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COMMENT

Brolucizumab: is extended VEGF suppression on the horizon?

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Anti-VEGF therapy has revolutionized the management of neovascular age-related macular degeneration (nAMD) in the last few years [1, 2]. It has become the first line treatment option for nAMD [3]. However, monthly dosing regimen was being bogged by multiple hospital visits, financial burden to the patient and healthcare system [4]. The researchers have explored newer treatment strategies such as Pro-re-nata (PRN), Treat and Extend (TREX) and three monthly interval (PIER) to extend dosing intervals [4–6]. However, the need of a longer acting anti-VEGF agent was felt.

Ranibizumab port delivery system, Abicipar, Faricimab and Brolucizumab are recent efforts to provide long term VEGF suppression. Amongst these, brolucizumab {Humanized single chain antibody fragment (scFv)} has reached closer to marketing approval [7–9]. Recently concluded phase 3 HAWK and HARRIER trials have proven its safety and efficacy in nAMD and the marketing approval has been sought from the FDA by Novartis [10, 11].

Brolucizumab was ideated by ESBATech (ESBATech AG—Schlieren ZH, Switzerland) as ESBA1008 as the smallest unit of a novel anti-VEGF monoclonal antibody i.e. an scFv molecule that binds to all isoforms of VEGF-A and blocks their action. ESBA1008 was developed by grafting complementarity-determining regions of the novel anti-VEGF antibody to a human scFv scaffold [12]. The pre-clinical data revealed that the retina had a 2.2 times higher exposure to the molecule when compared with ranibizumab. RPE/Choroid complex also had 1.7 times higher exposure. Higher tissue penetrance was attributed to the smaller molecular size (28 kDa, compared with 48 kDa of ranibizumab, 115 kDa of aflibercept) [13]. The higher penetrance was postulated to give better fluid control across layers of retina resulting in better visual outcomes, which was later proven in HAWK and HARRIER trials [10]. The smaller molecular weight has allowed a higher molar concentration of the drug to be fit into the 50 µl with formulations up to 120 mg/ml. 50 µl of 120 mg/ml formulation has 22 times molar excess than 0.5 mg/0.5 ml ranibizumab and 12 times more than 2 mg/0.5 ml of aflibercept [14]. The in-vitro studies have shown brolucizumab having affinity to VEGF similar to ranibizumab and higher than bevacizumab [15]. In-vivo studies in primates have revealed that the systemic exit of the drug is significantly less than ranibizumab or aflibercept, possibly due to better tissue uptake of the molecule. The reduced systemic exit can lead to less generation of anti-drug antibody, which play a major role in immunogenicity and treatment failure [16].

The phase 1/2 study evaluated the safety and efficacy of ESBA1008 with a new code- RTH258 and demonstrated non-inferiority of 4.5 mg and 6 mg dosing of RTH258 in central subfoveal thickness improvement compared to 0.5 mg ranibizumab, with the dosing interval safely being extended 30 days beyond the regular monthly interval making it a q8w dosing formulation [13].

Alcon Research (Ft. Worth, TX; Basel, Switzerland) took over further development of RTH258 in phase 2. The phase 2 OSPREY trial compared the molecule with aflibercept in a 56-week study duration on 89 eyes showed non-inferiority compared to aflibercept in a q8w dosing schedule and supported further development [15, 17].

Alcon Research initiated the phase 3 trials with 2 similarly designed HAWK and HARRIER trials in treatment naïve nAMD patients at 408 sites globally. 3 mg and 6 mg dosing of brolucizumab were compared with 2 mg of aflibercept in 1775 target eyes, whereas HARRIER trial was designed for head to head comparison of

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6 mg dosing with 2 mg of aflibercept targeting 1049 eyes. The studies were completed in March 2018 with 1082 patients in HAWK and 743 patients in HARRIER trials [10]. The brolucizumab dosing included 3 monthly loading doses at 0, 4 and 8 weeks and then every 12 weeks (q12w) injection interval, with an option to switch to q8w dosing based on disease activity. Aflibercept followed a q8w fixed dose interval schedule. At 48 weeks, the primary outcome, that was non-inferiority of BCVA in patients receiving brolucizumab compared to aflibercept was demonstrated successfully in both 3 mg and 6 mg dosing. 55.6% of the patients in HAWK and 51% of the patients in HARRIER trials in 6 mg group and 49.4% of patients of the 3 mg group maintained q12w dosing at the end of 48 weeks. When adjusted for the absence of disease activity during the first q12w interval, the probability of maintaining the dosing increased up to 85.4%. Brolucizumab resulted in significantly less disease activity and greater central subfoveal thickness reduction at the end of the 16-week period. The 16-week period was an important temporal landmark as till this point, all the arms had similar loading dose schedule and follow-up providing a head to head comparison to aflibercept. The molecule also showed to be significantly better in drying the macular oedema with more reduction in intraretinal fluid/subretinal fluid and sub-RPE fluid at weeks 16, 36 and 48. Serious adverse events were comparable in both groups during the 48-week period and has thus been established for the safety of the drug [10]. The 96-weeks reports are yet to be published after statistical analysis and are anticipated to give a better insight on the dosing requirement, maintaining the visual gain and stability of macular oedema reduction.

Spirited by the promising phase 3 results, Novartis has filed a biological licence approval application with USFDA and has secured an expedited approval for the drug. Brolucizumab is anticipated to be launched for clinical use by the end of 2019 following its USFDA approval [11].

The molecule has in conclusion, shown better promise than existing anti-VEGF options such as better molar dosing, better tissue penetration, less systemic exit, longer anti-VEGF suppression, non-inferior BCVA improvement and better anatomical outcome when compared with aflibercept and ranibizumab. The real-world translations of these promises are bound to be scrutinised after the marketing approval, as they have the potential to reduce the healthcare burden by shifting the treatment protocol to q8w or q12w dosing interval [7–9, 18].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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