

Anti-Vascular Endothelial Growth Factors; When to Stop

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Abstract: Age related macular degeneration is the leading cause of blindness in people over 50 in developed countries. Anti-vascular endothelial growth factors were introduced as the standard treatment for neovascular age related macular degeneration. Different regimen has been utilized to deliver those injections. The result is the numbers we are injecting are increasing over the years since we started treating with Anti-VEGFs. There are several reasons we cannot seem to stop giving those injections. However, with the new revelations about macular atrophy developing during or following those injections, it is time to stop and think when enough is enough.

Keywords: Age, macular, degeneration, aflibercept, ranibizumab, atrophy, geographic, subretinal, intraretinal, focal, laser, diabetic, maculopathy

1. INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of blindness in industrialized countries¹. Disease development is complex as it involves genetic as well as environmental factors². Neovascular AMD (nAMD) represents an average of 10% of the total AMD cases³. Anti-Vascular endothelial growth factors (Anti-VEGF) were introduced as the standard treatment for nAMD⁴. Without treatment, the prognosis for nAMD is normally poor with significant deterioration of vision. Ranibizumab was the first approved anti-VEGF for nAMD⁵. Later a fliobercept was introduced aiming to extend the period between injections and in the meantime, reduce the load on centers providing treatment. Although both medicines were introduced as a monthly injection for the first three injections, they differed in the way patients were treated after the loading dose.

2. DISCUSSION

Different treatment policies are now in place. However, after ranibizumab was first recommended to continue pro re nata following a loading dose of three injections, a fliobercept was recommended as 2 monthly injections for the rest of the first year after the first three loading doses. Later ranibizumab's new recommendation was to give monthly injections for a year. The term of treat and extend was later introduced. The treat and extend approach

which is proactive, reduces the burden on centers giving the injections monthly. Several studies with ranibizumab treat and extend showed that eyes sustained improvement in visual acuity in the first year of treatment⁶. Trials comparing pro re nata injections versus monthly injections were in favor of monthly injection in view of sustained vision⁷.

The concept of macular atrophy following and during treatment with Anti-VEGF was recently introduced. Areas of macular atrophy appear within the macular lesion. Those areas could simply be a part of the natural disease progression or extensive degenerative disease because of the use of anti-VEGF which reduces blood flow to the choroid, an essential part of blood supply to retinal pigment epithelium.

Should this macular atrophy be a result of the use of anti-VEGFs, it would be essential to know when to stop using them. In general, those medicines are quite expensive and it is not in anyone's best interest to overuse them. In real practice, we tend to over treat as there are several factors that encourage us to do.

Subretinal and intraretinal fluid tends to be perceived as a bad omen. They appear to most of us as a sign of active disease. We feel the urge to inject whenever we see them. Patients' visual acuity which tend to vary from day to day, can be another confusing factor. When we measure them on Snellen's chart a line above

and below the previous reading. However, when we measure them on ETDRS letters with nAMD playing the background of our mind, we tend to be less tolerant to any change in the number of letters read. Over the years, patients are monitored for nAMD patients, who are already in the age of developing cataract, develop the condition. This makes an originally confusing condition even more perplexing. The fact that many centers have no tolerance to both decrease in visual acuity and presence fluid lead to the patients being over treated for nAMD.

To make things even more confusing, elderly patient with AMD can have both AMD and diabetic maculopathy, both diseases can had genetic and environmental factors that lead to the condition. When diabetic maculopathy develops in an eye with nAMD, sometimes it is hard to distinguish where the fluid is coming from. Although the treatment for both conditions is about the same in terms of Anti-VEGFs injections, it is essential to distinguish what is what. Diabetic maculopathy might be treated with focal or macular grid. However, with nAMD in the background the proposed intolerance to fluid would make those patients more likely to receive a more expensive short lived treatment for their diabetic maculopathy.

One other confusing situation is when patients treated for nAMD and they develop an epiretinal membrane. Obviously not all epiretinal membranes are surgical. However some of them are. Would it hurt the pride of a medical retinal specialist to refer a nAMD to the surgical colleague who says no this is not a surgical case. Sometimes it does. Therefore patients with epiretinal membranes tend to be over treated with injections when all what is needed is the epiretinal membrane peeling. Criteria for surgical referral in cases with nAMD and epiretinal membrane is required.

3. CONCLUSION

The question now is when enough anti-VEGFs is enough. A large multicenter study is needed to assess criteria for stopping treatment with anti-VEGFs. Long term follow up of patients treated with anti-VEGFs with even some of them lost to follow-up shows that visual acuity loss go to the baseline level after 5-7 years of treatment⁸. Would it be wise to stop at a certain level of disease with some remaining possible activity rather than treating the disease completely and ending up with what we can call

it an anatomical rather than functional success. This is the situation where there is total disappearance of fluid but we are left with subretinal scarring or macular atrophy. Subretinal scarring is one of the criteria when we should stop anyway but are we stopping a bit too late in this condition. Should we accept a little bit of fluid here and there intrasubretinally if it is stable. Should we even wait a little when visual acuity is less on one assessment and repeat assessment perhaps sooner. Should we resort more to post or during treatment fluorescein fundus angiography to decide on the activity of the disease. Do we need new parameters to decide on the progression or regression of nAMD. In the author's view, a new set of criteria is required to decide when to give an injection after the initial loading dose. Neither of the treat and extend policy, continuous monthly or pro re nata injections appear to be a satisfactory way of giving those injections. Anti-VEGF manufacturers obviously fund many studies about their medicines. This helps to develop new regimens of giving more injections to control the disease. It cannot be that the only way to control nAMD is more and more injection. There must be an easier less invasive method to treat the condition.

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