The ROYAL COLLEGE of OPHTHALMOLOGISTS

www.nature.com/eye

COMMENT

Check for updates

Biosimilar ranibizumab interchangeability: what does it mean to retinal physicians?

Ashish Sharma[1]✉, Nilesh Kumar[2], Nikulaa Parachuri[3], Carl Regillo[4], Francesco Bandello[5] and Baruch D. Kuppermann[6]

Eye (2023) 37:1953–1954; https://doi.org/10.1038/s41433-022-02287-w

Biosimilar anti-VEGF molecules have gained significant attention in the recent past after the approval of two biosimilar ranibizumab molecules by the United States Food and Drug Authority (US-FDA). The first drug was Byooviz/ranibizumab-nuna (Byooviz, Samsung Bioepis, South Korea/Biogen, USA) with US-FDA approval in September 2021 and European Medical Agency (EMA) approval in August 2021 [1, 2]. The second drug was CIMERLI/ranibizumab-eqrn (Coherus BioSciences, CA, USA) with US-FDA approval in August 2022 [3]. The latter drug was already approved by UK Medicines & Healthcare Regulatory Agency in 2022 as Ongavia [4]. It recently received EMA approval as Ranivisio [5]. CIMERLI/ranibizumab-eqrn also received approval for interchangeability with reference ranibizumab (Lucentis, Genentech, USA) for all the five indications (neovascular age-related macular degeneration, retinal vein occlusion, diabetic retinopathy, diabetic macular edema, myopic choroidal neovascular membrane) with exclusivity for 12 months [3]. CIMERLI/ranibizumab-eqrn, in both 0.3 and 0.5 mg dosages, is now available for clinical use. Twelve-month exclusivity period starts from the time of the first commercial marketing of CIMERLI/ranibizumab-eqrn. The purpose of this index manuscript is to understand the nuances around the concept of interchangeability in the retinal space.

Biosimilar anti-vascular endothelial growth factors (anti-VEGF) drugs are relatively new to retina specialists worldwide except in India where the first ranibizumab biosimilar was approved back in 2015 [6]. However, interchangeability for biosimilar anti-VEGFs is a new concept to all retina specialists worldwide including India [7]. Similar to how generic drugs are frequently substituted for brand-name small-molecule drugs, an interchangeable biosimilar product may be substituted without the involvement of the healthcare professional who prescribed the reference product. State pharmacy laws apply to this, which is also known as pharmacy-level substitution. Similar to how they would prescribe a biosimilar or a reference product, a healthcare professional can also prescribe an interchangeable biosimilar product. The FDA claims that healthcare professionals and patients can be confident in the safety and efficacy of a biosimilar or an interchangeable biosimilar product, just as they would be for the FDA-approved original product. This is because of the FDA's stringent standards for approval. Interestingly, while the concept of interchangeability is recognized scientifically, Europe has not yet used it as a legal term like in the US. Laws pertaining to the so-called pharmacy-level substitution vary from state to state, and, to date, the FDA has approved only two other interchangeable biosimilars, insulin glargine-yfgn injection (Semglee) and adalimumab-adbm (Cyltezo) apart from CIMERLI/ranibizumab-eqrn [8] Another interesting fact is that the FDA has given interchangeable approval to CIMERLI/ranibizumab-eqrn without any switching studies. Usually, sponsors need to carry out switching studies to prove that the risk of diminished efficacy or safety from switching between a biosimilar and its reference product is not greater than the risk of using the reference product without such alternation or switch. However, for the first time, the FDA believed in the totality of evidence generated in case of CIMERLI/ranibizumab-eqrn and decided that switching studies were not required. When alternating or switching between CIMERLI/ranibizumab-eqrn and reference ranibizumab (Lucentis), FDA feels there is a low risk of a clinically significant immunogenic response from systemic anti-drug antibodies and intraocular inflammation. The risk of safety or impaired efficacy from alternating or switching between CIMERLI/ranibizumab-eqrn and reference ranibizumab (Lucentis) being not larger than the risk of using Lucentis ranibizumab (Lucentis) without such alternation or switch will not be informed from a switching study that compares immunogenicity and pharmacokinetics and/or pharmacodynamics. Waiving of additional studies will be taken case by case based on the evidence generated in the initial studies. Draft of 2019 by the agency on interchangeable biosimilars did mention the possibility of waiving of switching studies in some cases.

It is difficult to predict how interchangeability would be used practically in retinal practice as anti-VEGFs are not prescribed to patients to procure it from the pharmacy. Instead, they are supplied by the companies directly to the hospital or retina specialist, and the hospital or retina specialist stores and supplies them when advised by the retina physicians. Pharmacists do not have a direct role in this instance. Insurance companies might take advantage of a less-priced drug to be interchanged in place of the reference drug. Furthermore, it is yet to see whether molecules such as aflibercept biosimilars need to undergo switching studies, being a little more complex than ranibizumab in structure. The interchangeability designation of a drug may give treating physicians some measure of confidence in switching from the reference product to the biosimilar.

In the United States, the overall concept of interchangeable and non-interchangeable may act as a barrier to the adoption of non-interchangeable biosimilars by creating a nocebo effect in

[1]Lotus Eye Hospital and Institute, Avinashi Road, Coimbatore, TN, India. [2]Madhavi Netralaya, Ara, Bihar, India. [3]Department of Vitreoretina, Sankara Eye Hospital, Coimbatore, TN, India. [4]The Retina Service of Wills Eye Hospital, Mid Atlantic Retina, Philadelphia, PA, USA. [5]University Vita-Salute, Scientific Institute San Raffaele, Milano, Italy. [6]Gavin Herbert Eye Institute, University of California, Irvine, Irvine, CA, USA. ✉email: drashish79@hotmail.com

Received: 27 September 2022 Revised: 30 September 2022 Accepted: 7 October 2022
Published online: 17 October 2022

clinicians regarding non-interchangeable biosimilars. On the other hand, it might prompt companies to carry switching studies and get an interchangeable status to provide more confidence to clinicians about the efficacy and safety of these molecules.

REFERENCES

1. FDA approves Samsung Bioepis and Biogen's BYOOVIZ™ (SB11), LUCENTIS® Biosimilar (ranibizumab-nuna). https://investors.biogen.com/news-releases/news-release-details/fda-approves-samsung-bioepis-and-biogens-byooviztm-sb11. Accessed 7 Sept 2022.
2. Ranibizumab Biosimilar (Byooviz) Gains EU Marketing Authorization. https://www.centerforbiosimilars.com/view/samsung-bioepis-byooviz-gains-ema-marketing-authorization. Accessed 7 Sept 2022.
3. FDA approves Coherus' CIMERLI™ (ranibizumab-eqrn) as the first and only interchangeable biosimilar to Lucentis® for all five indications, with 12 months of interchangeability exclusivity. https://investors.coherus.com/news-releases/news-release-details/fda-approves-coherus-cimerlitm-ranibizumab-eqrn-first-and-only. Accessed 7 Sept 2022.
4. United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA) grants marketing authorization for FYB201, Formycon's biosimilar for Lucentis®[1], to be commercialized by Teva as ONGAVIA®. https://www.formycon.com/en/press-release/united-kingdom-medicines-and-healthcare-products-regulatory-agency-mhra-grants-marketing-authorization-for-fyb201-formycons-biosimilar-for-lucentis1-to-be-commercialized-by-teva-as-ongavia/. Accessed 7 Sept 2022.
5. European Commission approves FYB201/Ranivisio®[1] (Ranivisio - Ranibizumab), a biosimilar to Lucentis. https://www.formycon.com/en/press-release/european-commission-approves-fyb201-ranivisio1-ranivisio-ranibizumab-a-biosimilar-to-lucentis2/. Accessed 7 Sept 2022.
6. Sharma A, Reddy P, Kuppermann BD, Bandello F, Lowenstein A. Biosimilars in ophthalmology: "Is there a big change on the horizon?". Clin Ophthalmol. 2018;12:2137–43. https://doi.org/10.2147/OPTH.S180393.
7. Biosimilar and interchangeable biologics: more treatment choices. https://www.fda.gov/consumers/consumer-updates/biosimilar-and-interchangeable-biologics-more-treatment-choices#:~:text=An%20interchangeable%20biosimilar%20product%20may,subject%20to%20state%20pharmacy%20laws. Accessed 7 Sept 2022.
8. FDA approves Cyltezo, the first interchangeable biosimilar to Humira second interchangeable biosimilar product approved by agency. https://www.fda.gov/news-events/press-announcements/fda-approves-cyltezo-first-interchangeable-biosimilar-humira#:~:text=Cyltezo%20is%20the%20second%20interchangeable,for%20many%20serious%20health%20conditions. Accessed 7 Sept 2022.

ACKNOWLEDGEMENTS

BDK acknowledges an unrestricted grant from Research to Prevent Blindness to the Gavin Herbert Eye Institute at the University of California, Irvine.

AUTHOR CONTRIBUTIONS

AS: conception, analysis, drafting, integrity check, and final approval. NK, NP, CR, FB and BDK: drafting, revision, analysis, and integrity check.

COMPETING INTERESTS

AS: consultant for Novartis, Allergan, Bayer, and Intas. CR: consultant for Allergan, Chengdu Kanghong, Genentech/Roche, Novartis, Kodiak, Notal, Merck, Shire-Takeda, Adverum, Graybug, and Eyepoint and receives research support from Allergan, Chengdu Kanghong, Genentech/Roche, Novartis, Kodiak, Iveric, and Adverum. FB: consultant for Allergan, Bayer, Boehringer Ingelheim, FidiaSooft, Hofmann La Roche, Novartis, NTC Pharma, Sifi, ThromboGenics, and Zeiss. BDK: clinical research for Alcon, Alimera, Allegro, Allergan, Apellis, Clearside, Genentech, GSK, Ionis, jCyte, Novartis, Regeneron, and ThromboGenics; consultant for Alimera, Allegro, Allergan, Cell Care, Dose, Eyedaptic, Galimedix, Genentech, Glaukos, Interface Biologics, jCyte, Novartis, Ophthotech, Regeneron, Revana, and Theravance Biopharma. NK: none. NP: none.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Ashish Sharma.