Acta Scientific Ophthalmology (ISSN: 2582-3191)

Volume 5 Issue 5 May 2022

Opinion

Are Anti-vascular Endothelial Growth Factor Biosimilars Applicable for Treating Diabetic Macular Edema?

Avinoam Ophir*

Professor, Ophthalmology Clinic, 48 Sokolov, Ramat-Hasharon, Israel

***Corresponding Author:** Avinoam Ophir, Professor, Ophthalmology Clinic, 48 Sokolov, Ramat-Hasharon, Israel.

Received: March 14, 2022

Published: April 13, 2022

Keywords: Diabetic Macular Edema; Extrafoveal traction; Vasogenic Macular Edema; Dry Macular Edema; 3D-OCT; Pars Plana Vitrectomy; Grid Laser Photocoagulation; Focal Laser Photocoagulation; Anti-VEGF; Biosimilar; Ranibizumab; Aflibercept; Bevacizumab; Byooviz

Abbreviations

FDA: Food and Drug Administration; DME: Diabetic Macular Edema; DDME: Diffuse DME; nAMD**:** Neovascular Age-related Macular Degeneration; VA: Visual Acuity; BCVA: Best-corrected Visual Acuity; mGLP: Modified Grid Laser Photocoagulation; OCT: Optical Coherence Tomography; SD-OCT: Spectral-domain OCT; PPV: Pars Plana Vitrectomy; VFT: Vitreofoveal Traction; ERM: Epiretinal Membrane; -VEGF: -Vascular Endothelial Growth Factor; DRCR.net: Diabetic Retinopathy Clinical Research Network; CMT: Central Macular Thickness; PVD: Posterior Vitreous Detachment.

Byooviz (ranibizumab-nuna; Samsung Bioepis Co., Ltd. and Biogen Inc, South Korea) is the first antivascular endothelial growth factor (-VEGF) biosimilar approved by the U.S. Food and Drug Administration (FDA; September 2021) to treat retinal diseases [1]. Prior to approval, a randomized phase 3 multicenter study compared Byooviz with the reference ranibizumab in 705 patients, all with neovascular age-related macular degeneration (nAMD). The improvement in outcomes of best-corrected visual acuity (BCVA) and central macular thickness (CMT) from baseline, as well as the safety and immunogenicity profiles of both agents were comparable at all points up to week 52 [2,3]. By extrapolation, Byooviz has thus been approved for the treatment of the same previously indicated retinal pathologies by the innovative ranibizumab, except for diabetic macular edema (DME). The alleged FDA decision to withhold approval of Byooviz for the treatment of DME was undertaken without an examination or comparative examination of Byooviz in DME. It appears that the FDA may have based its decision on both the limitations of the major innovative ranibizumab studies for DME and their outcomes. This decision and its presumed causes may affect the strategy of other studies searching for agents to treat DME.

Possible reasons that could allegedly exclude Byooviz approval for DME treatment

A) Short-lived and commonly partial efficacy of the innovative ranibizumab vs. other long-lasting highly efficient therapies for DME

In order to avoid progressive foveal injury, the key aim of DME therapy is to achieve early, complete and durable macular drying; and secondly to improve current VA [4-6]. Treatment of focal DME by focal laser photocoagulation to leaking microaneurysms was often found to be efficacious and long-lasting [7,8]. In centrally-involved diffuse DME (DDME), when vitreofoveal (VFT; commonly termed 'vitreomacular') traction or an associated tractional epiretinal membrane (ERM) are detected, pars plana vitrectomy (PPV) is typically the procedure of choice for the achievement of long-lasting efficacy [9-11]. The enigma of DDME pathogenesis when macular traction was undetected has remained the major challenge for DME therapy. Therefore, therapies in these eyes were conducted for decades on a trial-and-error basis. These included, a) modified grid laser photocoagulation (mGLP) to achieve durable macular drying, but this has commonly failed [12,13]; b) various anti-VEGF and steroid medications administered intravitreally. However, these are short-lived and costly [14-18], and the prevalence of achieving even a temporary complete macular drying together with improved VA by effect of anti-VEGF in DME was found low [19]. Finally, when all failed, PPV was often considered, but frequently too late for VA revival [20,21].

The discovery of two novel pathogeneses of DDME in eyes that had been earlier considered as 'nontractional' DDME has turned out to be a game-changer in this fight for sight [22-26]. These pathogeneses are, a) the commonly overlooked extrafoveal vitreous traction in most such eyes. Its detection was mainly aided by 3D images and video clips of the spectral-domain optical coherence tomography (SD-OCT 1000; Topcon, Japan) (Figure 1); b) the vasogenic DDME, namely, eyes in which extrafoveal vitreous traction membranes (as well as VFT and ERM) were unequivocally excluded by the 3D SD-OCT [23]. Treatments that have been aimed towards these two DDME pathogeneses have enabled the achievement of highly efficacious and durable outcomes:

Figure 1: Extrafoveal vitreous traction membranes in diffuse DME. A-D) Clinical pictures of diffuse DME and the associated b-scans of 3D SD-OCT. The yellow vertical line in each clinical picture marks the corresponding OCT b-scan site. B,D) The fovea (B) having a lamellar hole is free from traction. Each of the two extrafoveal traction membranes (arrows) associated with an underlying retinal edema, is in continuum with an ERM ("Evi" membrane). E) 3D OCT figure demonstrating a broad posterior vitreous cortex membrane and multifocal sites of extrafoveal traction associated with the DDME (arrows and arrowhead). The vertical white line marks the fovea, which is free from traction.

- Early-PPV in DDME treatment-naive eyes has achieved 92%-100% efficacy in complete, durable macular drying; the common VA improvement was mainly dependent on the integrity of the foveal layers (n = 7 to 120 eyes, 3 to 24 months of follow-up) [27-30]. Additional studies have clarified the DDME association with vitreopapillary traction, and between DDME with vitreoretinal traction and ERM, the vitreoschisis phenomenon [31-33]. Others described the superiority of PPV over anti-VEGFs, whereas the histological dynamics in DDME underscore the importance of early PPV in DDME without detectable traction [11,34-36]. The long-lasting, favorable outcomes of PPV may be mainly explained by the removal of the commonly overlooked extrafoveal traction membranes [22-26], and probably by improved oxygenation in the remaining non-tractional eyes [37]. In contrast, delayed PPV also commonly results in complete macular drying but not infrequently only lessens the edema, leaving residual or recurrent edema in the eyes [20,21,38-40]. If this post-surgical vasogenic DDME is non-ischemic, consideration of treatment by focal / mGLP may be recommended in order to achieve a long-lasting effect (see below). In that regard, Berrocal summarized the benefits of early-PPV in severe non-proliferative and proliferative diabetic retinopathy, associated with attached or incompletely detached posterior hyaloid. Early surgery was found highly efficacious in order to avoid future tractional complications, including DDME, and vision loss [41];
- mGLP for vasogenic DDME was found to be durably efficacious in 72% (13/18) of eyes after 4-24 months (mean, 15.9) of follow-up [42]. The major cause of DDME recurrence was a mid-term (from month-5) emergence of incomplete posterior vitreous detachment associated with extrafoveal traction, which was treatable surgically. Presumably, DDME eyes with complete PVD or post-PPV may therefore react favorably and durably to focal / mGLP. PPV and laser treatment are also cost-effective therapies world-wide, and their machineries equipment is commonly available. A thorough discussion on that topic was previously presented [43].

B) Limitations of the pivotal anti-VEGF studies for DME

In a 2-year randomized controlled study, the pivotal DRCR.net Protocol-T compared the DME outcomes (n = 660) of the three most utilized anti-VEGF medications, ranibizumab (lucentis,

Genentech, San Francisco, CA), bevacizumab (avastin, Genentech) and aflibercept (eylea, Regeneron, Tarrytown, NY) [17,18]. However, considerable drawbacks of the methods used in that study have been elucidated [24,44], and agreed by the authors [45]. These included a mixture of therapeutic outcome calculations in each of the three treatment groups: The tight anti-VEGF therapies have been aided by focal/grid laser treatments as rescue therapy in ~45% of eyes, whereas the remaining eyes were not treated by laser. As well, of the eyes treated by laser, each group included a mixture of focal DME (good prognosis by laser) and diffuse DME, either with traction; (ERM and extrafoveal traction; predestined to poor focal/ mGLP prognosis) or without traction (good mGLP prognosis [42]). Furthermore, the efficacy of anti-VEGF therapy is lower in tractional than in non-tractional DDME eyes [46]. Under these mixed circumstances, an improvement in mean VA and CMT was described in each group, followed by prime, challenging, clinical recommendations. The aforementioned limitations and authors' agreements may also be relevant to the most other innovative DME studies and to some other studies that look for a new anti-VEGF biosimilar or alike [44-45].

The two novel DDME pathogeneses, tractional or vasogenic, may explain common failures or otherwise complete temporary drying respectively, after three monthly injections of one anti-VEGF medication [46,47]; (even if lessened, persistent residual (edema is still potentially harmful and should be considered a failure). An anti-VEGF failure in achieving temporary complete drying would often presumably occur due to the common presence of overlooked extrafoveal traction, as was reported in VMT and ERM [46]. As well, these pathogeneses may clarify why early outcome would commonly predict its long-term response [47]. In that regard, a switch to another anti-VEGF or alike following failure, in order to attain the major aims, would seem in vain, as was previously recommended [47]. In contrast, in vasogenic DME, either focal or diffuse, the two relevant laser therapies, focal or focal/ mGL, were commonly found efficacious in achieving complete and long-lasting dry macula [8, 42]. Therefore laser treatment may be considered to be the treatment of choice in vasogenic DME.

After completion the 2-year Protocol-T study it was extended to 3 more years (n = 317), during which eligible participants were managed via standard, real-world care [48]. However, each of the three medication groups was associated with a significant reduction in VA at the end of the study. Similarly, poorer outcomes of anti-VEGFs in comparison with the pivotal prospective controlled trials have commonly been reported in other real-world DME studies [49-50]. Indeed, following more than a decade of numerous DME trials using anti-VEGF medications, the DRCR. net authors concluded and affirmed their strategy, saying that "additional investigation into strategies to improve long-term outcomes in DME seems warranted, to determine if BCVA can be better maintained with different management approaches" [48]. Similar views have been stated by the EURETINA study group [8].

Conclusions

Based on the cumulative literature on the innovative ranibizumab, the FDA has allegedly determined to withhold approval of its biosimilar Byooviz for DME therapy even without its examination. Since study methods were similar [14-18,24,44,45], and the major aim of complete and durable macular drying was not achieved in both, this FDA approach may also challenge the current use of the innovative bevacizumab and aflibercept and their expected biosimilars in the treatment of DME. When investigating a new medication for DME, the aforementioned information seems to underscore the importance of, a) considering not to adhere to the study methods as of the pivotal anti-VEGF ones [14-18, 24, 44-48] and/ or, b) not relying on a non-inferiority comparison of outcomes between the agent under investigation and the reference anti-VEGF studies. Rather, the cumulative information guides toward adherence to the Tenets of Helsinki. That, by focusing on the DME pathogeneses and adopt the key purpose, i.e. to achieve in one-time an early and long-lasting complete macular drying in DME.

Conflict of Interest

The author declares on no conflict of interest.

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