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COMMENT

On label bevacizumab for retina: where it stands

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Retina as a subspecialty has been transformed since the introduction of anti-vascular endothelium derived growth factors (Anti-VEGF) in 2005, thanks to Dr Phil Rosenfeld et al., who discovered the use of bevacizumab (Avastin) for the management of retinal diseases as an off label therapy [1]. Since then multiple anti-VEGF molecules such as ranibizumab (2006), aflibercept (2011), brolucizumab (2019) have been approved by various authorities including the United States Food and Drug Administration (US-FDA) and European Medical Agency (EMA) [2–4]. From surveys related to anti-VEGF usage for retinal diseases in various regions, the use of off label bevacizumab (Avastin) has been found to be the most popular anti-VEGF agent primarily due to its comparable efficacy to the other anti-VEGF agents coupled with a significantly lower cost. This demonstrates the need and interest in a cost-effective therapy to provide healthcare access to the greatest population while minimising the financial burden on the world wide health care systems [5]. Off label bevacizumab (Avastin) costs approximately $50-$150 for one dose compared to approved biologics such as ranibizumab and aflibercept costing around $2000 per injection [5]. There was an effort to introduce bevacizumab biosimilars in the US for ophthalmic indications during supply chain issue of bevacizumab (Avastin) but it was not successful [6]. With bevacizumab (Avastin) being the highest used biologic despite it not being approved for ophthalmic use, this manuscript will discuss the challenges and opportunities for on label bevacizumab in the crowded space of anti-VEGFs in retina.

ON LABEL BEVACIZUMAB

Knowing the great success of off-label bevacizumab (Avastin) since the beginning of the anti-VEGF era in retina, it is understandable that some companies would want to bring on label bevacizumab for ophthalmic use, particularly since the patent for bevacizumab (Avastin) has expired. At present bevacizumab (Avastin) comes in a large 4 ml vial which has to be sent to compounding pharmacies for fractionation, which has created concerns among retinal physicians regarding impurities that could potentially be introduced during the process, sterility, and dosage consistency. There have been outbreaks of endophthalmitis which have been traced back to impurities introduced during preparation of the fractionated doses at compounding pharmacies. The ophthalmic version of bevacizumab, if approved, is anticipated to be in a single use vial to address the primary concerns about fractionation. At present, at least one pharmaceutical team, Outlook Therapeutics is trying to bring bevacizumab (ONS-5010/Lytenava) for ophthalmology [7]. ONS-5010/Lytenava has completed the NORSE ONE, NORSE TWO and NORSE THREE studies. NORSE ONE (proof of concept) and NORSE THREE (open label) studies were primarily to assess safety. Recently results of phase 3 NORSE TWO trials were presented at AAO [8]. This was a superiority trial design, ($N = 228$, 39 clinical trial sites) for safety and efficacy in patients with neovascular age-related macular degeneration (nAMD) to compare ONS-5010/Lytenava ophthalmic bevacizumab dosed monthly against ranibizumab's 3 monthly loading doses followed by a q12w dosing based on the PIER study [9]. Participants in the trial were treated for 12 months, with the primary endpoint at month 11 being the difference in proportion of patients who gained at least 15 letters (3 lines) in best corrected visual acuity (BCVA). The key secondary endpoint was the mean change in BCVA from baseline to month 11. The NORSE TWO pivotal data met both primary and secondary endpoints with statistically significant and clinically relevant results: In the trial, ONS-5010/Lytenava achieved highly statistically significant and clinically relevant primary data ($p = 0.0052$) and key secondary efficacy endpoints ($p = 0.0043$). In the intent-to-treat (ITT) primary dataset, the percentage of patients who gained at least 15 letters who were treated with ranibizumab was 23%, and the percentage of patients who gained at least 15 letters who were treated with ONS-5010/Lytenava was 41% ($p = 0.0052$). A mean change in BCVA was observed with ranibizumab of 5.8 letters and the mean change with ONS-5010 was 11.2 letters ($p = 0.0043$) [7].

Adverse events were similar in the two groups, with 45.1% of patients experiencing treatment-emergent ocular adverse events in the ONS-5010/Lytenava group versus 41.7% in the ranibizumab group. There was one serious ocular adverse event, iritis, in the ONS-5010/Lytenava group and none in the ranibizumab group. Investigators have reported that the most common adverse event was intravitreal injection related haemorrhage. Safety of ONS-5010/Lytenava has been at par with the reported results of the landmark trials evaluating bevacizumab (Avastin) such as Comparison of Age-Related Macular Degeneration Treatments Trials (CATT) [7].

Outlook Therapeutics plans to submit a new biologic license application (BLA) under the Public Health Service Act (PHSA) 351 (a) regulatory pathway during early 2022. If the BLA is approved, ONS-5010/Lytenava will be the only FDA approved ophthalmic bevacizumab formulation to get marketing exclusivity for 12 years to treat wet AMD. Furthermore, it will not be considered a biosimilar as there is no approved bevacizumab originator

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molecule for retina use. This will be considered as an innovator molecule, but it will have the advantage of gaining insights from the wealth of data from off label bevacizumab (Avastin) use. The Company also intends to initiate registration studies for ONS-5010/Lytenava for approvals in diabetic macular oedema (DMO) and branch retinal vein occlusion (BRVO) [7].

Single vial on label bevacizumab will likely provide a safer option by avoiding issues of fractionation. This will particularly be useful for countries where use of off label bevacizumab (Avastin) has still not reached a consensus or is not allowed [10]. Furthermore, it will potentially be creating competition for biosimilars of ranibizumab. Although on label bevacizumab will be a welcome drug, it has its own set of challenges. Since the main reason for the widespread use of bevacizumab (Avastin) is economical, its use in some regions would likely depend on how ophthalmic bevacizumab would be priced if approved. If priced significantly higher than the per dose cost of bevacizumab (Avastin), it may be difficult to penetrate price sensitive regions. Insights can be gained from bevacizumab (Lumiere®), which is an ophthalmic bevacizumab approved in Argentina [11], but not being used as commonly as bevacizumab (Avastin) (personal communications from retinal physicians in Argentina). The most probable reason may be due to its significantly higher cost. Each dose of Lumiere costs $180 compared to bevacizumab (Avastin) being available at $25-50 USD. In the United States, it is yet to be seen how ONS-5010/Lytenava is going to be priced if approved. The anti-VEGF space in retina is becoming more crowded at this point with the approvals of innovator molecules or products such as the port delivery system (PDS) with ranibizumab [12] and a few promising molecules which are in the final stages of FDA review such as faricimab [13]. Furthermore, the US-FDA has approved biosimilars of ranibizumab (Byooviz, Biogen, USA) to be marketed in July 2022 [14] along with many other biosimilars of ranibizmab and aflibercept in the pipeline [15].

In summary, the popularity of bevacizumab is unrivalled among the field of anti-VEGF agents used for retinal diseases in many countries worldwide. It is likely that an on label version of bevacizumab that comes in a single use vial from a pharmaceutical company without the need for fractionation from a compounded pharmacy will generate interest and use. However, given that a key component of the popularity of off label bevacizumab (Avastin) is its low price point, on label ophthalmic bevacizumab if approved will have unique opportunities and challenges.

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AUTHOR CONTRIBUTIONS

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

COMPETING INTERESTS

AS: CONSULTANT: for Novartis, Allergan, Bayer and Intas. AL: CONSULTANT: Allergan, Novartis, Roche, Notal Vision, FiorSightsLabs, Beyeonics, Bayer Healthcare. FB: CONSULTANT: Allergan, Bayer, Boehringer- Ingelheim, FidiaSooft, Hofmann La Roche, Novartis, NTC Pharma, Sifi, Thrombogenics, Zeiss. 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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