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Original

Consensus statement on the use of biosimilar drugs in immune-mediated diseases in Spain☆

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ABSTRACT

Objective: To improve knowledge about biosimilar medicines and to generate a consensus framework on their use.
Methods: Qualitative study. A multidisciplinary group of experts in biosimilar medicines was established (1 dermatologist, 1 hospital pharmacist, 1 rheumatologist, and 1 gastroenterologist) who defined the sections and topics of the document. A narrative literature review was performed in Medline to identify articles on biosimilar medicines. Systematic reviews, controlled, pre-clinical, clinical, and real-life studies were selected. Based on the results of the review, several general principles and recommendations were generated. The level of agreement was tested in a Delphi that was extended to 66 health professionals who voted from 1 (totally disagree) to 10 (totally agree). Agreement was defined if at least 70% of the participants voted ≥ 7.
Results: The literature review included 555 articles. A total of 10 general principles and recommendations were voted upon. All reached the level of agreement established. The document includes data on the main characteristics of biosimilar medicines (definition, development, approval, indication extrapolation, interchangeability, financing, and traceability); published evidence (biosimilarity, efficacy, effectiveness, safety, immunogenicity, efficiency, switch); barriers and facilitators to its use; and data on information for patients.
Conclusions: Authorized biosimilar medicines meet all the characteristics of quality, efficacy, and safety. They also significantly help improve patient access to biological therapies and contribute to health system sustainability.

Documento de consenso sobre los medicamentos biosimilares en enfermedades inmunomediadas en España

Palabras clave:
Medicamento biosimilar
Enfermedades inmunomediadas
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RESUMEN

Objetivo: Mejorar el nivel de conocimiento sobre los medicamentos biosimilares y generar un marco consensuado sobre su uso.
Métodos: Estudio cualitativo. Se seleccionó un grupo multidisciplinar de expertos en medicamentos biosimilares (una dermatóloga, un farmacéutico de hospital, un reumatólogo y un gastroenterólogo) que definieron los apartados y los temas del documento. Se realizó una revisión narrativa de la literatura en Medline para identificar artículos sobre los medicamentos biosimilares. Se seleccionaron revisiones sistemáticas de la literatura, estudios controlados pre-clínicos, clínicos y en vida real. Con esta información se generaron varios principios generales y recomendaciones. El grado de acuerdo con los mismos se estableció mediante un Delphi que se extendió a 66 profesionales de la salud que votaron de 1 (totalmente en desacuerdo) a 10 (totalmente de acuerdo). Se definió acuerdo si al menos el 70% de los participantes votaron ≥ 7.

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Resultados: La revisión de la literatura incluyó 555 artículos. Se votaron un total de 10 principios generales y recomendaciones. Todos alcanzaron el nivel de acuerdo establecido en el Delphi. El documento incluye datos sobre las características principales de los medicamentos biosimilares (definición, desarrollo, aprobación, extrapolación de indicaciones, intercambiabilidad, financiación y trazabilidad); sobre la evidencia publicada (biosimilitud, eficacia, efectividad, seguridad, inmunogenicidad, eficiencia, *switch*); sobre barreras y facilitadores a su uso, y datos sobre la información para pacientes.
Conclusiones: Los medicamentos biosimilares autorizados reúnen todas las características de calidad, eficacia y seguridad. Además, ayudan significativamente a mejorar el acceso de los pacientes a las terapias biológicas y contribuyen a la sostenibilidad de los sistemas sanitarios.

Introduction

In Spain, medicines are subject to strict regulation and control to ensure their safety and efficacy.

The process by which a traditional, chemically synthesised medicine is approved has been refined over the decades and now leaves little room for improvisation. However, the advent of biologics has been a major change, as neither manufacturers nor regulatory agencies have ever dealt with such structurally large and complex molecules. Moreover, unlike generic versions of traditional medicines, the possibility of copying the molecule of a biologic, once its patent has expired, is hampered by the need to develop an alternative manufacturing process, as the original process is protected by additional patents that have substantially longer validity.[1]

The large molecular size of biologics, combined with the variability associated with biological sources, means that the manufacturing model for conventional medicines is no longer applicable. Due to this natural variability of the biological source and each manufacturer's specific manufacturing process, there may be slight differences in composition between the biosimilar medicine and its reference product, just as there are differences between batches of the same biological reference medicine.[2]

There are currently more than 50 biosimilar medicines available in Spain, corresponding to 16 active ingredients, 4 of them for rheumatological, dermatological, and digestive tract immuno-mediated diseases: adalimumab (ADA), etanercept (ETN), infliximab (IFX), and rituximab (RTX). IFX was the first biosimilar medicine for this group of diseases and approved in 2015. Since then, biosimilar medicines have been widely used in Spain.[3]

However, data from a national survey suggest that the level of knowledge on many aspects (some very relevant) of biosimilar medicines, such as their development, rationale, access, or use in clinical practice, is very low.[4] Moreover, this study showed the great variability in their use in Spanish hospitals.[4] Therefore, the objectives of this study were to improve the knowledge and use of biosimilar medicines in immune-mediated diseases, and to create a consensus framework on their use. To this end, we undertook an extensive review of the literature and benefited from the opinion of a multidisciplinary group of experts. This document is intended as a reference for healthcare professionals involved in the management of patients with immune-mediated diseases using biosimilar medicines.

Methodology

Study design

Qualitative study. We followed the nominal group and Delphi methodology, with the help of a narrative literature review. The project was conducted in full compliance with the principles set out in the Declaration of Helsinki on medical research involving human subjects, in its latest version, and in accordance with the applicable regulations on good clinical practice.

Selection of participants and first nominal group meeting

First, a multidisciplinary group of four health professionals with extensive experience and knowledge of biosimilar medicines (a dermatologist, a hospital pharmacist, a rheumatologist, and a gastroenterologist) was selected. Following this, and with methodological help, the objectives, scope, users, and sections to be developed in the document were defined. These include:

1. Main characteristics of biosimilar medicinal products (definition, development, approval, extrapolation of indications, interchangeability, financing, and traceability).
2. Evidence (biosimilarity, efficacy, effectiveness, safety, immunogenicity, efficiency, switch).
3. Barriers to and facilitators for use.
4. Information for patients. On which the literature review was based.

Narrative literature review and preliminary recommendations

A narrative literature review was conducted with the help of an expert documentalist. Medline was interrogated using Pubmed's Clinical Queries tool and individual searches with controlled language (Mesh) and free-text terms (until July 2021). Our aim was to identify articles that analysed the main characteristics and use of biosimilar medicines in immune-mediated diseases in the specialties of rheumatology, dermatology, and gastroenterology. Systematic literature reviews, as well as preclinical development studies, randomised clinical trials (RCTs), and real-life studies were selected. Two reviewers independently selected articles (first by title and abstract, then after reading the full articles in detail) and collected data. Evidence and

Table 1
Delphi results.

#	General principles and recommendations	Mean	SD	Median	P25	P75	Min	Max	%≥ 7[a]
1	Biosimilars are medicines that are part of the therapeutic arsenal for immune-mediated diseases and access to them should be guaranteed	8.95	2.12	9	9	9	7	10	100%
2	Biosimilars are part of the strategy to ensure sustainable access to biological drugs and thus contribute to the sustainability of the system and access to innovative medicines	9.51	6.36	10	10	10	1	10	97%
3	Regulatory agencies approve a biosimilar medicine if it meets the same standards of quality, safety, and efficacy that apply to any other biological drug and if it has been demonstrated that any differences with the reference biological medicine do not affect the efficacy, safety, and quality of the biosimilar medicine	9.28	4.95	10	9	10	2	10	97%
4	There should be full transparency at all levels regarding biosimilar medicines (development, approval, prescribing, information, communication, etc.)	9.71	6.36	10	10	10	1	10	99%
5	Healthcare professionals involved in the use of biosimilars should have in-depth knowledge of biosimilar medicines, including development and approval conditions, key characteristics, and clinical evidence	9.27	5.66	10	9	10	1	10	97%
6	It is recommended that multidisciplinary and consensual structures and processes be established for the use of biosimilar medicines, adapted to the characteristics of the centre and available resources	9.21	6.36	10	9	10	1	10	97%
7	Active participation of healthcare professionals involved in the use of biosimilars is recommended in multidisciplinary structures and processes related to biosimilar medicines, such as pharmacy and therapeutics or biologics committees, or in the development of specific protocols	9.39	6.36	10	9	10	1	10	95%
8	Decisions on interchangeability should be explained to and agreed with the patient	8.44	6.36	9	8	10	1	10	86%
9	Patient information on biosimilar medicines is essential to promote adherence and avoid the nocebo effect	9.02	6.36	10	9	10	1	10	95%
10	It is recommended that potential barriers to the use of biosimilar medicines in routine practice be identified and actions implemented to break them down	9.20	5.66	10	9	10	1	10	95%

Max: maximum; Min: minimum; P25: 25th percentile; P75: 75th percentile; SD: standard deviation.
[a] Agreement was established if at least 70% of respondents voted ≥ 7 on a scale of 1 to 10.

results tables were generated. The 2011 Oxford scale was used to assess the quality of the studies.[5] With this information the coordinator generated a set of general principles and preliminary recommendations.

Second nominal group meeting

The results of the narrative literature review were presented and discussed at the second nominal group meeting, as well as the general principles and tentative recommendations. This resulted in the final recommendations, which were subjected to a Delphi process.

Delphi

The recommendations were voted on using the Delphi method to establish the level of consensus with the recommendations. This was done on-line, was anonymous, and was sent to 66 health professionals (medical specialists and hospital pharmacists). The level of agreement was rated by voting on a Likert scale from 1 (strongly disagree) to 10 (strongly agree). Agreement was established if at least 70% of the participants voted ≥7. Recommendations with a level of agreement below 70% were evaluated and, if appropriate, re-edited, and voted on in a second Delphi round. New recommendations were allowed for inclusion in the first Delphi round.

Editing the final document

The final document was drafted based on the literature review, the decisions of the nominal group, and the Delphi, and was circulated to the experts for final assessment and comments.

Results

Narrative literature review and Delphi

The review found more than 500 articles. With this information and the experts' opinion, a total of 10 general principles and recommendations were generated that reached a very high level of agreement (Table 1).

The experts consider biosimilar medicines to be part of the strategy to ensure sustainable access to biologic and other innovative medicines, thus contributing to the sustainability of the system. Access to them must therefore be guaranteed.

Furthermore, regulatory agencies must approve a biosimilar medicine only if it meets the same quality, safety, and efficacy standards that apply to other biologic drugs and once it has been demonstrated that any potential differences from the reference biological medicine do not affect these parameters.

It is therefore important that healthcare professionals involved in the use of biosimilar medicines are fully aware of their characteristics and participate in all the structures and processes related to them, such as pharmacy and therapeutics or biologics committees, or in the development of specific protocols.

The experts also highlight the role of the patient in the use of biosimilar medicines. For example, there is broad agreement that decisions on interchangeability should be explained to and agreed with the patient, and on the importance of the information provided to them.

Each of the sections assessed in the review and Delphi are explained in detail below.

Table 2
Main characteristics of biosimilar medicines.

#	Characteristic	Comments
1	Very similar to the reference medicine	• The biosimilar has physical, chemical, and biological properties that are very similar to the reference medicine
2	The variability of the biosimilar medicine is kept within strict limits	• All biological medicines (biosimilar and reference medicines) by their inherent nature have some degree of variability (differences in their composition) • Only a small margin of variability is allowed • This is achieved by a consistent manufacturing process, which ensures that all batches of the drug are of proven quality
3	No clinically significant differences from the reference medicinal product	• The clinical studies on which the approval of a biosimilar is based confirm that the differences will have no effect on safety and efficacy
4	The EMA follows very strict quality, safety, and efficacy standards for the approval of biosimilar medicines	• Biosimilar medicines must meet the same quality, safety and efficacy standards that apply to any other medicine in order to be approved

EMA: European Medicines Agency.

Table 3
Comparability process for a biosimilar medicine and its reference medicine.

#	Stage	Element evaluated
1	Physico-chemical comparison	• Physico-chemical tests using analytical techniques to ensure structural biosimilarity between the two medicines • The following attributes are analysed and compared: primary structure, higher order structures, content, purity (aggregates and fragments), isoforms (charge variants), glycosylation, etc.
2	Pre-clinical comparison	• In vitro, ex vivo and, if appropriate, in vivo studies to ensure equal biological/pharmacological activity • The most relevant biological functions for therapeutic action and toxicity are analysed and compared: binding to receptors or their biological targets, biological signal transduction, cell viability, etc.
3	Clinical comparison	• Bioequivalence studies, validated pharmacodynamic models, clinical trials, etc., to ensure the same pharmacokinetic, pharmacodynamic, and clinical behaviour • Efficacy, safety, immunogenicity, etc. are analysed and compared

Concepts, definitions, and development of biosimilar medicines

What is a biologic?

Biologics are medicines that contain one or more active ingredients produced or derived from a biological source of recombinant or extractive origin.[6] Their chemical composition varies widely and may include proteins, carbohydrates, nucleic acids, or combinations of these substances, or even consist of complete living organisms, such as cells or tissues.[6] Biological medicines can be obtained from multiple natural sources: human, animal or microorganisms.[7]

What is a biosimilar medicine?

The main characteristics of biosimilar medicines are listed in Table 2.

According to the European Medicines Agency (EMA), a biosimilar medicine is a biologic medicine that is very similar to another biologic medicine already on the market in the European Union (EU), referred to as the "reference medicinal product", with which it demonstrates biosimilarity.[7,8] Biosimilarity is the property of a medicinal product to show similarity and lack of significant differences in terms of quality, efficacy, and safety, to a reference medicinal product against which it has been compared.

Although the basic chemical structure of the biosimilar medicine may be identical to that of the reference medicine, when a protein is "translated", it undergoes additional modifications (glycosylation, sulphation, methylation, etc.). These modifications will be unique to each particular molecule, and therefore no two will be completely identical in a vial of any biosimilar medicine, and likewise there are differences between batches of the same reference biologic medicine. Therefore, each biological medicinal product has a certain set of critical quality attributes. These attributes are physicochemical and biological properties, some of which are more sensitive than others to variation, and include size, molecular charge, and glycosylation. All of these can be modified by changes in the process, e.g., in the type of cell used in the production process or by the culture conditions, pH temperature, etc.

Thus, during the manufacturing process of the biosimilar medicine, rigorous controls are always carried out to ensure that small differences do not affect the performance of the medicine or its safety. In other words, it is ensured that these differences are not clinically significant in terms of physico-chemistry, efficacy, or safety.[9]

How are biosimilar medicines approved?

All medicines produced by biotechnology must be authorised in the EU via the EMA through what is termed a "centralised procedure". This means that a single registration dossier is submitted to the EMA for evaluation by the EMA's scientific Committee for Medicinal Products for Human Use (CHMP) and for safety.[10]

When a biosimilar is submitted to the EMA for authorisation, the CHMP, and experts on EU biological medicines (Biologics Working Party) and biosimilar specialists (Biosimilar Medicinal Products Working Party) evaluate the studies submitted to assess whether it demonstrates biosimilarity.

Biosimilarity is demonstrated through a detailed comparison (Table 3). This is a direct comparison exercise between the biosimilar medicine and its reference medicine, which verifies that minor

Table 4
EMA regulatory documentation on biosimilars.

Topic	Document	Last updated
General principles	Guideline on similar biological medicine products	CHMP/437/04 Rev 1 October 2014 / April 2015
Quality	Guideline on similar biological medicinal product containing biotechnology-derived proteins as active substance: quality issues	CHMP/BWP/247713/2012 May 2014 / December 2014
Clinical and non-clinical studies	Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issue	CHMP/BMWP7/42832/2005 Rev 1 December 2014 / July 2015

EMA: European Medicines Agency.

differences in structure and function (physicochemical or biological activity) that may exist between the two do not affect the efficacy, safety, and quality of the biosimilar medicine.[6] These comparison studies are not only undertaken with biosimilar medicines, but also with reference medicines when they undergo modifications to their production processes or develop new galenic formulations. This comparative assessment is done on one or more sensitive indications, i.e., on the population where differences in clinical performance related to the biosimilar medicine can best be detected.

When the CHMP issues a favourable opinion on a biosimilar medicine, the EU approves the marketing of the medicine, which is automatically authorised throughout the EU. EPAR (European Public Assessment Report) reports are published on the EMA website with a summary of the scientific evidence supporting the authorisation of the biosimilar medicine.

In addition, due to the complexity and heterogeneity of biosimilar medicines, the EU has developed a specific regulatory framework based on different and more complex principles than for generic medicines. The directives and guidelines applicable to biosimilar medicines are also available on the EMA website and are summarised in Table 4.

In Spain, in addition to approval by the EMA, prior to marketing, a favourable resolution must be issued by the Ministry of Health, Consumer Affairs, and Social Welfare for funding from the Spanish National Health System and, where appropriate, the price must be set by the Interministerial Pricing Commission.

What is indication extrapolation?

Indication extrapolation is the extension of efficacy and safety data from a therapeutic indication for which the biosimilar medicine has been clinically tested to another therapeutic indication authorised for the reference medicine.

After successful completion of studies on the most sensitive indication(s), other indications for the reference medicinal product that the assessors consider appropriate in view of the results of the comparability study are extrapolated to the biosimilar. The extrapolation of data to other indications is always based on scientific data obtained in robust comparability studies.[7]

Extrapolation is a well-established scientific principle that has been used for many years in medicine, including for reference biological medicines.[11] Extrapolation is performed, for example, when a biological medicinal product with several authorised indications undergoes major changes in its manufacturing process (new manufacturing site, development of new galenic formulations, etc.). The potential effect of these changes on the clinical performance of the biological medicinal product is thoroughly assessed by comparability studies (in vitro and quality studies). If clinical studies are needed, they are conducted for a relevant indication and, based on all these data, extrapolation to other indications is usually possible.

What is interchangeability?

Interchangeability refers to the possibility of exchanging a medicine for another medicine that is expected to have the same clinical effect. This could mean exchanging a reference medicine for a biosimilar medicine (or vice versa), or replacing one biosimilar medicine with another.

This exchange can be done through a switch, where the change is made by decision of the prescriber, or substitution, where the change is made automatically at the pharmaceutical level without consulting the prescriber.

The EMA does not include recommendations on interchangeability with the reference medicinal product. Although they advise involving prescribers in the final decision, the joint position of the EMA and the European Commission is that Member States should decide whether biologic drugs and their respective biosimilars can be interchangeable.[12]

In Spain, order SCO/2874/2007 allows switching but prevents automatic substitution when there is no prior consensus with the prescriber,[13] in line with the position of countries' main rheumatology, dermatology, and oncology scientific societies.[9,14,15] However, this order refers to article 86 of Law 29/2006, of 26 July, on Guarantees and Rational Use of Medicines and Medical Devices, an article that falls under chapter IV, which refers to the rational use of medicines in pharmacies. Therefore, it does not apply to the hospital setting, where each Pharmacy and Therapeutics Committee (PTC) establishes whether a biosimilar can be exchanged and the criteria to be applied by consensus of all stakeholders (doctors, hospital pharmacists, primary care pharmacists, healthcare managers, and patients). Thus, exchange at the hospital level is allowed if it has been approved by the hospital PTCs, the regional committees, and the physician who is represented on these committees.[16]

How are biosimilar medicines funded?

In general, the decision on public funding of medicines goes hand in hand with their evaluation. Biosimilar medicines are no exception and follow the same economic evaluation guidelines as other biological medicines. With regard to the of funding medicines, there are multiple factors that can influence how they are priced by the authorities (incremental clinical effectiveness, cost-effectiveness and budgetary impact, burden of disease, and unmet medical need, size of the target population, domestic reference prices, international reference prices, cost of production, innovative nature of the product, ethical and equity considerations, contribution to GDP, and lobbying). These factors also apply to some extent to biosimilar medicines, although

price referencing them to the reference medicines is a major element.

What is traceability?

Traceability is defined as the ability to trace and follow a medicine through all stages of production, distribution, and use. Traceability, as a mechanism for tracking a medicine throughout its "lifetime", has been widely recognised as a fundamental element of patient safety.

Another important requirement for biosimilar medicines to ensure correct safety monitoring is the traceability of both their prescription and their administration to patients.

Evidence on biosimilar medicines

It is important to note first of all that while the objective of RCTs on the original biologics is to demonstrate clinical benefit and safety in patients, the objective of RCTs on biosimilar medicines is to exclude clinically relevant product-specific differences (non-inferiority studies).[8,17–22] However, we now also have a great deal of published real-life data.[23–26]

Below, we summarise the main evidence on the use of approved biosimilar medicines for immune-mediated diseases of rheumatological, dermatological, and digestive tract origin. More specifically, on biosimilar IFX, ADA, ETN, and RTX. Additional material shows a summary of the RCTs, the approved indications, the outcome variables used, and whether the switch has been studied.

Efficacy, effectiveness, immunogenicity, and safety

The efficacy of biosimilar medicines in immune-mediated diseases has been extensively demonstrated in RCTs and reported in several systematic reviews and meta-analyses.[17–21] These studies have shown that biosimilar medicines are very similar to reference drugs in terms of structure, physicochemical and biological properties, pharmacokinetics, efficacy, safety, and immunogenicity. For example, in patients with rheumatoid arthritis, no statistically significant differences have been found in ACR20, ACR50, or ACR70 at 12, 24, and 52 weeks between biosimilars and reference drugs, or in the rate of serious adverse events.[17–19] Neither have they been found in spondyloarthritis, including psoriatic arthritis.[20,21] However, their bioequivalence, efficacy, and safety have also been demonstrated in patients with cutaneous psoriasis.[22]

In inflammatory bowel disease, multiple observational studies have demonstrated the effectiveness and safety of IFX and biosimilar ADA.[23,24]

Similarly, data from observational studies in other immune-mediated diseases have been published with results in line with those obtained in RCTs.[25,26]

Efficiency

The impact on pharmaceutical spending as a result of biological drugs coming to the market is significant and growing.[27,28] Their unquestionable clinical value is accompanied by a price that is usually higher than that of chemically synthesised drugs. The introduction of biosimilar medicines has led to significant savings. One of the most important national studies was conducted by the Weber Foundation in 2017.[29] This analysis estimated a retrospective saving of 478 million euros between 2009 and 2016, which could be increased by 1,965 million euros from 2017 to 2020, according to their prospective analysis, with the use of biosimilars.

In this regard, it should be noted that the European regulatory framework is designed to promote and accelerate market access for biosimilar medicines. The aim is to promote competition in the market, contain pharmaceutical expenditure, and improve access to biological and other innovative medicines.

Switching from a reference biological medicine to a biosimilar medicine

In relation to switching, the NOR-SWITCH non-inferiority RCT, conducted in nearly 500 patients with various immune-mediated diseases, demonstrated that switching from the original IFX to the biosimilar CT-P13 is not inferior to continued treatment with the original drug in terms of efficacy, safety, and immunogenicity.[30,31] In this RCT, patients were given stable treatment with IFX for at least six months and then approximately half of them switched to the IFX biosimilar. The data show that efficacy and safety were comparable between groups, with a non-inferiority margin of 15%.

Published observational studies on switching show similar results in the different immune-mediated diseases.[32,33]

The use of biosimilar medicines in Spain

Barriers to and facilitators for the use of biosimilars

A nationally published survey concluded that many professionals are relatively cautious about using biosimilars in clinical practice.[4] The main barriers to the use of biosimilar medicines found in this survey, as in others conducted in neighbouring countries,[27,34–40] include lack of confidence, knowledge, or experience in the use of these medicines.

Furthermore, the survey showed great variability at hospital level in the management of biosimilar medicines (access, protocols, etc.).[4]

On the other hand, the main facilitators for their use are access to evidence (clinical trials and real-life empirical data) on availability, efficacy, safety, and interchangeability, together with the guidance provided by scientific societies, the opinion of relevant colleagues, and the development of local protocols.[4]

Patient information

Patient information and shared decision-making are essential to promote adherence and avoid the nocebo effect with the use of biosimilar medicines.[41] Studies have shown that their doctors, and other healthcare professionals, such as nurses and pharmacists, are the main source of information for patients, and that they want to be involved in decisions concerning their health.[42,43]

In this regard, with the use of biosimilar medicines, it is recommended that the main characteristics, safety, and suitability of the biosimilar medicine, as well as any potential changes throughout the course of treatment should be explained in detail. It is also advisable to involve patients in the pharmaceutical expenditure and the contribution of these medicines to the sustainability of the system.

There are now specific guidelines for patients,[44,45] and educational material (included in patient support programmes), a home delivery service, tele-pharmacy/tele-assistance, or counselling in patient associations.

Research Agenda

Table 5 summarises a proposal for potential future lines of work with the use of biosimilars.

Table 5
Research Agenda with the use of biosimilar medicines.

#	Proposed
1	Long-term, real-life studies in all indications
2	Biologics committee in hospitals: standardisation of structure, procedures, functions, protocols, etc.
3	Switch: definition of patient profile
4	Development of educational programmes for healthcare professionals
5	Development of patient support programmes

Discussion

Prior to the present work, our group examined the variability in the use of biosimilars to treat immune-mediated diseases in Spain.[4] This study found that the level of knowledge of rheumatologists, dermatologists, gastroenterologists, and hospital pharmacists about the key features of biosimilars and the regulatory framework governing them is insufficient, especially considering that most participants have been using biosimilar medicines for many years and have access to empirical data and information published by regulatory bodies.[7,46–54] There was also great variability in the management of these medicines in Spanish hospitals.

In this document, we have described in detail the most relevant aspects of biosimilar medicines. In addition, a group of experts generated a series of general principles and recommendations, endorsed in a Delphi process, which can serve as a framework for the use of biosimilar medicines. In this regard, we would like to highlight several of the messages generated. Firstly, we would like to comment on the recognition of biosimilar medicines as contributing to the sustainability of the system and access to innovative therapies, as reflected in various studies.[27–29] The experts also highlight that the requirements of regulatory agencies for approving these medicines are very demanding and rigorous, which guarantees the safety of their use in daily practice. Currently, authorised biosimilar medicines meet all the characteristics of quality, efficacy, and safety.[6,7,10] In addition to the evidence evaluated for their approval by regulatory agencies through RCTs, medium- and long-term real-life data continue to be published that support the use of these medicines.[17–26] Therefore, the experts consider it essential that healthcare professionals involved in the use of biosimilar medicines have up-to-date and comprehensive knowledge of the characteristics of these medicines, participate in structures and processes related to them, and inform patients in detail.

We are convinced that this article will make a very positive contribution to improving the level of knowledge and, secondarily, the use of biosimilar medicines. But we also believe that further work is required in the field of biosimilar medicines to reduce variability in clinical practice.

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Authors' contribution

Emilio Monte-Boquet contributed to the study design, analysis, and interpretation of the data, critically reviewed the article, and approved the version for publication. Ángeles Florez, Guillermo José Alcaín Martínez, and Agustí Sellas participated in the analysis and interpretation of the data, critically reviewed the article, and approved the version for publication.

Conflict of interests

GA has participated in training and consultancy activities with Fresenius, Nestlé, AbbVie, Janssen, Ferring, Pfizer, Tilots, and Galapagos. AF has conducted clinical trials and acted as speaker and consultant for AbbVie, Almirall, Amgen, Celgene, Janssen, Kyowa Kirin, Leo-Pharma, Lilly, Novartis, Pfizer, Roche Farma, Sanofi, Sun Pharma, Takeda, and UCB Pharma. The remaining authors have no conflict of interest to declare.

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Appendix A Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.reumae.2022.12.004.

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