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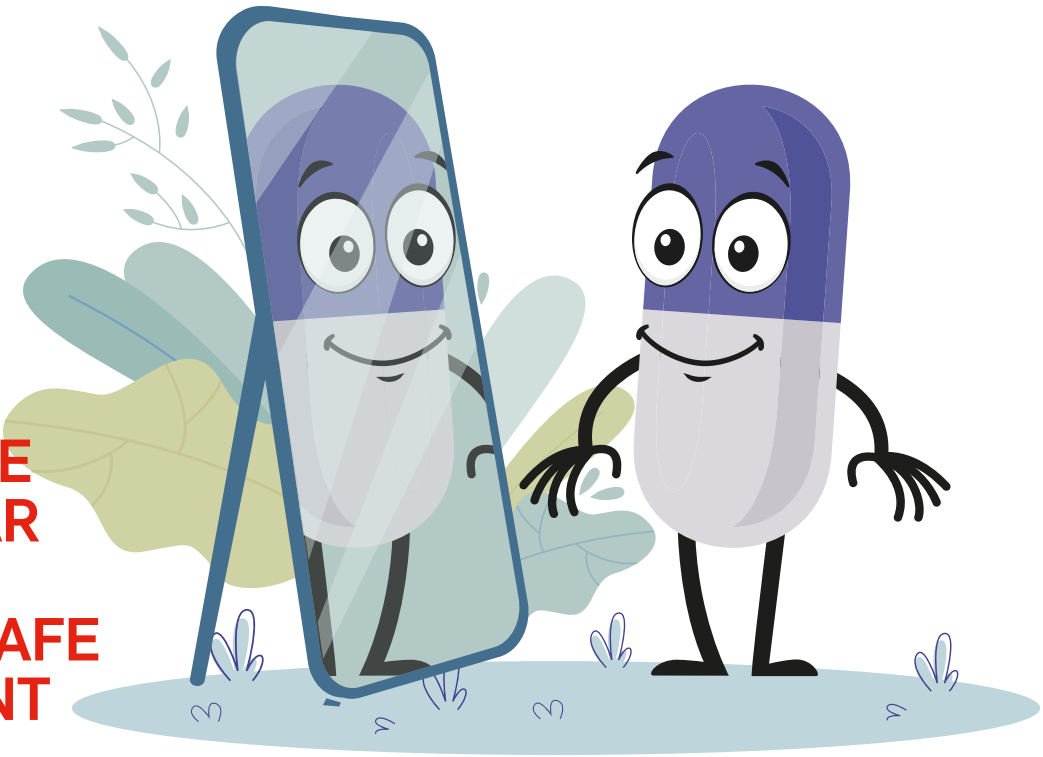

INTERCHANGE OF BIOSIMILAR MEDICINES: EFFECTIVE, SAFE AND EFFICIENT

INTRODUCTION AND OBJECTIVES A biosimilar is a biological medicine that is very similar to another one already marketed in the European Union (EU) whose patent has expired and the differences between which are not clinically significant, in other words do not affect clinical practice. More biosimilars are slowly being developed and, consequently, the experience with their use is increasing. The European Medicines Agency (EMA) considers the biosimilars approved in the EU to be interchangeable, and has signed a statement to reduce the uncertainty regarding interchangeability of biosimilars in clinical practice. The aim of this bulletin is to define the basic concepts, describe the comparability, authorisation and interchangeability processes, evaluate the scientific evidence regarding the efficacy, safety and economic impact of the switch, and to describe the current situation of biosimilars in Spain. MATERIALS AND METHODS A literature search was carried out for systematic reviews evaluating the efficacy/effectiveness, safety and immunogenicity or economic impact of the switching in Pubmed and Epistemonikos up to 28/11/2022. Documents from regulatory agencies and other publications of interest were also reviewed. Data regarding the consumption and economic impact of biosimilars in Spain were obtained from the Ministry of Health, and those for Navarre were obtained from the information databases of the Navarre Health Service-Osasunbidea (SNS-O). RESULTS AND CONCLUSIONS In general, the evidence available demonstrates that the switching of a reference medicine for a biosimilar does not affect the efficacy, safety or immunogenicity in any significant manner. Some reviews have identified a higher than expected discontinuation rate for the biosimilar after the switch, mainly due to a potential nocebo effect and a lack of confidence of healthcare professionals in the switching. A total of 147 biosimilar medicines are currently marketed in Spain, corresponding to 15 active substances. The introduction of biosimilars in Spain continues to increase, with a penetration of 67.6% having been estimated in a hospital setting in 2021. Similarly, a saving of more than 5 billion € between 2009 and 2022 as a result of their introduction has been estimated.

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Introduction

Since their introduction in 2006, extensive experience in the use of biosimilar medicines has been achieved in almost all the therapeutic areas covered by their indications. However, on occasions, doubts continue to arise in certain situations, especially the switching of these medicines. The aim of this bulletin is to compile the best evidence currently available in this respect to reduce this uncertainty.

Methodology

A literature search for systematic reviews published in Pubmed and Epistemonikos up to 28/11/2022 was carried out. Reviews that evaluated the efficacy/effectiveness, safety and immunogenicity or economic impact of the switch from a reference medicine to a biosimilar, or between biosimilars with the same active substance, were included. Reviews that evaluated the reverse-switch (from a biosimilar medicine to a reference medicine), multiple switching and the impact of the nocebo effect in switching studies were also included.

Similarly, documents from the main regulatory agencies and other publications related to this topic were also reviewed.

Data regarding the consumption and economic impact of biosimilars in Spain were obtained from the Ministry of Health, and those for Navarre were obtained from the information databases of the Navarre Health Service-Osasunbidea (SNS-O).

Concepts

Biological medicine

Biological medicines are those containing active substances extracted or synthesised from a biological source, such as living organisms or cells[1].

Some of these active substances are obtained directly from nature (e.g. albumin), whereas others are synthesised using biotechnological processes.

Biotechnology-derived medicines

Biotechnology-derived medicines are biological medicines that are synthesised using living cells or organisms (mainly yeasts and bacteria) into which genetic material is inserted using recombinant DNA techniques to convert them into producers of the active substance of interest[2,3].

Biosimilar medicine

A biosimilar is a biological medicine equivalent to another medicine already marketed in the European Union (EU), whose patent has expired (referred to as the reference medicine), in terms of quality, efficacy and safety[1,4,5].

In contrast to conventional medicines synthesised chemically, biosimilar medicines comprise large molecular structures, mainly simple (e.g. insulin, growth hormone) or complex proteins (e.g. coagulation factors, monoclonal antibodies)[1]. If the active substance is a protein, both the biosimilar and the reference medicine must contain the same amino acid sequence and same 3D structure (same protein folding), as these are main factors determining biological activity[1].

The active substances in biological medicines exhibit a minor inherent variability (microheterogeneity) as they are obtained from living organisms, which are variable by nature. Similarly, the manufacturing process for biotechnology-derived medicines is more complex than that for conventional medicines synthesised chemically[1]. These manufacturing processes are very sensitive, and small changes can lead to a small variability between the molecules of an active substance and between different batches of the same biological medicine, which is why it is often said that "the process is the product"[4]. This means that it is not possible to obtain an exact replica of the molecular microheterogeneity, therefore a biosimilar is not a generic of a reference biological medicine[1].

Biosimilarity

The impact of the variability that a biological medicine candidate for being a biosimilar for a reference medicine may have is evaluated by performing comparability studies with that reference medicine. In order for a biological medicine to be considered biosimilar, this variability must be within an acceptable range to ensure consistent safety and efficacy[1].

The main differences between generic and biosimilar medicines are listed in Table 1[1,2,4].

Evaluation of comparability

Comparability is evaluated by way of a stepwise process comprising the following steps[1]:

Comparative quality studies:
- Analytical: chemical and physical properties
- Functional: biological/pharmacological activity

Comparative non-clinical studies:
- Pharmacodynamics
- Toxicology

Comparative clinical studies:
- Safety and efficacy
- Pharmacokinetics/pharmacodynamics
- Immunogenicity

The authorisation for a biosimilar medicine is based on existing scientific knowledge regarding the safety and efficacy of the reference medicine acquired during its use in clinical practice. In the case of biosimilar medicines, the aim of clinical trials is to evaluate the biosimilarity with the reference medicine rather than to establish the safety and efficacy, as the latter have already been demonstrated for the reference medicine. As such, the comparative clinical trials are designed to rule out that the possible differences may affect the pharmacokinetics, efficacy or safety, including the immunogenicity, in other words to rule out the existence of clinically relevant differences. To that end, appropriate equivalence margins are selected for the primary efficacy endpoint, with these being specific for the indication studied. These margins represent the largest difference in efficacy that would not affect clinical practice and which, therefore, would not have clinical relevance. The difference observed between the candidate biosimilar medicine and the reference medicine will be considered to be acceptable if it falls within this range[1]. In that case, a medicine will be considered to be biosimilar.

Table 1. Main differences between generic and biosimilar medicines.

	Generic	Biosimilar
Synthesis	Chemical synthesis	Extraction or synthesis (biotechnology) from a biological source (living cells or organisms)
	Easy to reproduce	Difficult to reproduce
Molecular structure	Identical to reference medicine	High degree of similarity with reference medicine (microheterogeneity)
	Simple	Complex
	Small molecules, low molecular weight	Large molecules, high molecular weight
Immunogenicity	No	Yes
Comparability	Bioequivalence (equivalence in terms of rate and extent of release of the active substance-pharmacokinetics and pharmacodynamics)	Biosimilarity (similarity in terms of chemical structure, biological function, efficacy, safety and immunogenicity) Clinical equivalence
Need for clinical trials for authorisation	Only bioequivalence clinical trials	Yes (pharmaceutical quality, non-clinical and clinical studies comparing with reference medicine)
Development	Shorter time and lower cost	Longer time and higher cost
Authorisation	National or centralised procedure	Biotechnology-derived biosimilars: Centralised procedure (responsibility of the European Medicines Agency, European Commission)
Extrapolation of indications	Authorisation of all indications approved for the reference medicine without the need for additional clinical data	The efficacy and safety must be justified for each indication (although clinical trials for all indications may not always be required)
Interchangeability (switching)	Automatic	Not automatic (competence of EU Member States)

Procedure for approving biosimilar medicines

Biotechnology-derived medicines (reference medicines or biosimilars) are always authorised by way of a centralised procedure. During this procedure, the scientific committees for medicinal products for human use and safety at the European Medicines Agency (EMA) evaluate the registration dossier. If approval is granted, the European Commission issues a marketing authorisation for the medicinal product, which is applicable to all Member States[1,6].

Subsequently, in order to be used by the National Health System (SNS), the Ministry of Health must issue a resolution approving funding by the SNS and, if applicable, the Interministerial Pricing Commission must set the price[6].

In the case of biosimilar medicines, the biosimilarity is evaluated to rule out clinically significant differences

Extrapolation of indications

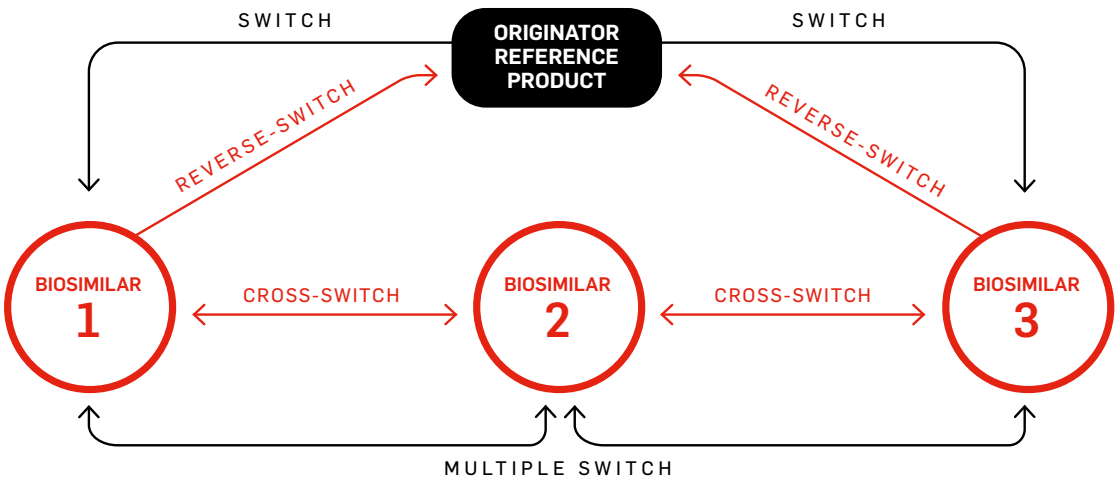
Extrapolation of indications refers to the authorisation of indications of the reference medicine for the biosimilar in the absence of specific clinical data obtained with the biosimilar medicine. This means that, if a biosimilar presents a degree of comparability in terms of safety and efficacy for a specific therapeutic indication, the data concerning its safety and efficacy may be extrapolated to other indications already authorised for the reference medicine[1]. The extrapolation of indications is established by the EMA[7].

Extrapolation may be accepted if all the scientific evidence available from the comparability studies, establishes the biosimilarity and can address all specific aspects of the extrapolated indication (for example, mode of action, potentially unique safety, or immunogenicity aspects). Fewer clinical trials with the biosimilar, or even none in some cases, are required for the extrapolation of certain indications. However, if the data for a specific indication are not directly applicable to the indication to be extrapolated in terms of safety or efficacy (for example if the indication belong to a different therapeutic area where the mode of action, posology or pharmacokinetics vary), additional studies will be required[1].

Interchangeability of biosimilars

This refers to the possibility of changing one medicine for another that is expected to have the same clinical effect. This involves changing a reference medicine for a biosimilar (switching), changing one biosimilar for another (cross-switching) or changing back from the biosimilar to the reference medicine (reverse-switching, retransitioning or switchback).

Figure 1. Switching between biological and biosimilar medicines. Adapted from Solitano et al. 2020[8]



Interchangeability involves a switch, which is when the prescriber decides to exchange one medicine for another with the same therapeutic intent, or a substitution, which is when one medicine is dispensed instead of another equivalent or interchangeable medicine at pharmacy level without consulting the prescriber[1].

Role of the regulatory agencies

The decision regarding whether to allow the interchangeability and replacement of the biological reference medicine by the biosimilar is taken nationally. When the EMA carries out a scientific review for a biosimilar, the evaluations do not include recommendation regarding whether the biosimilar is interchangeable with the reference medicine or, therefore, whether the reference medicine can be switched or substituted with the biosimilar. In the EU, prescribing and advisory practices for drug-prescribing professionals are the responsibility of the Member States, who have the required legal framework and draft regulations, guidelines and recommendations in their areas of competence.

To date, the biosimilars approved by the EMA can be used interchangeably if the national regulatory agency allows this. From a scientific viewpoint, the interchangeability of the biosimilars approved has always been considered to be acceptable, and the agencies have not noticed any warning signs[9].

The EU medicines regulatory network has recently decided to issue an explicit statement regarding the interchangeability of biosimilars. This is due to the fact that the absence of a clear EU-wide position on interchangeability has been identified as a factor that causes uncertainty among stakeholders on the use of biosimilars in clinical practice. As such, the EMA and the Heads of Medicines Agencies (HMA) consider it necessary to establish a clear and harmonised EU wide position regarding interchangeability to minimise any uncertainty that prescribers may have when deciding to prescribe biological medicines.

Consequently, in September 2022, the EU experts on biosimilar medicines [Biosimilar Medicines Working Party (BMWP)] and the HMA's Biosimilar Working Group have drafted a joint statement in which they explain the rationale for considering the biosimilars approved in the EU as interchangeable from a scientific perspective. This has also been endorsed by the Committee for Medicinal Products for Human Use (CHMP) and the Biologics Working Party (BWP). This joint statement considers that once a biosimilar is approved in the EU it is interchangeable[10].

In addition, they clarify that decisions regarding the substitution (the practice of dispensing one medicine instead of another without consulting the prescriber) are managed by each Member State and are not within the remit of the EMA.

Interchange or switching refers to the change of a reference medicine for a biosimilar

In Spain, the interchangeability is established by the Pharmacy and Therapeutics Commission at the hospitals and/or the Autonomous Community Commissions

The scientific arguments used to support interchangeability are based on the large number of biosimilar medicines that have been exhaustively reviewed and monitored over the past 15 years and which, based on extensive experience in clinical practice, have been shown to be comparable to their reference medicines in terms of efficacy, safety and immunogenicity.

Although the interchangeability of biosimilars has already been put into practice in many Member States, this joint position harmonises the EU approach, provides greater clarity for healthcare professionals and, therefore, helps patients to access biological medicines. Although this statement has no legal force, it is expected that its proposal can be transposed into each State's interchangeability-related legislation.

Indeed, agencies from several European countries have positioned themselves in favour of the interchangeability of biosimilars under the supervision of the prescribing physician, and support the automatic substitution of these medicines in a hospital setting[11].

Interchangeability process in Spain

In Spain, Order SCO/2874/2007 of 28 September establishes that biological medicines are not substitutable by the pharmacist[12]. Its interpretation has proved controversial as its scope of application is the dispensing of medicines by community pharmacies[13]. Biological medicines are currently mainly prescribed by specialists and are dispensed by hospital pharmacy services. The drug use policy in a hospital setting is determined by interdisciplinary commissions that promote the rational use of the medicines based on current law and best practice, including therapeutic interchangeability, as clarified by the Spanish Agency of Medicines and Medical Devices (AEMPS)[13]. As such, the choice of biosimilars is generally made by the Pharmacy and Therapeutics Commission (CFyT) at hospitals, and by the commissions of the Autonomous Community concerned.

Consequently, interchangeability in a hospital setting in our country is possible if approved by the CFyT and/or Autonomous Community Commission, and together with the prescriber's opinion, which is represented in this collegiate body[7]. These commissions are responsible for establishing the positioning of biosimilar medicines in the hospital's therapeutic arsenal and for establishing measures to guarantee the traceability and monitoring of adverse effects, as is the case for all other medicines.

In Navarre, Instruction 7/2018 issued by the Managing Director of the Navarre Health Service-Osasunbidea (SNS-O) proposes to always use the biological or biosimilar medicine that is most efficient after the tender process, and places the responsibility for monitoring and control of the recommendations approved in the hands of the Medical Directorates of SNS-O hospitals, through pharmacy services.

Evidence regarding the impact of the switching on health outcomes

Evidence from individual studies

The scientific evidence analysing switching may come from extension studies of randomised clinical trials (RCTs), RCTs for approval by regulatory bodies, registry-based observational studies and real-life studies. Figure 2 shows the different study types by design.

RCT extension studies analyse the differences between at least two groups with or without switching, after an initial period in which the efficacy of a biosimilar is evaluated versus the reference medicine in two randomised groups. Although they study the efficacy and safety of switching, they do not usually have sufficient power to reach robust conclusions, given that the primary outcome is based on efficacy or safety in the first period prior to switching.

The EMA considers biosimilars to be interchangeable

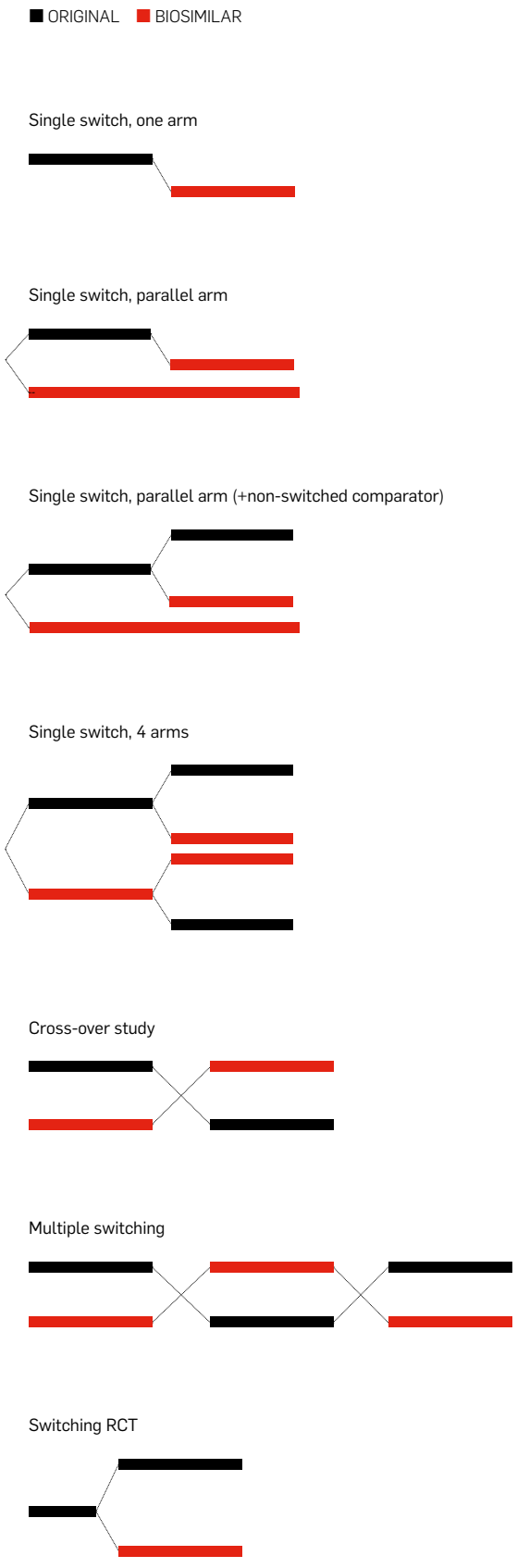
The switch does not significantly affect the efficacy, safety or immunogenicity

Some compare the safety and efficacy of a maintenance group taking a biosimilar and a group that switches from the reference medicine to the biosimilar, but with no comparator group that continues to take the reference medicine. Other RCT extension studies include three groups, dividing the reference medicine group into two for the extension phase: one group maintaining the reference medicine and the other switching to the biosimilar.

One such example is the study by Ye et al., a randomised, double-blind, phase III, 54-week, non-inferiority study that examined the efficacy and safety of the infliximab biosimilar CT-P13 versus the reference medicine in 220 patients with active Crohn's disease[14]. Patients were randomised to the biosimilar or the reference medicine and followed-up for 30 weeks. At week 30, participants in each arm were randomised again to continue with treatment or switch, thus leading to a total of four treatment arms. The primary endpoint of the study was to compare the efficacy between the biosimilar and reference medicine in terms of response rate at week 6, with no significant differences being found between the groups. Efficacy was maintained and was similar for all groups at weeks 6, 14, 30 and 54 (after switching), although the study did not have sufficient power to show statistically significant differences in secondary endpoints, including those after week 30, which are the ones that provide information about switching.

Observational studies that analyse the efficacy and safety of switching from a reference medicine to a biosimilar have also been carried out, in either single-arm studies or studies comparing with a comparator group receiving the reference medicine or biosimilar (e.g. cohort studies or studies with historical control).

Figure 2. Types of studies according to their design.



Only one RCT designed specifically to evaluate switching has been found to date:

The NOR-SWITCH study was sponsored by the Norwegian government and was the first randomised, double-blind, phase-IV non-inferiority study to examine the switching from infliximab eference medicine to the biosimilar CT-P13 in 481 patients aged 18 years or older who were clinically stable with infliximab for ≥6 months and with any of the following six inflammatory diseases: rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, ulcerative colitis, Crohn's disease and chronic plaque psoriasis[15]. This trial had an initial duration of 52 weeks and was designed to evaluate any worsening of the disease (according to specific criteria for each disease) upon switching in comparison with maintenance of the reference medicine.

The change of the reference medicine to the biosimilar was not inferior to continued treatment with the reference medicine, as per a non-inferiority margin of 15%, for the variable worsening of the disease (29.6% versus 26.2%), with a risk difference of –4.4% (95% confidence interval of –12.7 to 3.9), adjusted for diagnosis and duration of treatment. The frequency of patients who presented adverse events or serious adverse events was similar in both treatment groups and there were more patients with infusion-related reactions who suspended the study drug in the reference medicine group than in the biosimilar group. The immunogenicity, serum drug concentrations and appearance of anti-drug antibodies did not differ significantly between both groups.

The strengths of the NOR-SWITCH study were its randomised design and the inclusion of a large number of participants. Some limitations of the NOR-SWITCH study have also been mentioned, including the inclusion of populations with different diseases, thus requiring different definitions of efficacy to be combined, the lack of statistical power to obtain conclusions for each disease, or a non-inferiority limit that could have been stricter[16].

Evidence from systematic reviews

A total of 26 systematic reviews evaluating the efficacy or effectiveness, safety, immunogenicity and costs related to switching of biosimilars have been identified. Six of these reviews analysed the switching of various drugs in numerous indications, eight analysed the switching of anti-TNFα in various immune-mediated inflammatory diseases, six evaluated the switching of anti-TNFα (infliximab and adalimumab) in inflammatory bowel disease, one analysed the switching of anti-TNFα and rituximab in rheumatoid arthritis, and one concerned the switching of rituximab and trastuzumab in oncological diseases and in rheumatoid arthritis. Two reviews that specifically analysed the switching between biosimilars have also been identified: one analysing the reverse-

switching, and one intended to evaluate the possible existence and impact of a nocebo effect associated with switching.

The characteristics and findings of the reviews identified are provided in Annex 1. The majority of the evidence available comes from observational studies and, to a lesser degree, from RCTs and extension studies of them.

The drugs for which the strongest evidence regarding the impact of switching is available are anti-TNFα agents, mainly infliximab and, to a lesser extent, adalimumab and etanercept. With regard to the therapeutic indications, the evidence available mainly concerns inflammatory bowel disease.

This evidence mainly concerns switching from the reference medicine to the biosimilar, and very little evidence is available regarding switching between biosimilars, reverse-switching and multiple switching.

The discontinuations of biosimilar medicines were mainly due to a potential nocebo effect and a lack of confidence on the part of health professionals

In general, the reviews identified conclude that switching from a reference medicine to a biosimilar does not significantly affect the efficacy, as analysed using clinical variables (clinical response, clinical remission, disease activity, worsening before and after switching, etc.), safety, as measured using the incidence of adverse events, or immunogenicity, as measured using anti-drug or neutralising antibody levels. This conclusion can be generalised to the drugs and indications included in the reviews identified, with no drug or therapeutic area or specific indication showing a different pattern having been identified. In inflammatory bowel disease, no differences in clinical efficacy were found when switching was performed during induction or during the maintenance phase.

However, some reviews identified a higher-than-expected discontinuation rate for the biosimilar after switching, with this tending to increase with time. The discontinuation rate for biosimilars varies markedly between the different reviews. For example, the review by Liu et al. (2022), which included 66 real-life studies, identified an annual discontinuation rate for the biosimilar of 21% (95% CI: 15-25)[17]. Similarly, the review by Queiroz et al. (2020), which included 30 observational studies evaluating the switching of infliximab in inflammatory bowel disease, identified a discontinuation rate for the biosimilar of 8%, 14% and 21% at 6, 12 and 24 months, respectively[18]. In the review by Bakalos et al. (2019), a discontinuation rate for the biosimilar of more than 10% was identified for 11 of the 14 (78.6%) observational studies included (range: 12.2–28.2%)[19]. In the RCTs in the review by Numan et al. (2018), a discontinuation rate of 5–33% was identified for the group of patients with switching vs 4–18% for the control group[20].

Both the review by Yoo et al. (2018)[21] and others noted the main reasons for discontinuation of biosimilars as being a potential nocebo effect and the lack of confidence of healthcare professionals in the switch, with, in general, no objective clinical or biological evidence of inefficacy or safety problems having been identified.

The majority of publications agree that the switching of a reference medicine for a biosimilar can be considered to be safe in clinical practice, and that not performing switching due to hypothetical risks is disproportionate. There is some uncertainty regarding the actual financial impact of switching, as the cost-effectiveness studies found are generally incomplete, and also given the limitations for extrapolating their findings to other settings.

The two reviews concerning switching between biosimilars[22,23] concluded that this is a safe and effective practice, with no significant differences in terms of disease activity and response, adverse events or immunogenicity having been observed.

The only review concerning reverse-switching found that, after a follow-up of 12 months, approximately 8% of included patients presented transition[24]. There were fewer returns to the reference medicine in the studies including only patients with stable disease and in those studies implementing additional laboratory monitoring as part of the biosimilar implementation strategy, amongst other aspects.

However, the reviews available concerning reverse-switching and switching between biosimilars only include observational studies, and very little information concerning multiple switching is available. Consequently, it is not currently possible to extract firm conclusions regarding the possible impact of this type of multiple switches on the efficacy and safety, although relevant differences are not expected.

Impact of the nocebo effect in switching clinical trials

The nocebo effect can be considered to involve undesired results arising from an intervention as a result of negative expectations. As such, it is the opposite of the placebo effect. It has been reported for various medicines, although it has not been widely studied in the field of biosimilars.

The higher treatment discontinuation observed with biosimilars in some studies, especially observational ones, with similar efficacy and adverse event rates, suggests the existence of a nocebo effect[25].

A systematic review proposed to evaluate whether patients and/or healthcare professionals being aware of having switched from a reference medicine to a biosimilar was associated with an increase in the adverse events susceptible to a nocebo effect[26].

The hypothesis was that the incidence of subjective adverse events (for example, malaise) should be higher in non-blinded biosimilar studies, as it would be more likely for them to be affected by a nocebo effect. In contrast, the incidence of objective adverse events (for example analytical values) in open and double-blind studies should be similar, as they would be less likely to be affected by this effect. The authors reviewed studies reporting the efficacy and safety results for the switch of a reference medicine to a biosimilar, and compared the subjective and objective complications in blinded and open studies. They found that in infliximab studies, which represented the majority, the treatment-interruption rates for any reason, due to adverse effects and due to lack of efficacy were, in general, higher in open trials than in double-blind trials. This suggests that an awareness of a switch to a biosimilar may affect patients' perceptions and subsequent results.

It has been suggested that the relationship between the patient and the healthcare professional is a key factor as regards the acceptance of biosimilars, and that this could limit the nocebo effect[27]. As such, the awareness of both patients and healthcare professionals regarding the efficacy and safety of biosimilars should be promoted. Education about biosimilars should be adapted to each patient, and a positive focus is recommended.

Biosimilars marketed in Spain

As of 24 January 2023, a total of 147 biosimilar medicines, corresponding to 15 active substances, were marketed in Spain.

Their brand names, grouped by active substance and authorisation date, can be seen in table 2[28].

The penetration of biosimilars in Spain has resulted in a saving of more than 5 billion € between 2009 and 2022

Evolution of the consumption and economic impact of the introduction of biosimilars

In Spain

The penetration of biosimilars in Spain is very hete-rogeneous and depends on the active substance, hospital or community pharmacy dispensing, and the Autonomous Community. The consumption of biosimilars is mainly hospital-based. In 2021, a penetration of biosimilars of around 67.6% has been estimated for hospital settings (national average consumption of packages of biosimilar medicines divided by totals for these active substances)[29]. Those with the highest penetration in this setting are filgrastim (96%), pegfilgrastim (88.2%), infliximab (82.8%), erythropoietin (82.7%) and rituximab (79.1%). Based on the invoicing of drug prescriptions by the SNS, the national average is 18.2%, with the highest penetration being found for enoxaparin (47%) and follitropin alfa (41.1%)[29]. Marked variability is also seen between Autonomous Communities, with penetrations in a hospital setting ranging from 89% to 40%, and in primary care from 34.4% to 5.2%[29].

Some studies regarding the budgetary impact of the introduction of biosimilars have been carried out both internationally and in Spain. In Spain, a cost saving of more than 5 billion € has been estimated for the period 2009–2022, with somatropin, epoetins, infliximab and adalimumab having the greatest influence on that saving given the time they have been on the market, their consumption volumes and their price[30]. Around a hundred patents for reference biological medicines will expire between 2024 and 2029, and this may lead to the introduction of a large number of new biosimilars over the next few years. As such, biosimilars represent a major opportunity for promoting the sustainability of the SNS by providing the same quality and safety guarantee as the reference medicine.

Table 2. Biosimilar medicines marketed in Spain.

Active substance	Biosimilar medicine	Authorisation date	Reference medicine
Epoetin Zeta	Retacrit®	2007	Eporatio®
Epoetin Alfa	Binocrit®	2008	Eprex®
Filgrastim	Accofil®, Nivestim®, Zarzio®	2009	Neupogen®
Somatropin Recomb.	Omnitrope®	2014	Genotonorm® Humatrope® Norditropin® Nutropinaq® Saizen® Zomacton®
Infliximab	Flixabi®, Inflectra®, Remsima®, Zessly®	2014	Remicade®
Follitropin Alfa	Bemfola®, Ovaleap®,	2014	Gonal-F®
Etanercept	Benepali®, Erelzi®	2016	Enbrel®
Insulin Glargine	Abasaglar®, Semglee®	2016	Lantus®
Rituximab	Rixathon®, Ruxience®, Truxima®	2017	Mabthera®
Enoxaparin Sodium	Enoxaparina Ledraxen®, Enoxaparina Rovi®, Hepaxane®, Inhixa®,	2018	Clexane®
Trastuzumab	Herzuma®, Kanjinti®, Ogivri®, Ontruzant®, Trazimera®, Zercepac®	2018	Herceptin®
Adalimumab	Amgevita®, Hulio®, Hyrimoz®, Idacio®, Imraldi®, Yuflyma®,	2018	Humira®
Pegfilgrastim	Nyvepria®, Pelgraz®, Pelmeg®, Ziextenzo®	2018	Neulasta®
Teriparatide	Livogiva®, Movymia®, Terrosa®	2019	Forsteo®
Bevacizumab	Alymsys®, Aybintio®, Mvasi®, Oyavas®, Zirabev®	2019	Avastin®

The emergence of biosimilars has allowed competitive tendering in standardised public drug purchasing processes, thus resulting in greater efficiency and contributing to the sustainability of the public health system.

The Ministry of Health has launched an action plan to promote the use of market-regulating drugs in the SNS, especially biosimilar and generic medicines, which aims to develop measures to promote competition as a key element for efficiency and to guarantee the use of the most cost-effective drug[31].

In Navarre

The consumption of biosimilars in Navarre has increased steadily over the past few years, from 7631 packages of biosimilar medicines consumed in 2017 to 39,702 in 2021, with the expenditure thereof increasing from 2,109,825 € in 2017 to 16 million € in 2021 (table and figure 3).

In the hospital setting, the penetration of biosimilar medicines over the past five years has varied widely. The percentages of packages of biosimilar medicines consumed with respect to all medicines with the same active substance can be seen in table and figure 3.

Biosimilar medicines based on monoclonal antibodies (mAb) have generally been introduced slowly and are well accepted for treatment initiation, but there is more reticence as regards switching from the reference medicine, especially in the early years of their marketing. Even so, they have now reached values of more than 70% in almost all cases. In the case of infliximab, the first mAb to have a biosimilar medicine available, essentially all its consumption is currently the biosimilar. In the case of the biosimilar medicine of bevacizumab, the latest to reach the market, it has been the fastest to be introduced.

In the case of filgrastim, pegfilgrastim and erythropoietin, in contrast, the biosimilar medicines were incorporated immediately and have now completely replaced the reference medicines.

Somatropin reference medicine has not been subjected to an active recommendation to switch to a biosimilar medicine for financial criteria.

In the primary care setting, the penetration of biosimilar medicines over the past six years has been lower. The percentages of packages of biosimilar medicines consumed with respect to all medicines with the same active substance can be seen in table 4, figure 4 and figure 5.

Over this period, the use of biosimilars in primary care has increased slowly, with values still lower than 50% compared with the reference medicines in all cases. In the case of insulin glargine and enoxaparin, the use of the biosimilars has remained stable at around 10% compared with the reference medicines, whereas use of the follitropin and teriparatide biosimilars is increasing, although it still remains at around 50%.

The above results in a marked cost-saving, which in Navarre, in 2021, for the drugs with the highest impact in the hospital setting, can be estimated at approximately 9 million €, with bevacizumab making the greatest contribution to this value.

Table and figure 3. Consumption of biosimilars in Navarre 2017–2021.

Year	No. Packages	Amount (€)
2017	7,631	2,109,825
2018	16,010	3,871,665
2019	24,593	6,479,529
2020	32,409	11,198,701
2021	39,702	15,965,771

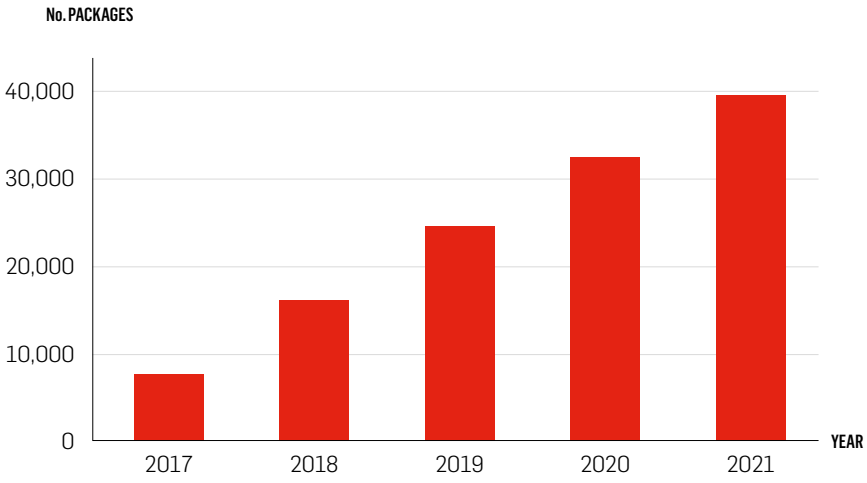


Table 4. Penetration in packages of biosimilars in the hospital setting in Navarre.

Active substance	2017	2018	2019	2020	2021
Filgrastim	100.0%	99.6%	100.0%	100.0%	100.0%
Infliximab	36.0%	44.3%	69.3%	92.2%	95.3%
Erythropoietin	31.0%	98.0%	98.0%	98.6%	98.8%
Somatropin	10.5%	.6%	18.4%	24.8%	26.1%
Insulin glargine	2.8%	0.7%	3.6%	3.8%	3.0%
Etanercept	2.1%	9.6%	45.3%	79.2%	76.7%
Rituximab	0.0%	0.0%	43.8%	74.8%	83.5%
Pegfilgrastim	—	0.0%	70.0%	100.0%	100.0%
Trastuzumab	—	0.0%	37.3%	45.8%	71.8%
Adalimumab	—	0.0%	0.3%	30.6%	51.7%
Bevacizumab	—	—	0.0%	6.4%	90.1%
Teriparatide	—	—	0.0%	0.0%	28.6%

Figure 4. Penetration in packages of biosimilar mAbs and related drugs in the hospital setting in Navarre.

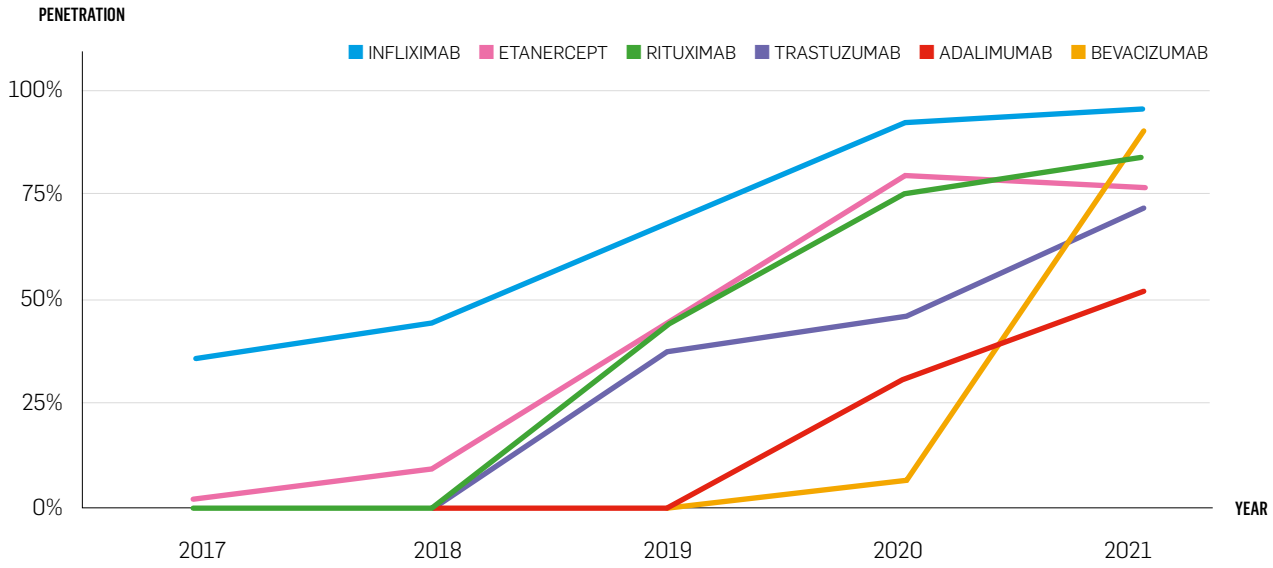


Figure 5. Penetration in packages of other biosimilars in the hospital setting in Navarre.

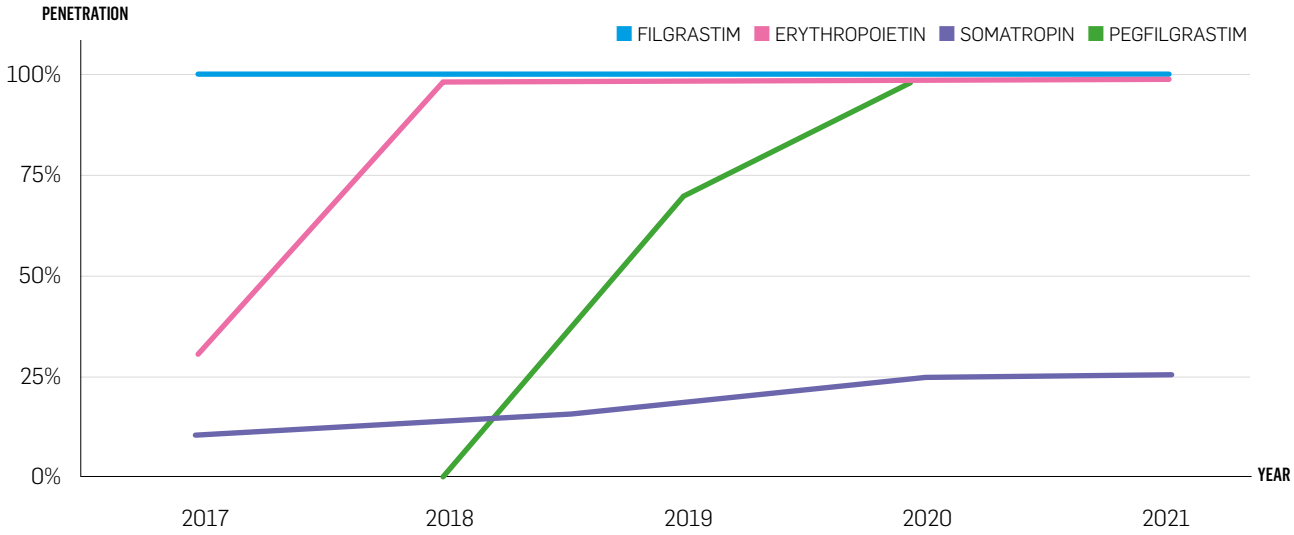


Table 5. Penetration in packages of biosimilars in the primary care setting in Navarre.

Active substance	2017	2018	2019	2020	2021
Insulin glargine	5.5 %	6.4 %	6.6 %	6.6 %	6.7 %
Follitropin	1.3 %	1.2 %	10.7 %	18.9 %	35.2 %
Enoxaparin	—	0.3 %	6.0 %	9.7 %	12.7 %
Teriparatide	—	—	14 %	21.8 %	44.1 %

Figure 6. Penetration in packages of biosimilars in the primary care setting in Navarre.

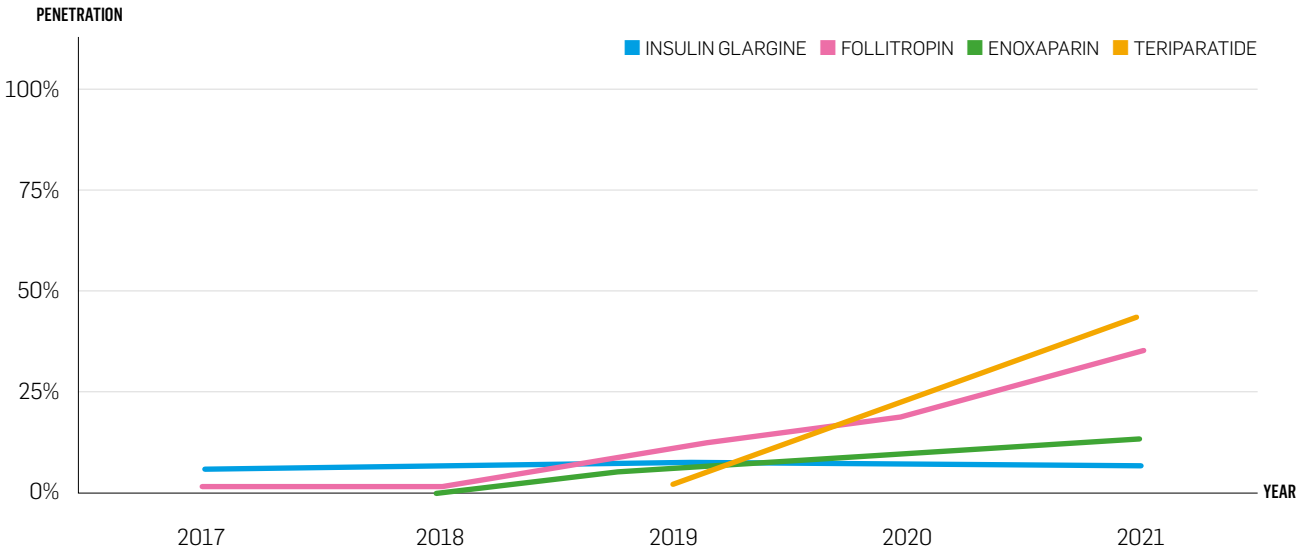


Table 6. Estimated saving with the use of the biosimilars with the greatest impact in the hospital setting in Navarre in 2021.

Active substance	Saving (€)
Bevacizumab	3,081,245
Infliximab	1,814,896
Adalimumab	1,252,320
Trastuzumab	1,098,176
Rituximab	918,694
Etanercept	702,038
Total	**8,867,369**

Annex 1
Summary of the characteristics and findings of the reviews identified

AUTHOR, YEAR	FUNDING AND CONFLICTS OF INTEREST (COI)	No. AND DESIGN OF STUDIES	DRUGS EVALUATED	CLINICAL AREAS OR INDICATIONS EVALUATED	EFFICACY/EFFECTIVENESS, SAFETY, IMMUNOGENICITY, COSTS	INTERPRETATION AND CONCLUSIONS
DIFFERENT DRUGS, DIFFERENT THERAPEUTIC AREAS						
Barbier et al., 2020[22]	KU Leuven (MABEL Fund). Authors with CoI with pharmaceutical companies	178 studies (n=140 non-randomised real-life studies, n=38 open extension studies of RCTs), n=6 multiple switching, n=3 switching between biosimilars	Somatropin, epoetin, filgrastim, insulin, anti-TNFs (adalimumab, etanercept, infliximab), follitropin, mAbs oncology (rituximab, trastuzumab).	Immune-mediated inflammatory diseases	Simple switching was not associated with any major efficacy, safety or immunogenicity issues. Some studies identified an increased discontinuation rate after switching, which was mainly attributed to a nocebo effect.	
Cohen et al., 2018[23]	No funding. Authors with CoI with pharmaceutical companies	90	Multiple drugs	Immune-mediated inflammatory diseases, CKD, growth alterations, neutropenia, cancer, healthy volunteers	No significant differences in ADAs after switching in comparison with patients who did not switch. No increase in ADs or loss of efficacy related to switching. Multiple switching did not result in significant differences in efficacy or safety. Two studies reported a loss of efficacy or increase in drop-out rates.	The risk of immunogenicity-related safety concerns or diminished efficacy is unchanged after switching from the reference medicine to the biosimilar.
Inotai et al., 2017[24]	Funded by Egis Pharmaceuticals PLC. Authors linked to Syreon Research Institute, which is funded by Egis Pharmaceuticals PLC.	58 (n=12 empirical papers, n=5 systematic reviews, n=41 non-empirical papers)	Multiple drugs	Multiple indications	No additional risk or negative clinical outcomes in patients switching to biosimilars.	Preventing the switch to biosimilars due to anticipated risks seems to be disproportional compared to the expected cost savings and/or improved patients access.
Liu et al., 2019[25]	Funded by AbbVie. Authors with CoI with AbbVie	54 (n=23 budget impact models, simulations, cost studies, n=26 cohort studies, n=3 national database analyses, n=1 interview, n=1 policy review)	Multiple drugs	Multiple indications	Increased healthcare resource utilization in patients with biosimilar non-medical switching	The overall economic impact of biosimilar medicines remains uncertain.
McKinnon et al., 2018[26]	Funded by Medicines Australia and pharmaceutical companies. Authors with CoI with pharmaceutical companies	57 (n=22 RCT, 1 non-RCT, n=34 observational)	Multiple drugs	Multiple indications	The majority of studies did not find statistically significant differences in efficacy. The majority of studies reported a similar safety profile.	There are evidence gaps around safety of switching.
Hillhouse et al., 2022[27]	Funded by AbbVie. Authors with CoI with pharmaceutical companies	49 (n=41 cohort studies, n=2 interviews, n=2 simulations, n=1 post-marketing study, n=3 database studies)	Multiple drugs	Multiple indications	An increased healthcare resource utilization and costs associated with non-medical switching was found when compared with the period prior to switching or with non-switched patients.	It is suggested that the expected overall saving due to the lower price of biosimilars may be reduced due to an increase in healthcare resource utilization and associated costs. The overall economic impact of these medicines in renal clinical practice is uncertain as the majority of studies only consider the cost of these medicines without taking into account other healthcare costs.
SPECIFIC DRUGS OR DRUG GROUPS, DIFFERENT THERAPEUTIC AREAS						
Bakalos, et al., 2019[28]	Medical writing support by F. Hoffmann-La Roche Ltd. The author is employed by F. Hoffmann-La Roche Ltd	14 observational	Infliximab (biosimilar: CT-P13)	Immune-mediated inflammatory diseases	78.6% of the studies reported a biosimilar discontinuation rate >10% (range: 12.2–28.2%). A lack of effect and AEs accounted for biosimilar discontinuation rates ranging from 1.4–28.1% of all patients. Infusion-related reactions and ADAs were infrequent, and no increase was identified upon switching.	The discontinuation rate after switching, which was higher than expected, may be attributed, in part, to a subjective disease worsening or subjective AEs, which may be indicative of a potential nocebo effect in switching studies.
Ebbers et al., 2019[29]	Funded by Biogen International GmbH. Authors with CoI with Biogen	31 (n=6 journal articles, n=2 journal letters, n=23 congress abstracts). *Naïve* patients and patients with switching	Etanercept (biosimilar: SB4)	Immune-mediated inflammatory diseases	The switch acceptance rate was 51.6–98%. Patient-support programs had a positive effect on acceptance. Disease activity was similar before and after switching (over a 3-month period). A retention rate of at least 75% was identified (up to 12 months of follow-up). The differences in discontinuation rate were attributed to possible differences in treatment practices, lack of clinician confidence and the nocebo effect. No new safety signals were identified.	In general, the experience with switching to the biosimilar was positive, with no loss of efficacy or detriment to safety or tolerability. The results with the biosimilar were similar to those for the reference medicine in naïve patients. The evidence shows that the biosimilar etanercept is as effective and safe as the reference medicine in both switched and naïve patients.
Reagan et al., 2019[30]	Funded by Janssen Pharmaceuticals. Authors with CoI with pharmaceutical companies	70 (n=13 RCT, n= 53 observational, n=4 case series/reports)	Infliximab (biosimilar: SB2, CT-P13, BOW015)	Immune-mediated inflammatory diseases	No significant risks associated with single switch identified.	The limitations include the fact that the studies available only report simple switching and the majority are observational studies with no control group. The evidence supports the efficacy and safety of simple switching between the reference medicine and biosimilar.
SPECIFIC DRUGS OR GROUPS OF DRUGS, DIFFERENT THERAPEUTIC AREAS						
García-Beloso et al., 2022[31]	No funding. Author with CoI with pharmaceutical company	21 (n=12 RCT, RCT extension studies, 9 observational). No naïve patients	Adalimumab (biosimilar: ABP501, SB5, FKB327, MSB11022, GP2017, PF-06410293, CTP17)	Chronic immune-mediated inflammatory diseases	The efficacy results in the switching groups were comparable to those obtained in the arms of continuous biosimilar and continuous reference adalimumab. No significant differences in treatment emergent AEs or ADAs or neutralising antibodies were observed among the three groups. Higher incidence of injection site pain in thee switching group.	Switching between reference adalimumab and biosimilars has no impact on efficacy, safety and immunogenicity in patients with rheumatoid arthritis, psoriasis or IBD. This finding is consistent for the different adalimumab biosimilars analysed. The higher incidence of injection pain observed upon switching groups in non-randomised studies may be due to a nocebo effect.
Laurat et al., 2020[32]	No funding or CoI	16 (n=1 RCT, n=5 observational) in patients switching from reference medicine to biosimilar 12 (n=9 RCT, n=3 observational) in patients naïve to the biosimilar	Infliximab (biosimilar: CTP-13)	Chronic immune-mediated inflammatory diseases	Frequency of ADAs in switched patients: 4.7%, 95% CI: 3.5–6.1% (inhetergeneity). Frequency of ADAs in patients naïve to the biosimilar: observational studies: 21.1%, 95% CI: 13.1–30.3% (heterogeneity); RCT: 30.7%, 95% CI: 18.2–44.9% (heterogeneity).	Immunogenicity was not favoured by non-medical switching to the biosimilar, but was associated with treatment discontinuation.
Liu et al., 2022[33,34]	Funded by AbbVie. Authors with CoI with AbbVie.	66 real-world studies (n=29 full-text articles, n=35 abstracts, n=2 letters to the editor).	Anti-TNF (infliximab, etanercept)	Gastroenterology, rheumatology	The annualized biosimilar discontinuation was 21% (95% CI: 18–25%). The annual switch back rate among switching participants was 14% (95% CI: 10–17%), and 62% (95% CI: 44–80%) among biosimilar discontinuers. The annualized incremental biosimilar discontinuation rate was 18% (95% CI: 4–31%).	Biosimilar discontinuation was found to be prevalent among patients who underwent non-medical switching from the reference medicine to the biosimilar. Switchback to the reference medicine was common following biosimilar discontinuation.
Mezones-Holguín et al., 2019[35]	Authors with CoI with pharmaceutical companies	5 (n=2 RCT, n=3 RCT open-label extension studies)	Infliximab (biosimilar: CTP-13, SB2)	Gastroenterology, rheumatology, dermatology	The two double-blind RCTs did not find differences in efficacy or safety between the group maintained with the reference medicine (IFX/ref/IFX/ref) (maintenance group) and the group of switching patients (IFX/ref/CTP-13) (interchangeability group). The three open-label extension studies did not find differences in efficacy or safety between the maintenance and interchangeability groups. The inclusion of biosimilars implied a saving of 5,784,780 (USD =5,330).	
Numan et al., 2018[36]	Funded by AbbVie. Authors with CoI with AbbVie.	91 (n=17 RCT, n= 74 real-world evidence studies)	Anti-TNF: Infliximab (biosimilar: CT-P13, SB2, BOW015) Adalimumab (biosimilar: ABP 501, BI 695501, GP2017, FKB327, CHS-1420) Etanercept (biosimilar: SB4, GP2015)	Immune-mediated inflammatory diseases	Discontinuation rates in RCT: 5–33% switching group vs 4–18% comparison group Discontinuation rate in real-world evidence studies with comparator group: Infliximab: 0–87% Etanercept: 8–17%	The evidence shows heterogeneity and inconclusiveness as regards the efficacy, safety and immunogenicity of switching. The safety and efficacy of switching from the reference anti-TNF medicine to the biosimilar has not yet been fully demonstrated. The decision to switch in patients with a good response should be taken with care and evaluated on a case-by-case basis.
INFLAMMATORY BOWEL DISEASE (IBD)						
Bernard et al., 2020[37]	Funded by Janssen Inc. Authors with CoI with pharmaceutical companies	49 studies (n=40 observational studies, n=3 RCT, n=1 case series)	Infliximab (biosimilar: CT-P13)	IBD	RCTs: -Efficacy: in general, no significant differences. -Safety: no significant differences. -Discontinuation at 52 weeks: 4% in group with reference medicine vs 4% in the switching group (n=1 study). -Immunogenicity: 1 study: 7% new ADAs in group with reference medicine vs 8% in the switching group. Remainder: no significant differences in ADAs.	It was concluded that non-medical switch is safe and effective.
Dipasquale et al., 2022[38]	No funding information. No CoI	9 (n=8 retrospective, n=1 prospective)	Infliximab (biosimilar: CT-P13)	IBD Paediatrics.	No significant differences in clinical response or remission rate were identified after induction or during maintenance with the biosimilar in comparison with the reference medicine (clinical response 88–90%, remission rate 67–68% with biosimilar). AEs with the biosimilar were mild, with upper respiratory tract infections being the most common. Switching to the biosimilar did not have a significant impact on immunogenicity.	
Gisbert et al. 2018[39]	No funding information. Authors with CoI with pharmaceutical companies	25 (n=9 retrospective, 16 prospective)	Infliximab (biosimilar: CT-P13)	IBD	Disease control (no worsening after switching) with the biosimilar was confirmed in the majority of patients (weighted mean 88%; 95% CI: 85–89%) No unexpected AEs were reported in any of the studies. Switching was not associated with immunogenicity concerns.	The risk of switching seems to be purely theoretical and are not supported by the (still limited) real-world clinical practice experience. Switching may be considered acceptable. In any case, switching should only be considered once the disease is well controlled with the reference medicine during a sufficient time.
INFLAMMATORY BOWEL DISEASE (IBD)						
Mitoiain et al., 2019[40]	Public funding. No CoI	29	Infliximab (biosimilar: CT-P13)	IBD	The biosimilar was found to be safe and equally efficient as the reference medicine for both induction and maintenance therapy, with no loss of response being found. Switching from the reference medicine to the biosimilar was noninferior to continuous biosimilar use. Switching from the reference medicine to the biosimilar did not affect the efficacy, safety or immunogenicity in comparison with continuous biosimilar use.	Switching is acceptable, although scientific and clinical evidence is lacking regarding reverse switching, multiple switching and cross-switching among biosimilars.
Solitano et al., 2020[41]	No funding. Authors with CoI with pharmaceutical companies	15 (n=7 retrospective, n=5 retrospective)	Infliximab (biosimilars: CT-P13, SB2) Adalimumab (biosimilars: BI 695501, Exemptia, SB5, ABP 501)	IBD	A high similarity between the reference medicines and biosimilars was found, with the efficacy, safety and immunogenicity of reference infliximab medicine and its biosimilar being comparable. The evidence regarding adalimumab biosimilars in IBD is limited.	Adoption of biosimilars in clinical practice represents a great opportunity from an economic point of view, reducing healthcare costs and increasing patients' access to effective biologic treatments.
Queiroz et al., 2020[42]	No funding. Author with CoI with pharmaceutical companies	30 observational	Infliximab (biosimilars: CT-P13, SB2)	IBD	The discontinuation rates were 8%, 14% and 21% at 6, 12 and 24 months, respectively. The main reasons for discontinuation were worsening of the disease (2%), remission (4%), loss of adherence (4%), AE (5%), loss of response (7%). The subjective symptoms that led to discontinuation of the biosimilar were infrequent.	The discontinuation rates following a switch to a biosimilar increased with time. It was not possible to confirm the nocebo effect as a reason for discontinuation.
RHEUMATOID ARTHRITIS (RA)						
Yoo et al., 2018[43]	No funding. Author with CoI with pharmaceutical companies	35 (n=17 RCT, extension studies, n=1 RCT, n=17 real-word observational studies)	Infliximab (biosimilars: CT-P13, SB2) Etanercept (biosimilar: GP2015, SB4) Adalimumab (biosimilar: ABP 501, BI 695501, SB5, FKB327, GP2017, CHS-1420) Rituximab (biosimilar: CT-P10, GP2013, BCD-020)	RA	Switching was safe and effective in the majority of studies. Real-world data showed a slightly lower retention rate for switched biosimilars. Most discontinued patients have shown no objective clinical or biological evidence supporting inefficacy, therefore this small difference in discontinuation might be associated with a possible nocebo effect or other confounding factors.	A fear of biosimilars or their immunogenicity is often exaggerated and is based on small studies and theoretical worries rather than on solid evidence.
ONCOLOGY						
Declerck et al., 2018[44]	No funding information. Authors with CoI with pharmaceutical companies	8 (n=5 randomised, n=3 non-randomised)	Rituximab (biosimilar: CT-P10, GP2013, PF- 05280586, BCD-020) trastuzumab (biosimilar: ABP 980)	Cancer, RA		The consequences of switching between the reference medicine and the biosimilar in the oncology setting are yet unknown.
SWITCHING BETWEEN BIOSIMILARS						
Allocati et al., 2022[45]	No funding information. No CoI	19 observational (n=10 cohort studies; n=8 single-arm studies; n=1 studies with historical control)	Switching between anti-TNF biosimilars (infliximab, adalimumab, etanercept)	Immune-mediated inflammatory diseases	Switching between one biosimilar and another and multiple switching is safe and effective in terms of disease activity, remission rate, loss of response, AEs and immunogenicity. Switching did not result in a change in immune response, exhibiting similar ADA levels.	
Cohen et al., 2022[46]	Funded by Novartis Pharma AG. Authors with CoI with pharmaceutical companies	23 Observational studies. Switching between biosimilars	Anti-TNF, rituximab	Immune-mediated inflammatory diseases, cancer	No reduction in effectiveness or increase in ADs was detected in biosimilar-to-biosimilar switching.	Biosimilar-to-biosimilar switching is considered to be safe and effective.
REVERSE SWITCHING						
Medsoom et al., 2022[47]	No funding. No CoI	37 (n=36 cohort studies, n=1 case series)	Anti-TNFs (etanercept, infliximab, adalimumab), multiple drugs	Gastroenterology, rheumatology, multiple indications	The weighted median cumulative incidence of retransitioning was 7.6% (95% CI: 6.8–17.2%). The incidence of retransitioning was lower when extra laboratory monitoring was performed (1.6% vs 8.1%).	Retransitioning was lower in studies including only patients with stable disease, in studies that did not offer the option of retransitioning at the introduction of the biosimilar, and in studies that implemented extra laboratory monitoring as part of the biosimilar-implementation strategy.
NOCEBO EFFECT						
Odinet et al., 2018[48]	No funding. No CoI	31 studies (n=4 double-blind RCT, n=27 open-label observational)	Infliximab, etanercept	Gastroenterology, rheumatology, dermatology, multiple diseases	The median discontinuation rate for any reason was 14.3% (range: 0-33.3%) in open-label studies vs 6.95% (range: 5.2–21.0%) in double-blinded studies. The discontinuation rate for AEs was 5.8% (range: 0–24.2%) in open-label studies vs 3.1% (range: 2.0–5.2%) in double-blinded studies, suggesting a nocebo effect. Subgroup analyses of ADA development and infusion reactions were similar in open-label and double-blinded studies. Infliximab: the discontinuation rates for any reason, for AEs and for lack of efficacy of the biosimilar were higher in open-label studies than in double-blinded studies. Etanercept: the discontinuation rate for any reason for the biosimilar was similar in open-label and double-blinded studies. The incidence of injection site reactions and discontinuation rate for AEs were higher in the double-blinded than in the open-label studies.	Current evidence is insufficient to confirm a biosimilar nocebo effect, although higher discontinuation rates in open-label studies support this theory.

ADA Anti-drug antibody
AE Adverse event
anti-TNF Anti-tumour necrosis factor
CoI Conflicts of interest
CI Confidence interval
CKD Chronic kidney disease
IBD Inflammatory bowel disease
IFX Infliximab
mAbs Monoclonal antibodies
RA Rheumatoid arthritis
RCT Randomised controlled trial

EXPAND VIEW

Annex 2

Biological medicine and biosimilar medicine

BIOLOGICAL MEDICINE AND BIOSIMILAR MEDICINE. WHO IS WHO?

Gobierno de Navarra · Nafarroako Gobernua · Agenda 2030

—What is a biological medicine and a biosimilar medicine?
Biological medicines are those obtained from living cells and organisms. A biosimilar is a medicine equivalent to another biological medicine that already exists.

—Is a biosimilar medicine the same as a generic medicine?
A generic medicine contains exactly the same active substance as the reference medicine. Biosimilar medicines are very similar versions of the reference medicines, although they are not identical. In both cases, the safety and efficacy are similar to those of the reference medicine.

—Is there any difference in quality, safety and efficacy between a reference medicine and a biosimilar medicine?
No, as a biosimilar medicine must meet the same quality, safety and efficacy standards as its reference medicine.

—If I start a biological treatment, is there any difference between doing so with the reference medicine or with a biosimilar in terms of quality, safety and efficacy?
No, as both medicines (reference and biosimilar) are biological medicines subjected to the same quality, efficacy and safety requirements by the regulatory agencies.

—Can a biological medicine be changed for another?
Yes. Your doctor, based on his/her own criteria and having informed you beforehand, may change one biological medicine for another with the same therapeutic goal.

—Must the doctor inform me of a change of biological medicine?
Yes. As is the case when starting any treatment, your doctor will inform you about the new treatment, its administration and any other relevant information.

Biosimilar medicines contribute to the sustainability of the public health system while maintaining treatment safety and efficacy.

—Is the safety of biosimilar medicines monitored once they are marketed?
Yes. Safety is controlled permanently by official drug regulatory agencies. That is why it is important for you to notify any adverse reaction to your doctor, pharmacist or nurse, or directly via https//www.ram.navarra.es If possible, save the package, as it is useful when notifying the adverse reaction.

—Are the side-effects of the reference medicine and the biosimilar medicine the same?
Yes. The possible side-effects of a reference biological medicine and its biosimilar are the same.

—What is the best way to obtain information about biosimilar medicines?
The main source of information should be your doctor, pharmacist or nurse.

+ OPEN

Conclusions

A biosimilar is a biological medicine that is very similar to another medicine already marketed in the European Union (EU) whose patent has expired.

In the case of biosimilars, studies evaluate the biosimilarity with the reference medicine.

To be considered biosimilar, the existence of clinically relevant differences must be ruled out.

Biotechnology-derived medicines are authorised by the EMA through a centralised procedure.

The extrapolation of indications is established by the EMA.

Interchange or switching refers to the change of a reference medicine for a biosimilar.

Interchange or switching is the competence of the EU Member States.

In Spain, the interchangeability is established by the Pharmacy and Therapeutics Commission at the hospitals and/or the Autonomous Community Commissions.

The EMA considers biosimilars approved in the EU to be interchangeable.

In general, the evidence available shows that switching does not significantly affect the efficacy, safety or immunogenicity.

In the reviews identified, discontinuation of biosimilars was mainly due to a potential nocebo effect and a lack of confidence on behalf of healthcare professionals.

In the Spanish hospital setting, a penetration of biosimilars of 67.6% has been estimated for 2021.

It is estimated that the introduction of biosimilars in Spain has represented a cost-saving of more than 5 billion € between 2009 and 2022.

Biosimilars contribute to the sustainability of the public health system while maintaining treatment efficacy and safety.

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