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COMMENT

Fear of safety compromise with biosimilar anti-VEGF—perception or truth

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The first biosimilar of ranibizumab (Byooviz, Biogen, USA) has received approval from the United States- Food and Drug Administration (US-FDA) and European Medicines Agency (EMA) recently [1, 2]. And the International Retina Biosimilar Study Group (Inter BIOS Group) has conducted a survey (Bio-USER- unpublished data) which has revealed that many retinal physicians from Europe and the US have concerns regarding the safety of biosimilars. Safety is predominantly related to drug-induced intraocular inflammation (IOI) apart from nonocular safety parameters. Anti-vascular endothelial growth factors (Anti-VEGF) are biologics under the category of monoclonal antibodies. Biologics are exogenous proteins and thus, inherently have the potential to cause immunogenicity [3].

In this manuscript, we will try to compare the safety of ranibizumab biosimilar and innovator ranibizumab (Lucentis, Genentech, USA) by analyzing parameters used to assess safety in the landmark phase 3 trial that has led to the approval of these molecules [4–6]. All the biosimilar ranibizumab molecules are compared against the innovator (reference- Lucentis) molecule during the phase 3 trial. For better understanding, we will use the brand name in this manuscript.

Lucentis was approved based on the results of the ANCHOR (Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD) and MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD) trials [4, 5]. The MARINA trial was designed as a phase 3, randomized, multicentre, double-masked, sham-controlled study enrolling 716 patients with minimally classic lesions or occult with no classic lesions. Patients were randomized 1:1:1 to either sham ($n = 238$), ranibizumab 0.3 mg ($n = 238$), or ranibizumab 0.5 mg ($n = 240$). The ANCHOR trial, also a phase 3 randomized, multicentre, double-masked study, was designed as an active treatment-controlled study. All of the patients in the study ($n = 423$) had predominantly classic lesions. Randomization was 1:1:1 with 143 patients assigned to PDT, 140 patients to treatment with ranibizumab 0.3 mg, and 140 patients to ranibizumab 0.5 mg.

Biosimilars require only one equivalence trial compared to two superiority or non-inferiority trial for innovator molecules. SB11 (Byooviz) long-term safety data were published in the recent past [6]. It was a randomized, double-masked, parallel-group, phase III equivalence study. Patients were randomized 1:1 to either SB11 ($n = 351$), or Lucentis 0.5 mg ($n = 354$).

Here is the comparison of various safety parameters between the approved innovator and biosimilar ranibizumab.

INTRAOCULAR INFLAMMATION

The ANCHOR trial demonstrated inflammation in 17.1% of cases. Most of the cases had trace cells (8%) followed by 1 + (2.2%), 3 + (1.5%) and 2 + (0.7%) during the cumulative 12 months period. The MARINA trial demonstrated inflammation in 20.9% of cases. Most of the cases had trace cells (14.6%) followed by 1 + (3.3%), 4 + (1.3%), 2 + (0.8%), and 3 + (0.8%) during the cumulative 24 months period. The above-described rate of inflammation was noticed with the commonly used dose of 0.5 mg of ranibizumab. The phase 3 trial results of SB11 demonstrated inflammation in 0.9 % of cases {(iridocyclitis (0.3%), uveitis (0.3%) and vitritis (0.3%))}.

OTHER OCULAR ADVERSE EVENTS

ANCHOR and MARINA studies showed endophthalmitis rates of 1.4% and 1.3% respectively. Whereas in the SB11 trial it was 0.6%. None of the cases in the ANCHOR study showed vitreous hemorrhage, retinal tear, or lens damage whereas the MARINA trial showed vitreous hemorrhage, retinal tear, and lens damage in 0.4% of each. The SB11 trial showed retinal hemorrhage at 0.3%, and retinal pigment epithelium tear in 0.3% of cases.

NON OCULAR ADVERSE EVENTS

There was no myocardial infarction or stroke event in the SB11 trial. The ANCHOR trial revealed myocardial infarction in 2.1% and stroke in 0.7% of cases. The MARINA trial showed myocardial infarction in 1.3% and stroke in 2.5% of cases. The ANCHOR and MARINA trials showed hypertension in 6.4 and 16.3% of cases whereas the SB11 trial showed hypertension in 0.9% of cases. Deaths were 0.6% during 12 months (52 weeks) of the SB11 trial whereas it was 1.4% and 2.6 % in the ANCHOR and MARINA trials respectively.

As per the above-described safety data of the ANCHOR (12 months), MARINA (24 months), and SB11 phase 3 trials (52 weeks), except for retinal hemorrhage and retinal pigment epithelial tears, numerically the ANCHOR and MARINA trials had more adverse events. However, this comparison may not be

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completely decisive due to the time gap of 12 years between these trials. This might have led to minor changes in the manufacturing process of Lucentis. It is important to look at the direct comparison of safety data of Lucentis used in one of the treatment arms of the SB11 equivalence trial. Numerically IOI (iridocyclitis, uveitis, and vitritis) was more with SB11(0.9%) compared to Lucentis (0%). Similarly, cataract (0.6%) and retinal pigment epithelial tear (0.3%) was numerically higher in SB11 compared to Lucentis (0%). However, retinal artery occlusion was seen in 0.3% with Lucentis compared to SB11 (0%). Non-ocular adverse events such as hypertension (HT) and atrial fibrillations (AF) were more with SB11 (HT-0.9%, AF-1.1%) compared to Lucentis (HT-0%, AF-0.8%). Congestive cardiac failure was numerically equivalent in both groups (0.6%). None of the adverse events related to ocular and nonocular were different statistically.

To summarize, landmark trials of Lucentis and SB11 along with head to head Lucentis and SB11 comparision data shows that the biosimilar candidate SB11 is safe. However, historically the uptake of biosimilars has been slow even in non-ophthalmic diseases [7]. Physicians need real-world data to develop more confidence in these molecules. Though the fear of safety with biosimilar anti-VEGF is not completely true, it is rather a hesitation towards the adoption of a new molecule. Clinicians are more vigilant with any new molecule after their experience with brolucizumab which has surprised us in the real world with the higher incidences of retinal vascular occlusion compared to the trial results. This comparative safety data might be of help in educating physicians to mitigate the undue fear of biosimilars for retinal diseases which are coming in a wave with multiple molecules in the pipeline for approval [7, 8].

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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

Ashish Sharma: Consultant: for Novartis, Allergan, Bayer and Intas. Francesco Bandello: Consultant: Allergan, Bayer, Boehringer- Ingelheim, FidiaSooft, Hofmann La Roche, Novartis, NTC Pharma, Sifi, Thrombogenics, Zeiss. Baruch D Kuppermann: 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. Nilesh Kumar: None. Nikulaa Parachuri: None.

ADDITIONAL INFORMATION

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