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Biosimilars for Psoriasis: Worldwide Overview of Regulatory Guidelines, Uptake and
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What's already known about this topic?

- The introduction of biosimilars for inflammatory diseases has become a fast evolving field.
- Development of biosimilars is anticipated to increase access to biologic drugs and relieve part of the economic burden on health systems worldwide by providing lower cost medications.

What does this study add?

- The current article describes the uptake of biosimilars for patients with psoriasis in various countries.
- There are substantial differences in biosimilar regulatory strategies and market access for biosimilars around the world.
- The International Psoriasis Council advocates that dermatologists take an active role in the development of biosimilar prescribing policies worldwide.

Abstract

The introduction of biologic drugs for the treatment of patients with psoriasis has revolutionized treatment paradigms and enabled numerous patients to achieve disease control with an acceptable safety profile. However, the high cost of biologics limits access to these medications for the majority of patients worldwide. In recent years, the introduction of biosimilars for inflammatory diseases has become a fast evolving field. The future use of biosimilars offers the potential for decreased cost and increased access to biologic drugs for patients with psoriasis. For their approval, different regulatory agencies use highly variable methods for definition, production, approval, marketing, and post-marketing surveillance of biosimilars. Due to potential interchangeability between biologics and biosimilars, traceability and pharmacovigilance are required to collect accurate data about adverse events in psoriasis patients; spontaneous reporting, registries, and use of "big data" should facilitate this process on a global basis. The current article describes biosimilar regulatory guidelines and examples of biosimilar uptake in

clinical practice in several countries around the world. As it is apparent that biologic treatment decisions may become more physician-independent, the International Psoriasis Council recommends that dermatologists should take an active role in the development of biosimilar prescribing policies with their respective healthcare settings and governmental agencies.

Keywords: psoriasis, biosimilars, biopharmaceuticals, biologics, clinical practice, dermatology

Introduction

Biosimilars are drugs that are highly similar to an original marketed biologic product.^{1,2} One of the most persistent problems related to biologic prescribing and use for psoriasis patients has been the high cost of these products.³ Biologic cost limits access to these life-changing drugs, often to individuals who most need them. Under-treatment of moderate-to-severe psoriasis has been well documented for many years within the dermatology community.⁴ The signature promise of biosimilars is that they will decrease cost and increase access to biologic drugs for individuals who suffer from psoriasis, improving the larger problem of under-treatment of this disease.⁵

Although leading organizations in the dermatology community have produced initial guidelines regarding biosimilars, dermatologists require the most current information in this rapidly evolving field.^{6,7} Individual countries and regulatory agencies are taking different standpoints on the definition, production, approval, and marketing of biosimilars. This article, written by members of the International Psoriasis Council, is the third paper in a series of reviews on biosimilars.^{1,2,8,9} Herein, we describe regulatory perspectives and concerns of biosimilars that may impact daily medical practice for dermatologists throughout the world, including monitoring of safety, traceability, cost, and physician clinical decision making.

Current Concerns for Dermatologists

Post-marketing Safety Issues for Biosimilars

Post-marketing safety is essential when introducing new biosimilar drugs into the market. Pharmacovigilance is the process and science of monitoring the safety of drugs, and taking action to reduce the risks and to increase the benefits of drugs.¹⁰ *The IPC suggests that registries of patients treated with biosimilars be established, since no long-term efficacy and safety psoriasis studies are performed for biosimilars prior to their approvals.*² Another important issue regarding pharmacovigilance is traceability. Traceability means the ability to reliably identify the drug, its producer, and its manufacturing history (e.g., lot number). *The IPC suggests that each biosimilar name be easily distinguishable from its biologic counterpart by a unique identifier.*^{11,12} The FDA released a biosimilar naming guidance in January 2017, directing the attachment of a four letter meaningless suffix to the non-proprietary name to biologics and biosimilars to distinguish them from each other.

Cost Considerations for Use of Biosimilars and Physician Choice

As it is for originator biologics, we anticipate that the cost of biosimilars will be a major issue in the future. Although generic versions of small molecule drugs are up to 90% less expensive than brand-name products, the cost-savings for biosimilars are expected be reduced to only 20-30% of the original product price.¹³ The relatively modest cost reduction reflects the complex nature of the manufacturing process for biosimilars,¹ which are more costly to produce when compared to traditional chemical compounds. This smaller price difference will likely make it easier for manufacturers of brand-name biologics to compete with biosimilars. Nevertheless, the overall market for biologics is so large that the absolute economic savings due to biosimilars may still be significant. *Regardless of what the actual pricing of biosimilar drugs will be in the future, the IPC suggests that the cost of biosimilars should be low enough to genuinely improve access of these drugs to psoriasis patients worldwide who may not otherwise be able to afford them.*

Another substantial problem with the introduction of biosimilars into daily practice is that biologic treatment decisions may become more and more physician-independent. *The IPC recommends that dermatologists should be notified prior to any originator or biosimilar drug substitution being made; dermatologists should be given explicit authority to override any suggested substitutions.* The physician and patient should make the decision whether an

originator biologic should be substituted with a biosimilar after reviewing safety, efficacy, and cost considerations.

Biosimilar Use in Different Clinical Settings Worldwide

Australia

In Australia, the Therapeutic Goods Administration (TGA), the agency responsible for medication approvals,¹⁴ has defined a biosimilar medicine as a version of a registered biological medicine with similar physicochemical, biological, immunological, safety, and efficacy characteristics,¹⁵ which may be registered following performance of laboratory and clinical studies to demonstrate comparability. The TGA has adopted a number of European guidelines specific to biosimilar medicines¹⁶⁻²¹ as well as the ICH guidelines on the assessment of comparability.²² For a biosimilar to be registered in Australia, the reference medicine must be a biological medicine that has been registered and marketed in Australia for a substantial period of time and have a volume of marketed use, so that there is likely to be a substantial body of acceptable data regarding the safety and efficacy for the approved indications.¹⁵

The Pharmaceutical Benefits Advisory Committee (PBAC) is an independent expert body appointed by the Australian Government whose primary role is to recommend new medicines for listing on the Pharmaceutical Benefits Scheme (PBS).²³ In 2015, the PBAC advised that biosimilar products would be suitable for substitution at the pharmacy level, where the data are supportive of this conclusion. The PBAC considered that this would be the Committee's default position.²⁴ The PBAC decision is in contrast to 'Guiding principles for the governance of biological and biosimilar medicines in Australian Hospitals' produced by the Council of Australian Therapeutic Advisory Groups in May 2015,²⁵ which includes the recommendations: biologics/biosimilars should be prescribed by both the active ingredient name and the brand name; a biologic is not interchangeable with its biosimilars at dispensing and should only be substituted with the prescribers knowledge and consent; patients should be fully informed when receiving treatment with a biologics/biosimilar; and switching between a biologic and its biosimilars should be in accordance with a drug and therapeutics committee-approved treatment protocol that includes a monitoring plan.

Brazil^{26,27}

There is currently no set of universal guidelines for biosimilar use in Latin America, where approval and regulatory status vary immensely among different countries.²⁸ In Argentina, Brazil, Chile, Cuba, Mexico, and Venezuela, regulations for biosimilars have been enacted. In other countries, including Bolivia, Ecuador, and most of the Central American countries, no regulations have been provided so far.²⁹ In Brazil, regulations follow two different systems: comparability, where comparative data are required at all approval stages, and an individual development process, in which certain requirements of comparative data may be omitted.³⁰ A recent survey among 200 rheumatologists in Brazil evaluated specific medical aspects related to biosimilar use and pointed out major concerns related to the approval of biosimilars, which include limitation of bioequivalence tests, safety matters, and establishment of bioefficacy.³¹

Canada

In Canada, the Biologics and Genetic Therapies Directorate (BGTD) regulates biologic products under divisions of the Food and Drug Regulations of Health Canada.³² Subsequent entry biologics (SEBs) are subject to all the current regulatory requirements for biologics, and manufacturers are required to file a New Drug Submission (NDS) for review to receive market authorization. The extent of the clinical data required may be different from that required for the innovator's product,³² however, required clinical data are not well defined. Submission requirements for SEBs are determined on a case-by-case basis and include many important aspects as would be expected by an innovator drug application. An extensive document serving as an administrative instrument was published under the authority of the Minister of Health from the Health Products and Food Branch, entitled: "Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs)" in 2010.³³ One SEB of infliximab has been approved and extrapolated to the clinical indication of psoriasis despite no clinical studies in plaque psoriasis or psoriatic arthritis. Studies were performed in a rheumatoid arthritis and ankylosing spondylitis patient population. Initially, infliximab SEB were not approved for extrapolation to inflammatory bowel disease. Nevertheless, Health Canada later reversed its decision and approved infliximab SEB for inflammatory bowel disease.

Chile

The Chilean regulation regarding biotechnological products, including biosimilars, was enacted on August 24th, 2014. This regulation defines a biosimilar drug, outlines comparability rules, and discusses indication extrapolation. This regulation also allows for interchangeability, but only for medical reasons after approval by both the physician and patient. Remsima (Celltrion lab, Korea), a biosimilar of Remicade, was introduced in Chile in December 2013. The pharmaceutical company presented studies for rheumatoid arthritis and ankylosing spondylitis to Chilean authorities. Although Remsima was requested to be approved in Crohn's disease, the ISP (Public Health Institute, Chilean regulating authority for drugs) approved Remsima only for rheumatoid arthritis and ankylosing spondylitis in adults. There have been attempts to use Remsima in other diseases, with physician opposition. The price of Remsima is approximately 20% less than Remicade. There are currently no approved indications for Remsima in dermatology in Chile.

Denmark

In Nordic countries, all citizens have free, equal, and universal healthcare access. In Denmark, there are treatment guidelines for use of biologics in psoriasis, which should be followed regarding the use and choice of first and second line biologic treatment. The biosimilar medications Remsima, Benepali and Inflectra are available in Denmark. All psoriasis patients treated with Remicade (infliximab) were required to be switched to Remsima (infliximab biosimilar) as of June 2015. This was also the case for all the other infliximab indications. Benepali, a biosimilar etanercept, has been available since May 1, 2016, and all patients above the age of 18 treated with Enbrel have been switched to Benepali. After some uncertainty, particularly in the beginning among patients switched from originator product to a biosimilar, the process has been without problems. It is not mandatory to use a biosimilar before other new generation biologics for the treatment of psoriasis. Interchangeability (substitution), without the agreement of the prescriber is not obligatory.

India^{34,35}

Biologic drugs are expensive, and hence are not covered by insurance for psoriasis patients in India. There are a few government agencies in India that reimburse the cost of a biologic (e.g., the Central Government Health Scheme for government employees). Therefore, biosimilars, with the promise of lower costs have a substantial potential impact in India. Regulations and guidelines regarding the use of biosimilars, however, have yet to be enacted in India, neither by the government nor by the Indian Academy of Dermatology Venereology and Leprology. Despite this, the drug regulator of India has approved a few biosimilar drugs. Proof of biosimilarity is required by trials comparing the drug with its original biologic compound in an Indian setting, especially with regards to safety. Pharmacovigilance is performed by reports to the drug regulator. Exemptia (Zydus Cadilla labs), a copy of adalimumab, was approved for psoriatic arthritis in 2014 based on comparative trials and molecular fingerprinting. It has recently been approved for adult and pediatric (children age 8 and above) patients with plaque psoriasis by extrapolation of the data from psoriatic arthritis trials. The proposed biosimilar products Infilimab (Ranbaxy Labs), a copy of infliximab, and Etacept (Cipla Labs), a copy of etanercept, are under development, with no trials for these two drugs yet to be published.

Israel^{36,37}

In April 2014, the Ministry of Health published guidance for registration and use of biosimilar drugs in Israel. Biosimilar drugs may be registered in Israel only if the registration file includes data that demonstrate similarity with the reference drug, with no significant differences in the quality, safety, and efficacy between the biosimilar and the original drug. Substitution by a medical institution may be performed only at the start of drug use, but not after the drug is already in use. In Israel, for surveillance purposes, biosimilar drugs are labeled in a way that differentiates them from the original drug; pharmacovigilance is performed in a proactive way by the drug company that registers the biosimilar drug. Indication extrapolation is only allowed when the mode of action of the biosimilar and the original drug are identical. Remsima (manufactured by Celltrion Inc., South Korea) is expected to be launched in Israel shortly.

Italy

The registration of biosimilars in Italy is dependent on centralized registration at the European level by the European Medicines Agency (EMA). When central registration occurs, the price and reimbursement policies are then negotiated between the Italian Drug Agency (Agenzia Italiana del Farmaco, AIFA) and the manufacturer. According to rules defined by the Interministerial Economic Planning Committee (Comitato interministeriale per la programmazione economica, CIPE), negotiations should ensure a price reduction of at least 20% compared to the price of the originator. In accordance with European legislation, the Italian legislation considers biologic medications similar, but not identical, to originators, and are excluded from the procedures of automatic substitution that apply to nonbiologic generics. Decisions concerning substitution are made on a clinical basis and are left to treating physicians. Despite such principles, several Italian regions have implemented actions to promote substitution of originators by biosimilars and to favor selection of biosimilars, rather than originator biologics, at treatment onset. No national safety registry has been activated by AIFA to monitor biosimilars, but several registries have been started by scientific societies. Compared to other countries, the penetration of biosimilars in the Italian market has been limited. For example, biosimilar uptake of Epoetin is about 20% of the overall use, as compared to 53% in Germany and Sweden. There are also variations among Italian regions, with higher uptake in northern regions and lower uptake in southern regions of the country.

The Netherlands

Currently, the biosimilars Inflectra and Remsima have been approved for the same treatment indications as the originator product infliximab (Remicade). A biosimilar for etanercept, Benepali, has recently been approved for the same treatment indications as Enbrel. The Netherlands Society for Dermatology and Venereology requests studies in psoriasis to show that the biosimilar medicines are similar to reference products with respect to quality, safety and efficacy. There are no objections to the registered biosimilar as a new drug launch. To enable pharmacovigilance, the particular drug must be clearly identified via a specific brand name and batch number, and patients must be followed in a registry. Substitution of an originator biologic with a biosimilar is not recommended for patients who are responding well to an original biologic. The decision to switch to a biosimilar is restricted to the physician, in close

consultation with the patient. For example, a switch to a biosimilar may be considered after a biologic holiday (e.g. treatment interruption for 6 months or longer).

Norway

The Norwegian government has previously announced that biosimilar drugs should be used interchangeably; however, after complaints over this policy, a large controlled trial with infliximab (The NOR-SWITCH Study), fully sponsored by the Norwegian government, has been initiated in patients with psoriasis, rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, and Crohn's disease to assess the safety and feasibility of interchanging originator biologics and biosimilars. The study results demonstrated no significant effect in efficacy, immunogenicity, or adverse events in patients switched from the originator Remicade to the biosimilar Inflectra^{3,38}.

Spain³⁹

All biologics are currently considered in Spain as hospital drugs and can only be prescribed by hospital-affiliated dermatologists. In October 2015, Remicade, Inflectra, and Remsima were all included in a set (code H104) with a reference price of 402.21€ per 100 mg vial. Official reference pricing of drugs is decided by the Inter-Departmental Commission, with representatives of the Autonomic Health Systems. When the final payer is the National Health System (or any of the Autonomic Health Systems that integrate it), the official reimbursement price tag (Precio de Venta de Laboratorio) is reduced by decree: 7.5-15% discount.^{40,41} Every new indication of a given drug that might expand the target population leads to a renegotiation of the reference price. Further discounts can be obtained following tenders by Autonomous Communities' Health Authorities or final buyers (Hospital Pharmacies). On the other hand, the Autonomous Health authorities are pushing forward with forfait reimbursement of anti-inflammatory biologics to chartered Hospitals (namely, a fixed amount per patient-month, which varies according to the indication/specialty, currently being 866 €/month for Dermatology, which is lower for Rheumatology and higher for Gastroenterology).

Biosimilars will likely only be used for initiation of new treatments; substitution of biologic drugs cannot be performed automatically by the (hospital) pharmacy, but requires a medical

prescription.⁴² Thus, biosimilars and originators can be interchanged only with express authorization and under the responsibility of the prescribing physician (or according to Hospital regulations), but the tender may result in only one representative of the H104 group being available at a given Hospital or Autonomous Community.

United Kingdom⁴³⁻⁴⁵

In the UK, biosimilar medicines are approved by the European Commission through a centralized procedure, which is overseen by the European Medicines Agency.^{46,47} In 2008, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) issued guidance that recommended doctors should prescribe biologic medicines by brand name to *ensure that “automatic substitution of a biosimilar product does not occur when the medicine is dispensed by a pharmacist”*.^{48,49}

EU pharmacovigilance legislation mandates that all new biologic/biosimilar medicines approved after the January 1, 2011 be subject to additional safety monitoring for up to five years.⁵⁰ The MHRA,⁵¹ in accordance with EU legislation in July 2012,⁵² have recommended that documentation of brand name and batch number should be used to ensure accurate tracking, reporting, and analysis of suspected adverse reactions.⁴⁷

UK regulators consider extrapolation of indications on a case-by-case basis, with approval supported by post-authorization monitoring and pharmacovigilance of the biosimilar in clinical use.⁵³ The first infliximab biosimilars (Remsima, Celltrion/Napp and Inflectra, Hospira Biologics) were licensed and launched in February, 2015 for use in the UK.^{54,55} More recently, an etanercept biosimilar (Benepali, Biogen) was launched for use in rheumatoid arthritis, psoriasis, psoriatic arthritis, and ankylosing spondylitis. An adalimumab biosimilar (ABP 501, Amgen) is likely to be available soon.

United States

Utilizing the “biosimilar pathway,” less clinical data are needed for Food and Drug Administration (FDA) approval of biosimilar drugs for psoriasis when compared to approvals for originator drugs.^{56,57} An infliximab biosimilar (Inflectra (infliximab-dyyb); Celltrion) was

approved by the Food and Drug Administration for use in psoriasis and other immune-mediated conditions in April 2016 and was launched at the end of 2016.⁵⁸ Celltrion did not seek an interchangeability designation during the approval process. Thus, Inflectra cannot be substituted for Remicade within the US. In August 2016, the FDA approved Erelzi (etanercept-szzs), a biosimilar to Enbrel® (etanercept), for multiple inflammatory diseases.⁵⁹ In July 2016, a panel of FDA advisers voted 26-0 for approval of Amgen's adalimumab biosimilar drug ABP 501 to treat seven chronic inflammatory conditions, including psoriasis.⁶⁰ In September 2016, FDA approval was granted for Amjevita (adalimumab-atto) as an adalimumab biosimilar to Humira for multiple inflammatory conditions, including psoriasis.⁶¹ Currently, none of the approved biosimilars for psoriasis have been approved for interchangeability (according to the FDA, an interchangeable biological product, in addition to meeting the biosimilarity standard, is expected to produce the same clinical result as the reference product in any given patient). Unfortunately, Inflectra's wholesale price is only 15% that of Remicade.⁶² Biosimilars for etanercept and adalimumab, although approved by the FDA, are currently not available due to ongoing court battles over patent restrictions, which are likely to persist for several years.

Discussion

The regulatory pathways for the approval of biosimilars described here each follow rigorous sets of criteria, many of which are based on FDA and EMA guidelines. However, many differences exist between countries regarding use of biosimilars in the clinic. In some cases, substitution at the pharmacy level is allowed with or without consultation with the prescribing physician. In some government hospitals, physicians are mandated to use biosimilars over the reference products unless a medical reason is specified. There are also differences in country requirements for post-marketing surveillance and reporting. For example, India requires a Phase IV study of at least 200 patients to be carried out within 2 years of approval, whereas other countries will capture adverse events in patient registries (Brazil, Italy, and the UK). The penetrance of biosimilars into the global markets is varied. Cost differences between originators and biosimilars range from deep discounts due to government pricing (70%, Norway) to moderate discounts (30%, India) to small discounts (15%, US). As the market grows and competition peaks, biosimilar costs are expected to decline.

Summary

Biosimilars have been added to the list of biologic agents used to treat moderate-to-severe psoriasis in multiple countries. However, challenges on their use in practice are common. The possibility of substitution at the pharmacy or institution level, lack of traceability of a prescribed biosimilar, and poor monitoring of safety events are key remaining concerns. Pharmacovigilance registries have been established in a few countries, which we believe are critical for establishing long-term safety profiles of biosimilars. The International Psoriasis Council advocates that dermatologists take an active role in the development of biosimilar prescribing policies in their respective healthcare settings and governmental agencies. This approach will significantly improve access to biosimilar drugs for our psoriasis patients worldwide in urgent need of these important medications.

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Professor Sergio Chimenti passed away prematurely at the end of February 2016. He spent his successful career by teaching dermatology and by researching with a special focus on dermatology and psoriasis. He was Chairman and Professor in Dermatology at the University of Rome “Tor Vergata”, Italy. Not only was Sergio an excellent teacher, but also a marvelous team leader who could motivate people and promote excellence. His last achievement was the successful campaign of the Italian bidding committee to host the next World Congress of Dermatology in Italy in 2019. Professor Sergio Chimenti will never be forgotten.

Arnon D. Cohen takes responsibility for the integrity of the work as a whole, from inception to published article.

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