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ANTI VEGF - VIEWPOINTS

The introduction of intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents has led to paradigm shifts in the management of retinal disorders of various etiologies. We have come a long way from macular photocoagulation for neovascular age-related macular degeneration (nAMD) and grid laser photocoagulation for macular edema secondary to vein occlusions (RVO) and diabetic retinopathy (DME). The therapeutic implications of anti-angiogenesis were first recognized in the 1970s in the field of oncology. The development of anti-VEGF agents, with the first agent reaching ophthalmic clinical practice in 2004, has revolutionized the treatment paradigms for many retinal diseases. The fact that intravitreal injections have become mainstay in the treatment of these diseases is common knowledge now and most ophthalmologists do not hesitate in initiating treatment. Though there is no large-scale survey amongst general ophthalmologists in India about which regimen they prefer, we suspect that many may not be convinced about benefits of a loading dose or relentless reinjections despite persistent disease activity. In this Panel discussion we aim to provide answers to certain dilemmas in the practice of anti VEGF.

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Questions

1. **In the management of PDR which according to you has an upper edge, AntiVEGF or Lasers?**

   Dr Muna Bhende: The role of PRP for PDR has stood the test of time, and is definitely a more practical mode of management for our population. This includes affordability and follow-up, the latter being the most important caveat for anti VEGF monotherapy in PDR. I think the current pandemic has proved to be the best judge of this with our recent experiences in surgery for complications of PDR. However, performing a good PRP requires time, patience and a certain degree of skill in addition to access to a laser machine. The last two are relative, considering that one would expect a retina specialist or for that matter anyone who treats retinal conditions to have adequate skills and access to a laser machine. I would use a combination of laser and anti VEGF if there is concurrent PDR and macular edema.

   Dr Sourav Sinha: For PDR, I would prefer laser photocoagulation. In case of PDR with CSME then an antiVEGF or two to decrease macular edema and then start PRP within 2 to 3 weeks.

   Dr Manish Nagpal: I don't think there is anything like an upper edge. Both have their indications and are complimentary to each other. Once a PRP is indicated then laser sittings are a must. Nowadays we typically inject an anti VEGF along with laser sittings which helps overall regression of the retinopathy faster and also prevents occurrence of secondary oedema to laser. The only contraindication to anti VEGF s is presence of existing traction or traction causing impending lifting of macula so as not to worsen that status unless one is planning surgery for the same and in that case it may be given as a preparatory role.

   Dr Anand Rajendran: In the management of the neovascularisation of PDR, I believe Laser PRP holds prime position , for being a finite and permanent therapy.

2. **When would you consider switching of AntiVEGF agents?**

   Dr Muna Bhende: In neovascular AMD , RAP or PCV I would switch if I do not see any anatomical or functional response with 2 consecutive monthly injections, generally after the loading dose. If there is a recurrence due to lack of followup after a few injections, I would look at previous records and the response before deciding whether to restart the same medication or switch. In DME or RVO in addition I would particularly look at topical and systemic medications and systemic status before deciding that the anti VEGF is not working. We also see cases where a previously effective agent gradually stops showing its effect, despite adherence to strict protocols, this is another situation where one would like to switch agents. In PCV and DME, after repeat imaging one may even add on focal treatment with laser in extrafoveal lesions .

   Dr Sourav Sinha: In neovascular AMD or PCV I would switch after 2 or maximum 3 injections if I don't see any substantial visual improvement, For DME or RVO I would switch to Ozurdex .

   I am increasingly using Ozurdex now a days even in minimally cataractous patients with severe DME as a naive treatment.

   Dr Manish Nagpal: For a typical diabetic oedema which is treatment naïve I would usually start with one or two injections of antiVEGF. Most of the time the response is good and adequate... if after that there is a recurrence or if the response is inadequate then I would shift to Ozurdex to get better efficacy. I usually do not switch from one antiVEGF to another.

   However if the oedema is quite extensive to begin with and has sub foveal serous fluid or lot of central lipid deposition, I would start right away with Ozurdex instead of antiVEGF as the efficacy of a steroid is better in those situations.

   In AMD I usually don't switch anti VEGF agents typically unless it's a case of atypical AMD or IPCV or a non-resolving PED when I may switch from Accentrix to Eyelea.

   Dr Anand Rajendran: For DME, I would think of switching Anti-VEGF agents if I find no discernible improvement (100 micron reduction in central subfoveal thickness) after 3 consecutive anti-VEGF injections. For Neovascular AMD, my threshold is lower - I would consider switching Anti-VEGF agents earlier - if I find no definitive improvement (100 micron reduction in central subfoveal thickness) after 2 consecutive monthly anti-VEGF injections.

3. **Has the introduction of Brolucizumab in the armamentarium of AntiVEGF affected your choice of drug?**

   Dr Muna Bhende: The published efficacy data of Brolucizumab is indeed encouraging. From the experiences I have heard from my professional colleagues in various webinars, it is widely used and effective. However for me, it is the risk of inflammation and occlusive vasculitis that is yet

not clearly defined and understood. The practicality of adhering to the special post injection follow-up described by many is also hard, given our patients may not be living close enough. We need to understand that patients enrolled in a clinical trial do not always match our routine patient population so it is difficult to extrapolate all safety data. Hopefully we will have more information on safety that will help me confidently add it to my choice of agents.

Dr Sourav Sinha: Prefer to use in refractory CNVM secondary to ARMD or recurrent CNVM or rarely as a naïve therapy in a PCV with a loading dose of 3 monthly injections. (have been using it very sparingly)

Dr Manish Nagpal: Haven't used it at all

Dr Anand Rajendran: I have used it very sparingly, and hence it has not significantly altered my choice of therapeutic agent yet.

4. **Do you think prolonged treatment with AntiVEGF is more detrimental vis-a-vis under treatment in AMD?**

Dr Muna Bhende: In this context, I think you mean progression of geographic atrophy with prolonged treatment and the opinion that some fluid is good for vision. In our part of the world, beyond a point, most of us follow a PRN regime which runs the least risk of progression of atrophy. However, there is a need to clinically assess the macula as well as pay attention to various biomarkers that would indicate worsening of function despite anatomical success. It is important to determine whether lack of response actually translates into vision loss - especially for type 1 CNV. There is also the need to decide when treatment is futile and decide regarding stopping treatment - especially if there is increasing fibrosis in a lesion.

Dr Sourav Sinha: Prolonged treatment is necessary till patient maintains and what patient feels is "good" vision. Undertreatment is not an option, except for the financial issues (maintain on Bevacizumab if necessary).

Geographic atrophy is to be looked for, but in an eye with fibrosis it is possibly time to slow down / stop treatment.

Dr Manish Nagpal: I use antiVEGFs based on their need and indications and when there is distinct activity of the membrane. Hence their role is to prevent progression and worsening of the status. I use them on PRN basis only in most situations unless there is are multiple recurrences in which case I like to keep them on a 3 monthly injection even after drying up to reduce risk of further recurrence. But I would not use anti VEGFs if the macula is dry on oct on the follow ups.

Dr Anand Rajendran: No, the data suggests that the prime cause of patients not achieving optimal visual potential is undertreatment.

CONCLUSION:

Although new agents like Brolucizumab are touting longer durability and better drying effects, its acceptability amongst our experienced and esteemed panelist seems to be an issue due to the documented side effects of inflammation and occlusive vasculitis.

Treatment protocols as described in myriad of studies actually differ in the real world.

One of the most important bottle-neck limiting the use of Anti VEGF is the reinjections causing an immense financial burden. However we are going to witness developments in delivery systems in the form of Port delivery systems and hydrogel implants which probably could reduce this burden in the near future.

There is no doubt that the introduction of anti-VEGF therapy has had a greater effect on the world of retina than any other advance in the past few decades.