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COMMENT

Biosimilar anti-VEGF—Yardsticks to ensure biosimilarity

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The United States—Food and Drug Administration (US-FDA) and European Medicines Agency (EMA) has recently approved the first biosimilar of ranibizumab (ranibizumab-nuna, Byooviz, Biogen, USA) [1, 2]. The International Retina Biosimilar Study Group (Inter BIOS Group) had conducted a survey (Bio-USER-unpublished data) which revealed that many retinal physicians from Europe and the US have concerns regarding the safety and efficacy of biosimilars. Safety and efficacy are the major parameters on which biosimilar molecules are tested. Biosimilarity needs to be established which leads to the similar efficacy and safety of these drugs. In this paper, we will discuss the yardsticks which are defined by the regulatory agencies (FDA and EMA) that make sure these drugs are similar to the originator (reference molecules) in all aspects except for some differences which are not clinically meaningful. It is a stepwise approach consisting of the following steps [3, 4].

STRUCTURAL BIOSIMILARITY

This is one of the most important steps for companies that are involved in the development of biosimilars as this step decides the remaining steps to prove the biosimilarity of the proposed product. This does not require clinical testing rather the structure of the proposed biosimilar molecule is analysed with the help of analytical methods. The structural analysis includes matching the primary structures such as amino acid sequences, secondary, tertiary, and quaternary structures including aggregation, post-translational modifications, and biological activities of the protein chains such as glycosylation and phosphorylation with the reference molecule. Apart from these, other potential variations such as protein deamidation and oxidation are also assessed. Chemical modifications such as PEGylation sites and other characteristics are tested as well. The above-described structural analysis is to be performed in multiple lots to check variability. Additionally, the structural analysis should include excipient, process-related impurities, and stability. It is mandatory that the company should have state of the art technology for the characterization of references of the proposed biosimilar products [3, 4].

FUNCTIONAL BIOSIMILARITY

The pharmacological activity of proteins categorized structurally in the previous step is checked by various assays. It would be either in vitro or in vivo. It is mandatory to use comparative assays to avoid any false variation. Functional analysis helps in the understanding of the mechanism of action, detecting any difference in activity that was not picked up in the structural characterization. It is helpful to establish structural–functional relationships. Biosimilar companies need to provide information about sensitivity, specificity, and validation of the assays to provide guidance for the next step [3, 4].

ANIMAL STUDIES

Based on the data generated from the structural and functional analysis, the regulatory agency decides the necessity of animal testing. Till now, the approved ranibizumab biosimilars either have not required animal testing or have only needed minimal studies as they have had sufficient structural and functional similarity evidence to minimize this step based on the regulatory requirement. Furthermore, animal safety data is not required if the drug has already been used in countries other than the USA on humans and has shown safety. If animal data is not required, regulatory agencies might sometimes need to get additional in vitro testing on human cells as a preclinical measure of biosimilarity [3, 4].

CLINICAL STUDIES

Clinical study design and population

These are typically equivalence designs with equal superiority and inferiority equivalence margins to make sure any potential difference is detected if results are beyond the margin. The study population is chosen in line with the population chosen for the reference molecule trials [3–5].

Pharmacokinetic (PK) and pharmacodynamics (PD)

It is very important to understand the nature and scope of human studies based on the evidence of biosimilarity collected in the previous steps. Pharmacokinetic (PK) and pharmacodynamic (PD) profiles in humans might not be reflected completely with the functional assays in the initial stages of testing hence, these are usually the important part of a clinical study for biosimilars. If a relevant PD measure is not available, then PK is the most important measure to assess the biosimilarity. PK study assesses the serum concentration of the drug over the time between the proposed biosimilar and reference molecule and is important as serum concentration has an impact on drug safety. Furthermore, assessing serum concentrations over a period of time, gives a clear measure of similarity in systemic distribution, metabolism, and elimination of the drug. Ideally, PK measurement is to be done with a vitreous concentration in cases of anti-VEGF. However, it is

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not feasible and unethical as per the regulations and hence serum concentrations are considered surrogate markers for PK. Human PK and PD parameters are much more sensitive to establishing biosimilarity compared to the clinical effects [3, 4].

Clinical immunogenicity

This is an essential part of the clinical study for biosimilar anti-VEGF to assess the human immune response to the drug. The implication of different immune responses not only can affect safety and efficacy but can also affect PK by neutralizing the drug molecule. The major reason to perform a clinical study in the case of anti-VEGF biosimilars is the assessment of immunogenicity in humans as it cannot be predicted in the earlier steps and hence is a key element in establishing biosimilarity. The extent of clinical immunogenicity testing depends on the immunogenic potential of reference drug such as for ranibizumab biosimilars it would be to a lesser extent (in a limited subset of patients) due to already established safety profile of the reference drug (Lucentis, Genentech, USA). In future if a brolucizumab biosimilar were to come, it would need a larger patient data of clinical immunogenicity because of higher immunogenic potential of reference drug (Beovu, Novartis, Switzerland). The selection of study population and end point of immunogenicity (serum and clinical), both need to be well defined to prove biosimilarity. Follow-up duration is based on the appearance and disappearance of immune response (generation of neutralizing antibodies). The similarity of assays makes sure there is no difference in the assessment [3–5].

Outcome assessment time

Outcome assessments are done at the steeper part of the dose-response curve to detect differences rather than at the plateau which might not be able to detect the differences. Hence endpoints are short in equivalence trials of biosimilars [3–5]. Outcomes are selected based on the current information and clinical use of the reference molecule. Typically for ranibizumab, a loading dose curve is selected as it is the maximum change expected to be brought about by the drug in the shortest possible time. The longer response also needs to be maintained but here the variable parameters start to increase.

Extrapolation

Extrapolation of anti-VEGF biosimilars is allowed because of the same target, mechanism of action, and population characteristics [3–5].

CONCLUSION

To summarize, regulatory agencies have robust yardsticks to ensure biosimilarity of anti-VEGF to detect any clinically meaningful differences. PD and PK parameters are much more sensitive compared to clinical studies in detecting differences between the reference and biosimilar molecules hence clinicians should not be concerned about the safety and efficacy of these molecules. Once this understanding is achieved, biosimilar anti-VEGFs can realize their full potential by increased access to treatment along with reducing the financial burden on healthcare systems and patients with similar safety and efficacy.

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AUTHOR CONTRIBUTIONS

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

COMPETING INTERESTS

AS: CONSULTANT: for Novartis, Allergan, Bayer and Intas. FB: CONSULTANT: Allergan, Bayer, Boehringer- Ingelheim, FidiaSooft, Hofmann La Roche, Novartis, NTC Pharma, Sifi, Thrombogenics, Zeiss. BDK: CLINICAL RESEARCH: Alcon, Alimera, Allegro, Allergan, Apellis, Clearside, Genentech, GSK, Ionis, jCyte, Novartis, Regeneron, ThromboGenics; CONSULTANT: Alimera, Allegro, Allergan, Cell Care, Dose, Eyedaptic, Galimedix, Genentech, Glaukos, Interface Biologics, jCyte, Novartis, Ophthotech, Regeneron, Revana, Theravance Biopharma. NK: None. NP: None.

ADDITIONAL INFORMATION

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