages from February 2019[40] will facilitate the traceability of these drugs, and will help allow potential adverse events to be attributed to a particular medicinal product, further clarifying the safety profile of certain biosimilars with respect to others, and with respect to the original biologics.

At the administrative level, access to biosimilars could be speeded up by making it easier to include them in the hospitals' pharmacotherapeutic guidelines. Currently, their inclusion is usually agreed by consensus between the medical service, the hospital's pharmacy service, and the medical and financial directors, or else is decided by the Pharmacy and Therapeutics Committee. On the other hand, where public tenders are held, short-term contracts should be awarded to several successful bidders to promote competition and, consequently, the availability of biosimilars in the long run. Contracts should not be awarded solely on the basis of price, but should also consider quality aspects including, among other things, the scientific evidence provided, the availability of patient support programs, the quality of the packaging material, the information included on the label, or the administration device. This would help strengthen the confidence, commitment, and preference of patients and healthcare professionals for biosimilar mAbs.

When considering the specific topic of switch and substitution, automatic substitution is not allowed in Spain without the prescriber's permission, as per order SCO/2874/2007[41]. Consequently, pharmacy services can only substitute original biologics for their biosimilars if this has been previously agreed with the prescribers in the Pharmacy and Therapeutics Committee, and must always inform the prescriber of the drug used in each case. Many prescribers prefer to continue to decide which biosimilar or original biological should be used in each case, and prejudices against biosimilars persist, even though they are not justified in light of the available evidence. Meanwhile, prescribers willing to switch their patients may find it difficult to compare all the dimensions of the different biosimilars on offer. Similarly, it can be particularly difficult for different departments in the same hospital to reach a consensus on interchangeability of a given biosimilar, especially when the availability of switch data varies considerably among therapeutic areas.

At the national level, countries such as Portugal, France, and the United Kingdom require that biosimilars approved by the EC undergo an additional cost/benefit evaluation before being included in lists of reimbursed drugs. In Spain, this evaluation is not a prerequisite for price and reimbursement negotiations, and this shortens marketing delays. However, Spain has not yet established abbreviated negotiation procedures for biosimilars, as has been done in Germany and Italy[35]. The implementation of measures to encourage the use of biosimilars (training, prescription incentives, use/penetration targets) also fall under the remit of each member state. In Spain, targets have been set in some regions (Madrid, Catalonia)[35], but this strategy can be counter-productive, as it involves restricting the freedom of prescription for economic reasons. Therefore, if implemented, it should preserve the decision-making capacity of prescribers by, for example, encouraging them to start biosimilar treatment in naïve patients instead of compelling them to switch to biosimilars in patients with established treatment regimens. Similarly, acceptance of prescription targets could be improved if the savings achieved with the use of biosimilars are reinvested in health care, and this measure is adequately communicated. Additionally, there is a need for specific regulations on interchangeability at the national level. The adoption of these measures would speed up the entry of new biosimilars into the Spanish health system, increasing treatment options for prescribers and patients. But also, it would reduce uncertainty among the companies marketing biosimilars, help protect the investment involved in the development of biosimilars, and stimulate innovation[35].

Finally, patient-related factors must also be bore in mind. Particularly, patients developing a negative attitude towards the drug received may experience a subjective worsening of their symptoms, known as the "nocebo effect"[42]. This effect has been documented in observational studies with biosimilar mAbs[43], and may be especially relevant in the case of patients who self-administer the drug, as they are more familiar with their usual medication. In this context, the role of prescribers and pharmacists is very important, as they can convey their confidence in biosimilars to patients. Also, they can provide patients with sufficient, easily understandable information and involve them in treatment decisions, so that any switch is agreed with the patient. As frequently the healthcare professionals' workload renders this difficult, patients should have access to information resources which are reliable, easy to access and understand. An example of this is the patient-oriented biosimilar document available on the EC website[44].

In conclusion, European regulations for the approval of biosimilars of mAbs ensure that these products are highly similar to their original biologicals in terms of quality, efficacy and safety. Penetration of biosimilars in the health system is expected to increase as prescribers become aware of this option and more knowledgeable of the totality of evidence that justifies aspects such as extrapolation and switching. However, additional national/institutional measures are required to accelerate the access to biosimilars and support innovation. Educating and involving patients in the decision process will be key to increasing acceptance of biosimilars and overcoming the nocebo effect.

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