Original Article

Ophthalmology and Allied Sciences
Volume 2 Number 2, July - December 2016
DOI: http://dx.doi.org/10.21088/oas.2454.7816.2216.4

How Anti-Vegfs have Changed the Management of Retinal Diseases

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Abstract

The discovery of Vascular Endothelial Growth Factors (VEGF) and its role in retinal diseases has provided insight in the retinal diseases and as an example of translational medicine, invention of anti-VEGF molecules has provided new modality of therapy for retinal diseases. This review article comments on the utility and the changes in the therapy of retinal diseases brought up by the availability and use of these Anti-VEGF molecules.

Keywords: Anti-VEGF, VEGF, Diabetic retinopathy, Eale's Disease, Retinoblastoma, Retinopathy of Prematurity.

In last decade it has been obvious by various experimental and clinical studies that Vascular Endothelial Growth Factor (VEGF) is one of the major cytokines which play an important role in inflammatory and ischemic processes in the eye. VEGF was first identified in guinea pigs, hamsters, and mice by Senger et al. in 1983 [1]. It was purified and cloned by Ferrara and Henzel in 1989 [2].

It is a signal protein produced by cells that stimulates vasculogenesis and angiogenesis. It is part of the system that restores the oxygen supply to tissues when blood circulation is inadequate such as in hypoxic conditions [3]. It has an important role in the normal development, maintenance and repair of vasculature system, however over expression of various isoforms and their role has been identified in various diseases in breast cancer, rheumatoid arthritis, angiosarcoma and colon cancer.

It is also known that altering the available VEGF can be helpful in management of cancer. Solid cancers cannot grow beyond a limited size without an adequate blood supply; cancers that can express VEGF are able to grow and metastasize.

Over expression of VEGF can cause vascular disease in the retina of the eye and other parts of the body. Drugs which can neutralize the available VEGF have been designed to treat the related conditions. Although there are many anti-VEGF described in the literature like Bevacizumab, Ranibizumab, Pegaptanib, Anecortave acetate, VEGF-trap, Squalamine lactate, Combretastatin A4 Prodrug, AdPEDF, SiRNA, Cand5, TG100801, the most studied and frequently used are Bevacizumab (Avastin; Genentech, Inc., CA) Ranibizumab (Lucentis; Genentech, Inc., CA).

The availability of these new class of molecules have made an paradigm shift in the management of various eye diseases. The article will discuss the change in the intervention strategy in these disease after the advent of Anti-VEGF molecules.

Wet ARMD (Age Related Macular Degeneration)/ Choroidal CNVM (Choroidal NeoVascular Membrane).

Azad et al. were the first to publish the results of Bevacizumab for treating wet AMD in the Indian population in 2008 documenting improved vision in all AMD lesion types[4]. Before that the mainstay of treatment was Antioxidants as preventive modality and LASERs to treat aggressive and obvious

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CNVM with associated permanent central scotoma. The Photodynamic Therapy (PDT) helped in cases with occult CNVM and resulted in lesser collateral damage as seen with direct photocoagulation.

Overall the aim of these pre-AntiVEGF therapies was to stabilize future progression of disease but no improvement could be anticipated. With the popular use of Anti-VEGF it was possible to treat wet ARMD with an anticipation of improving and stabilizing the central vision with no collateral damage whatsoever. in this context the use of anti-VEGF for AMD in India, most would use Bevacizumab monotherapy on a loading dose followed by PRN dosing. Ranibizumab may be preferred in affordable patients and in poor-responders/those developing tachyphylaxis to Bevacizumab [5].

Diabetic Retinopathy

Diabetic retinopathy was being treated with Pan Retinal Photocoagulation (PRP) since the publication of DRS (Diabetic Retinopathy Study) and subsequently ETDRS (Early Treatment Diabetic Retinopathy Study) [6] defined the roles of PRP and Macular Grid laser for PDR (Proliferative Diabetic Retinopathy) and macular oedema respectively.

Introduction of steroids for management of PDR and macular oedema changed the scenario of management of diabetic retinopathy in a way that the macular grid laser went out of practice though soon it was realized that the long term effects of Steroids resulted in poorer visual outcome when compared to laser therapy because of associated adverse effects of long acting steroids like cataract and glaucoma [7].

Anti-VEGFs provided better outcomes in terms of visual gain and reduction in retinal thickness when compared to LASERs, and this was true for both Ranibizumab [8] and Bevacizumab [9]. In the short term, intravitreal Anti-VEGF result in greater VA and retinal thickening outcomes when compared to LASERs. However, these agents require maintenance with repeated injections and also have longer-term associated side effects and higher costs [10].

Another use of Anti-VEGF agents have been in the PDR where Vitrectomy is indicated for traction, ERM (Epi-Retinal Membrane), or repeated vitreous haemorrhages. In these cases prior injection of Anti-VEGF agents has resulted in better outcome in terms of visual gains and lower incidence of repeat haemorrhages [11].

Eale's Disease

In Eales disease the peripheral retinal ischemia results into excessive secretion of angiogenic factors [12]which promote neovascularisation and subsequent complications like vitreous haemorrhage, anterio-posterior traction, tractional retinal detachment and combined retinal detachment [13]. Peripheral ischemic areas as evident on clinical evaluation and angiography is treated by LASER photocoagulation to ablate the relevant retina and reduce the angiogenic factors. No this is accomplished by use of anti-VEGF injections and has promising results [14]. Though it is also important to note that the anti-VEGF agents cause aggravation of traction which is very common in these patients [15].

Retinal Venous Occlusions

Retinal vein occlusions are a group of vascular occlusions comprising of central retinal vein occlusion, hemi retinal vein occlusion and branch retinal vein occlusion. The vision loss is related to immediate ischemia, macular oedema, and subsequent neo-vascularisation and its complication comprising of vitreous haemorrhage, epi-retinal membranes causing Vitreo-macular traction and glaucoma.

Clinical trials have shown benefits of LASER to the affected ischemic areas by reducing the incidence of neovascularisation and reducing oedema. Intravitreal steroids and anti-VEGF agents have been Various trials have conclusively studied the benefits of anti-VEGF given intra-vitreally in these patients of Retinal vein occlusion diseases [16].

The macular oedema in CRVO and BRVO responds to intravitreal therapy of steroids and various anti-VEGF agents. Best visual acuity results at 1 year are found after aflibercept 2 mg and Bevacizumab 1.25 mg in CRVO, and Ranibizumab 0.5 mg in BRVO. The CRUISE (Ranibizumab for the Treatment of Macular Oedema After Central Retinal Vein Occlusion Study: Evaluation of Efficacy and Safety) study [17] and The BRAVO (Ranibizumab for the Treatment of Macular Oedema Following Branch Retinal Vein Occlusion: Evaluation of Efficacy and Safety) study [18] reported low incidence of cataract progression and no incidence of cataract surgery or endophthalmitis.

Neo-Vascular Glaucoma (NVG) in the patients of retinal venous occlusions has poor prognosis and the treatment options are limited to aggressive drug therapy, shunt surgery, cyclodestructive procedures and photocoagulation. Each one having its limitation in terms of outcome and patient acceptability. The use of anti-VEGF agents has proven to be of value in NVG by inducing regression of anterior segment

ischemia and controlling of Intra Ocular Pressure (IOP) [19].

Retinopathy of Prematurity

Retinopathy of prematurity (ROP) is a group of intraocular finding due to aberrant retinal vascularisation due to ischemia in the developing neonate eye. The vision loss associated with ROP is due to retinal detachment due to traction caused by the aberrant vascularisation. The treatment as per STOP ROP trial is to treat the peripheral un-vascularised retina by LASER photocoagulation so as to anchor the retinal tissue and to reduce the load of angiogenic factors.

The first multicenter randomized, controlled trial was the BEAT-ROP study which demonstrated an advantage of intravitreal Bevacizumab over laser therapy for zone I or zone II with stage 3+ ROP by improving structural outcomes, decreasing recurrence, and allowing continued development of peripheral retina [20].Though there is still controversy about the short term concerns like recurrences, endophthalmitis, choroidal rupture, retinal haemorrhage, and endophthalmitis. The long term complications and systemic adverse effects are not known due to recent application of anti-VEGF in this disease [21].

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