Faricimab- Can it Reset the Recent Safety Doomed Innovations in Retinal Pharmacotherapy?

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ABSTRACT

After the consecutive success of multiple anti-VEGF molecules in the last decade such as ranibizumab, bevacizumab and aflibercept, innovations in the retinal pharmacotherapy has gone through a rough phase in the recent past. Multiple promising molecules such as brolucizumab and aflibercept faced drug induced inflammation. Furthermore ranibizumab port delivery system was associated with procedure related vitreous hemorrhage, which though improved after modification in the surgical procedure, still is a challenge. Faricimab is another innovative molecule that has shown excellent safety and efficacy in the phase 3 trials. We hope that entry of Faricimab might reset the recent safety doomed innovations in retinal pharmacotherapy?

Keywords: Faricimab, Anti-VEGF, Long acting.

Long-term vascular endothelial growth factor (VEGF) inhibition has been a desire for clinicians for the management of VEGF mediated retinal vascular diseases. Evidences have shown that regular monthly injections have visual acuity benefit. However, monthly (Q4) injections are not followed in the real world.[1]

Multiple molecules with the possibility of a Q12 or more extention have been explored in the recent past. Abicipar, Brolucizumab, Ranibizumab port delivery system (RPDS) and Faricimab were the innovative molecules on the forefront with the ability to provide long term VEGF inhibition.[2-5] However, some of these key molecules (Abicipar and Brolucizumab) encountered a few adverse events, in particular, significant ocular immune reactions.

In this editorial, we will discuss how newer retinal pharmacotherapy is facing a setback and if Faricimab will be able to break the chain and be a realistic and safe molecule for long term VEGF suppression.

The fact we all need to understand is that biologics which include anti-VEGF molecules consist of amino acid chains (protein) and utilize living cells either animals or microorganisms during their development process.[6] A protein has an inherent capability to incite immune reactions (immunogenicity). Immunogenicity might get overshadowed in sick patients like patients with various cancers. However, the eye is not only a window of systemic diseases, but also a very transparent window to detect immunogenicity in the form of cells, flare, vasculitis, sometimes endophthalmitis and even vascular occlusions. Eyes give a real challenge to the manufacturers involved in research and development of newer biologics in the field of ophthalmology. Challenges are in terms of refined techniques, control on endotoxins and various other factors which the industry is still unaware of, as in the case of brolucizumab.[7] Brolucizumab was an excellent molecule, that all of us retina specialists were waiting for with excitement.[8] The Industry was equally excited to provide this therapy to us and ultimately to our patients for their benefit. However, an immune response which was never seen before with any of the other anti-VEGFs in the form of retinal vasculitis including retinal vascular occlusion dampened the excitement and its usage around the globe.[9] This was a setback in the advancement towards new generation anti-VEGF molecules. None of us including the

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manufacturing company still exactly don't know what is wrong and how it can be fixed. It's just that we have been witnessing the pubmed data getting richer with reports of intraocular inflammation predominantly and retinal vascular occlusions with vision loss in very few cases. There was some hint of immunogenicity in the published results of HAWK and HARRIER.[3] However, it might have skipped the investigators eye as they would have never experienced retinal vascular occlusions with anti-VEGF therapy which was revealed after careful analysis of the HAWK and HARRIER cases with immunogenicity in retrospect.[10] Brolucizumab received US-FDA approval and is also approved in many other countries. However, due to inflammation, its use has been limited. In the pivotal phase-III HAWK and HARRIER studies of treatment-naïve nAMD patients, an overall rate of 4.6% of any IOI was reported following a review by the safety review committee (SRC). The rate of the development of retinal vasculitis was reported to be 3.3% (36/1088) and that of concomitant retinal vasculitis and retinal vascular occlusion was 2.1% (23/1088). The overall incidence of moderate vision loss due to IOI was < 1%.[10] Until now, none of the real world data published is reassuring enough for clinicians to use it without any safety concerns. We have designed a guideline (BRAVE SAVE) that might help mitigate the risk.[11,12]

Another setback in the advancement of retinal pharmacotherapy was the denial of the US-FDA approval to Abicipar due to immunogenicity.[13] Abicipar was the first effort to introduce a non-monoclonal antibody drug in the armamentarium of retinal pharmacotherapy. Abicipar was designed on a completely different, exciting and innovative platform called designed ankyrin repeat proteins (DARPins). DARPins are derived from naturally occurring ankyrin protein repeats. The repeats are usually limited to four to six in number and thus result in a right-handed solenoid structure with a hydrophobic core and a large, grooved, solvent accessible binding surface. Libraries of DARPin molecules of varying repeat numbers have been generated by a patented technology of protein engineering and recombinant DNA.[14] In the early trial results, incidence of immunogenicity was very high (15.1-15.7%).[15] However, it was identified that inflammation in the abicipar group may have been the result of impurities remaining from the bio-engineered E. coli cells used to generate the abicipar molecules. It underwent change in the purification process which lead to the subsequent reduction in the incidence of immunogenicity (8.9%) but wasn't enough to call it safe for the patients.[16] Among patients with IOI associated adverse events in the abicipar groups, the IOI was reported to have resolved without sequelae in 74.5%, resolved with sequelae (primarily vision loss) in 10.9 % of patients. Retinal vasculitis occurred in 1.8% of abicipar-treated patients.[15] Again the industry had no clue on how to further reduce the immunogenicity with Abicipar. There could be an argument that when we are aware that biologic protein have inherent antigenicity then shouldn't we accept these rare adverse events? Answer to this is that, the safety bar has been set very high by the off label bevacizumab and approved anti-VEGFs such as ranibizumab and aflibercept. There have been incidences of anterior segment reactions and rarely posterior segment with the existing anti-VEGF molecules but the percentage was very low and it was tolerable with none of the cases feared of vision loss.[17,18]

Ranibizumab port delivery system (RPDS) is again a ground-breaking effort towards sustained long term VEGF inhibition.[4] However, here, it does not pertain to molecular innovation. It's predominantly advancement of the delivery system. Trial results are promising but need of surgical intervention and associated vitreous hemorrhage (4.5 % after surgical procedure optimization) might limit its usage on a larger scale.

Another exciting front that is soon going to be opened in the retinal pharmacotherapy worldwide is the approval of biosimilars of ranibizumab and aflibercept. There are drugs which are similar to the already approved molecules with established safety profiles and some of these biosimilars have shown successful results in phase 3 trials. However, there is no innovation here, similar drugs are being produced with lower investments leading to lower cost of the drug.[19,20,21]

Faricimab is probably the only molecule now, which is seen with lots of excitement and hope after its successful phase 3 trial results in the recent past. The YOSEMITE and RHINE studies in DME assessed two dosing regimens of faricimab given every two months or at personalised treatment intervals (PTI) of up to four months, compared to aflibercept given every two months. Patients in the PTI arm could receive treatment every one, two, three or four months, adjusted based on their disease activity. The TENAYA and LUCERNE studies in nAMD assessed faricimab given at fixed intervals of every two, three or four months - selected based on their disease activity at weeks 20 and 24 - compared to aflibercept given every two months. These studies consistently showed that faricimab, given at intervals of up to four months, offered non-inferior vision gains compared to aflibercept, given every two months. Approximately half of people eligible for extended dosing with faricimab were able to be treated every four months in the first year in the YOSEMITE and RHINE studies in DME and the TENAYA and LUCERNE studies in nAMD. IOI was low (1-5-2.5%) in all the studies with no cases of retinal vasculitis.[5]

Faricimab is an innovative molecule different from the previous anti-VEGF molecules. It is a bispecific antibody developed on the CrossMAb platform which directly blocks Ang-2 as well as VEGF action. The lock and key model ensures heterodimerisation with each molecule having one anti-Ang-2 domain and one anti-VEGF domain. Inhibition of Ang-2 may thus result in reduced neovascularization as well as reduced vascular permeability and inflammation. Secondarily, in the absence of Ang-2, Ang-1 will have better binding to the Tie-2 receptor making the vessels that have already been formed more mature and stable. [22] Hypothetically this might result in the conversion of exudative nAMD to non-exudative nAMD which could be the ultimate objective of any advanced therapy. Furthermore, the probable reason for faricimab being less immunogenic is due to its structure which is similar to the full length antibody and in addition, the Fc region of faricimab has been engineered to abolish binding interactions with all Fc gamma receptors and neonatal Fc receptors, resulting in lower systemic concentrations compared to wild-type IgG1 antibodies, and a reduced potential for platelet activation.

There was a time few years ago when we had a plethora of drugs in the innovation pipeline for the advancement of retinal pharmacotherapy. Now, we lack such a strong pipeline and is not a great sign for the future of retinal pharmacotherapy.

The Faricimab Phase 3 trials are promising in terms of efficacy and more importantly safety.[5] We hope that there is no disconnect between the trial results and the real world similar to brolucizumab because faricimab could be the key molecule to reset the recent safety doomed innovations in retinal pharmacotherapy.

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