Consensus Document on the Use of Avastin (Bevacizumab) in Retinal pathologies

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BACK GROUND

This document was created, debated, amended and approved by the members of the vitreoretinal association of Pakistan. This exercise was carried out on behalf of the Ophthalmic Society of Pakistan. The central council of the OSP had expressed with concern that while the use of Avastin was increasing exponentially, most Ophthalmic practioners had limited knowledge and experience in the use of this drug. There was as yet no information available in textbooks. It was therefore incumbent on the people who had acquired the most knowledge of this drug to share their knowledge and the fruit of their experience for the benefit of patients.

Vitreo Retinal Association of Pakistan (VRAP) therefore took up this task.

INTRODUCTION

The members of the Vitreo-retinal Association of Pakistan recognize that Bevacizumab (Avastin) is a powerful anti VEGF-A agent. Its use in Ophthalmology is currently off label, however it cannot be withheld from patients as it is

1. The only treatment available for certain disorders at a reasonable cost.
2. An effective adjunct to treatment of certain disorders where no on label treatment is available.

Like any other powerful agent it has certain side effects and the procedure of intra-vitreal injection can have complications, therefore is used carefully. As things stand today not enough textbook data is available on the use of this drug to guide fellow professionals. We therefore feel that it would be prudent to create a consensus document that pools our experience. It is also important to emphasise that new information is emerging and more experience is being acquired and therefore the guidelines or suggestions for use of intra-vitreal Avastin are expected to change over time.

Bevacizumab (Avastin) is an anti VEGF-A agent. VEGF (vascular endothelial growth factor) promotes endothelial cell proliferation and increases vascular permeability. It is therefore natural to assume that retinal vascular pathologies where the underlying problem is new vessel formation, increased leakage from capillaries or both could be potential targets for therapy with Avastin. Therefore the possible list of diseases which, could be subjected to treatment by Avastin are:

1. Choroidal Neovascularization (CNV)
2. Proliferative Diabetic Retinopathy (PDR) without Vitreous haemorrhage.
3. Proliferative Diabetic Retinopathy (PDR) with vitreous haemorrhage.
4. Clinically significant macular oedema.
5. Eales Disease.
6. Coats disease and other heredetary telengectasia
7. Retinopathy of Prematurity (ROP).
8. Central Retinal Vein Occlusion (CRVO)/ BRVO.
9. Neo-vascular glaucoma.

However before we describe our cumulative experience in the management of these problems a word of caution would not be misplaced. Avastin is non-specific and it closes down all collaterals and care should be taken when injecting patients who are at risk of either stroke or myocardial infarction (MI). They may still receive an injection as the reported

incidence of these complications is quite low. Therefore informed consent is important.

Full aseptic measures need to be taken during the injection in an operating theatre as the recipients are either immunocompromised or develop a significant cumulative risk as they may require multiple injections. (Appendix 1)

In the pre-amble it is also important to emphasise that the effects of Avastin on retinal vasculature are often transient.

Dose: The dose of Avastin may be 1.25 to 2.5 mg.

Repeat: When indicated it may be repeated between four to six weeks after the first injection.

Role of Avastin in

1. CNV: All forms of CNVs (secondary to ARMD, myopia and angioid streaks) respond to Avastin injection. We recommend three injections at monthly intervals in the induction phase and later on injection may need to be repeated if the CNV does not resolve completely or recurs. OCT and FFA judge the efficacy of treatment.

   However some CNVs do not respond at all to intravitreal Avastin and some relapse early and fail to respond again. Tachyphylaxis exists as well. Combination therapy may be tried in these cases.

2. Proliferative Diabetic Retinopathy (PDR) without Vitreous haemorrhage:

   In PDR there is no cause to give an injection of Avastin as primary and sole treatment if there is no vitreous haemorrhage. The treatment of PDR is pan retinal photocoagulation (PRP) according to ETDRS criteria.

3. Proliferative Diabetic Retinopathy (PDR) with vitreous haemorrhage:

   At the present moment there is no established treatment modality that causes the vitreous haemorrhage to resolve. Vitreous haemorrhage resolve either spontaneously or through surgery. Avastin temporarily closes down new vessels and could be helpful in preventing recurrent vitreous haemorrhage. Therefore Avastin may have role in helping natural resolution by preventing small recurrent haemorrhages. However this effect would only be significant in someone who has a low density vitreous haemorrhage. Natural resolution of dense vitreous haemorrhages is too unpredictable. Avastin can also cause sudden closure of new vessels and make their fibrous component predominant. It can enhance the any pre-existing traction retinal detachment (TRD) or create a TRD if there was a strong fibro-vascular component at the posterior pole. We have also observed that if the natural vasculature is already compromised then intravitreal Avastin may completely completly shut it down.

   We also feel that recurrent vitreous haemorrhages in eyes with adequate PRP are indicative of an anatomical structural abnormality and in these cases conservative treatment probably has no value.

   In light of these observations we suggest that a single or maximum of two intravitreal injections of Avastin may be used if the vitreous haemorrhage is of

   - Fresh low density (dense enough not to allow PRP, but still allows some retinal view or atleast a good red reflex).
   - Flat retina on B scan.

   It should not be used

   - If the vitreous haemorrhage is old (in excess of 3 months / white vit haemorrhage) and not resolving.
   - In dense vitreous haemorrhage (haemorrhage with no retinal view)
   - Pre-existing TRD seen directly or on B scan.
   - Recurrent vitreous haemorrhages especially those who have previously received Avastin.

4. CSMO: The primary treatment for CSMO is focal laser treatment. In cases of intractable Diabetic macular oedema i.e. macular thickening not responsive to laser treatment, especially that associated with Cystoid Macular Oedema (CME) Avastin, with or without Triamcinolone, is a good adjunct to focal laser treatment. Eyes with vitreous traction or taut hyloid face should not receive Intra-vitreal injection.

5. CRVO: Blood vessels tend to re-canalize as the clot in the lumen of the vessel lyses. However the internal retinal layers may suffer permanent damage either due to ischemia or oedema. Our overall experience is that no significant positive visual gain was achieved after intravitreal

injection of Avastin in Ischemic CRVO. However the subject is still under study. Some positive gains may be achieved in non-ischemic CRVO. Visual acuity and OCT are important guides.

6. We have so far found that telengectasia in Coats disease do not shutdown as a result of intravitreal Avastin. It may however be used if macular edema has freshly developed in an eye secondary to Coats disease. For para foveal telengectasia.
7. ROP: ROP is a most difficult area. The disease is incompletely understood; the infants are premature, very fragile, grossly underweight and often belong to previously infertile parents. The natural history of stage IV disease is not good. There is very limited data available world wide on this disease. Great caution therefore needs to be exercised when using Avastin in this disease.
8. Chronic Uveitis: Needs more evaluation.
9. Neo-vascular Glaucoma: Judicious use along with PRP and other surgical procedures may be considered.

Glaucoma

The future of glaucoma management may change entirely as genome-wide association studies succeed in discovering the ultimate cause of disease.

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