Clinical Ophthalmology

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REVIEW

Emerging roles for antiangiogenesis factors in management of ocular disease

This article was published in the following Dove Press journal:
Clinical Ophthalmology
12 March 2013
Number of times this article has been viewed

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Abstract: The first antivascular endothelial growth factor (anti-VEGF) was developed as an anticancer drug for colonic carcinomas. Since then, anti-VEGFs have developed in scope and indications. They have revolutionized the treatment of exudative macular degeneration and have had a major impact on treatment of several other conditions. This has resulted in an increased number of patients seeking treatment with new treatment options and has had a considerable financial impact on health care resources. Anti-VEGFs have been used in the treatment of all age groups of the population ranging from infants where it is used for treatment of retinopathy of prematurity to the elderly where it is used in exudative macular eegeneration.

Keywords: ranibizumab, bevacizumab, pegaptanib, retina, aflibercept, indications

Introduction

Vascular endothelial growth factors (VEGFs) were first described by Hata et al to contribute to retinal angiogenesis under hypoxic conditions.[1] These were thought to be the major underlying cause for retinal neovascularization in multiple retinal conditions such as retinopathy of prematurity (ROP), proliferative diabetic retinopathy (PDR), and ischemic retinal vein occlusions (RVO), etc. Early studies in the 1990s showed elevated levels of VEGFs in the vitreous of patients with subretinal neovascularization and choroidal neovascular membranes (CNVs).[2,3] Aiello et al first reported anti angiogenic effects of chimeric anti-VEGF agents in 1995.[4] Although bevacizumab was used and licensed for treating colon cancer, Ferrara et al,[5] Hurwitz et al,[6] and Michels et al[7] described the use of bevacizumab for the treatment of age related macular degeneration. Since then, anti-VEGF agents have been used for a number of indications. We describe the evolution of anti-VEGF agents, the evidence base, and subsequent practice in various ophthalmic subspecialties.

Pharmacological agents

Bevacizumab (Avastin®; Genentech, San Francisco, CA, USA) is a monoclonal antibody with a molecular weight of 149 kDa that inhibits VEGF. This binds with isomers of VEGF receptors A and B and reduces the drive for angiogenesis and vascular permeability. It is licensed for colonic tumors, metastatic breast cancer, and unresectable small cell lung cancer. Bevacizumab has been used in various ocular conditions and has been delivered by the intravitreal, subconjunctival, intracameral, and intracorneal routes. The ocular use of bevacizumab is on an off-license basis but appears to have become popular in comparison with other anti-VEGFs because of financial and economic considerations.

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Dovepress
http://dx.doi.org/10.2147/OPTH.S31016

Ranibizumab (Lucentis®; Lucentis; Genentech USA; Novartis International AG, Basel, Switzerland) is a monoclonal antibody fragment closely related to bevacizumab. This is smaller in size than bevacizumab with an approximate molecular weight of 48 kDa. It strongly binds to VEGF A receptors and inhibits vasculogenesis. It is licensed for neovascular macular degeneration and macular edema due to RVO and diabetic retinopathy. It is in widespread use for the treatment of neovascular macular degeneration.

Aflibercept (Eylea®; Regeneron Pharmaceuticals, Inc, Tarrytown, NY, USA; Bayer, Leverkusen, Berlin, Germany) is a fusion protein with binding domains for native VEGF receptors. It binds VEGF-A, VEGF-B, and placental growth factors 1 and 2 with high affinity. Studies have demonstrated that aflibercept suppresses choroidal neovascularization. Recent studies have suggested that aflibercept has a longer duration of action compared with other anti-VEGF drugs.

Pegaptanib sodium (Macugen®; OSI Pharmaceuticals, Melville, NY, USA; Pfizer, New York City, NY, USA) is a pegylated anti-VEGF aptamer which binds specifically to VEGF 165 receptor. It inhibits angiogenesis and reduces vascular permeability. It is a single strand of nucleic acid. Pegaptanib is licensed for use in neovascular macular degeneration. It is not recommended for neovascular macular degeneration by the National Institute of Clinical Excellence (NICE) in the UK.[8]

Verteporfin (Visudyne®; Novartis International AG, Basel, Switzerland) is a photosensitizing agent for photodynamic therapy (PDT) and is used for specific types of neovascular macular degeneration. Treatment involves an intravenous infusion of verteporfin and subsequent laser treatment to the area of interest. This produces highly reactive oxygen radicals and causes local endothelial damage and subsequent neovascular blockage. Classic and predominantly classic choroidal neovascular membranes were usually treated with this method. This treatment method has generally been superseded by anti-VEGF intravitreal injections but does have some indications in specific conditions. Other indications include periocular basal cell carcinomas.

Indications

Anti-VEGFs in neovascular macular degeneration

Michels et al first described the use of intravenous bevacizumab in age-related macular degeneration (AMD).[7] The same group reported on Phase I/II trials with intravitreal ranibizumab, which showed better results and was subsequently adopted as the preferred route of delivery of anti-VEGF agents into the eye.

The early results of these anti-VEGF agents showed significant promise for treatment of abnormal vasculogenesis, especially CNV. This encouraged large randomized trials for neovascular macular degeneration. Prior established treatment was PDT, which had limited success. In addition, there is now a large amount of clinical data which supports the use of anti-VEGF agents including bevacizumab, ranibizumab, and pegaptanib sodium in neovascular AMD. The first two seem to have achieved significant use in neovascular macular degeneration.

The MARINA trial was a multicenter, 2-year, double blind, sham-controlled trial with ranibizumab against sham injections. The trial concluded that intravitreal administration of ranibizumab at monthly intervals for 2 years prevented visual loss and improved the visual acuity in one quarter to one third of patients with minimally classic or occult CNV secondary to AMD.[9] This study had implications for previously untreatable variants of neovascular AMD such as minimally classic and occult CNV. The study showed that classic (all types) as well as occult CNVs were likely to benefit from intravitreal ranibizumab injection. Previous treatment options had included PDT, which was limited, restricted to specialized treatment centers and only recommended for classic or predominantly classic CNV (NICE guidance T68).[10]

The ANCHOR trial was a 2-year multicenter, randomized, double blind trial, which studied the response to two different dosages of intravitreal ranibizumab (0.3 mg and 0.5 mg), sham injections, and verteporfin for the treatment of predominantly classic neovascular AMD. Monthly intravitreal injections of ranibizumab were found to be superior with respect to visual gain, Early Treatment Diabetic Retinopathy Study visual chart performance, and stabilization of vision compared to verteporfin and sham injections. The 0.5 mg dose of ranibizumab was superior with respect to visual gain in all groups. The rates of serious ocular adverse events were low.[11]

The PRONTO trial was an open label, prospective, single center, uncontrolled clinical trial using an ocular coherence tomography guided variable dosing regimen with intravitreal ranibizumab. The study results showed comparable outcomes with respect to vision and central retinal thickness when compared with previously published continuous dosing of ranibizumab at monthly intervals. Fewer intravitreal injections were required compared to the Phase III MARINA clinical trial.[12] An initial course of three intravitreal injections of anti-VEGF agents followed by monthly follow-up and as-required injections can give equivalent results to continuous monthly

dosing. This is the basis of current practice of three loading doses of ranibizumab followed by pro re nata injections.

The CATT study[13] compared intravitreal bevacizumab versus intravitreal ranibizumab. One- and 2-year results reported near equivalence of both drugs used for neovascular AMD with an almost similar efficacy, visual stabilization, and adverse effect profile.[13] The CATT study concluded that ranibizumab and bevacizumab had similar effects on visual acuity over a 2-year period. The study also showed an almost similar adverse effect profile at 2-years. The study was not conclusive for differences in rates of serious systemic adverse effects.

The CATT trial showed almost similar treatment efficacy of two drugs with a significant cost difference. The CATT study quoted the average cost of drug per patient for the first year as US$13,800 in the ranibizumab as-needed group and US$385 in the bevacizumab as-needed group.

The IVAN trial was a similar multi-centered, randomized trial in the UK comparing the efficacy of bevacizumab and ranibizumab in neovascular AMD. The 12-month visual gain was slightly superior in the ranibizumab group (bevacizumab group visual gain minus ranibizumb group visual gain was −1.99 letters). These results may suggest that ranibizumab and bevacizumab are almost equivalent with regards to visual improvement. The slightly better visual improvement in the ranibizumab group is so small that it may or may not be perceived in clinical terms as significant. There was no difference between the drugs with respect to serious systemic adverse effects. Treatment costs were £6398 per patient per year for ranibizumab and £1509 for bevacizumab. Bevacizumab was less costly for continuous and as-needed treatment regimens ($P < 0.0001$).[14] The cost for a single dose of ranibizumab is quoted as approximately £742 and bevacizumab as approximately £45 in the UK.[15,16] The significantly high cost of ranibizumab may reflect the cost of research and development of the drug. However, the high cost makes it unaffordable for many patients worldwide.

The bevacizumab versus ranibizumab trials have opened up significant ethical, economic, and patient centered issues, which will continue to challenge healthcare providers in many countries. Bevacizumab comes as a vial for injection. There is always the theoretical risk of contamination of bevacizumab batches when it is split and repackaged for single use. In this context, outbreaks of endophthalmitis/toxic anterior segment syndrome-like episodes have been reported with bevacizumab. Rates of infection and endophthalmitis with both drugs are low, as reported in the CATT trial (0.7% for ranibizumab and 1.4% for bevacizumab over a 24-month follow-up period).[13]

A significant number of physicians around the world use ranibizumab or bevacizumab, depending upon the patient's insurance or entitlements, or the affordability for the patient. The CATT and IVAN trials seem to validate the physician's choices based on health economics, economic realities, and the patient's best interest. This is a controversial issue in many countries due to legalities of drug licensing laws. Bevacizumab is still used (despite being off-label) while there is an approved drug (ranibizumab) available. The ethical and economic problems and issues for the use of bevacizumab are also applicable to its use in diabetic maculopathy and RVO.

Pegaptanib has also been used for neovascular AMD, to prevent visual decline due to subfoveal CNV. The VISION trial reported pegaptanib to be a safe drug with low levels of systemic adverse events.[17] Reports about the efficacy of pegaptanib have been mixed with most series reporting outcomes better than sham injections. Pegaptanib efficacy comparisons with ranibizumab report inferior or almost equivalent results in the literature.[18] In comparison to ranibizumab or bevazicumab, pegaptanib has not seen widespread acceptance, primarily because of its perceived lesser efficacy in comparison with ranibizumab. However, good results comparable with ranibizumab have been reported in small and early lesions.[19]

VIEW 1 and VIEW 2 trials for aflibercept (Eylea) report good visual outcomes comparing aflibercept and ranibizumab. After an initial loading phase of monthly injections for 3 months, intravitreal injections of aflibercept every 2 months appeared to be noninferior to ranibizumab.[20] CLEAR-IT 2 1-year data showed good visual and anatomic outcomes with aflibercept. After one injection per month for 3 months, on average one to two more injections were needed per eye on an as-required basis and average time for reinjection was reported as 129 days.[21] These results appear to be comparable to the ANCHOR, MARINA, and PRONTO ranibizumab trials in the initial monthly regime of three injections, but more importantly indicate the need for less frequent dosing as compared to intravitreal ranibizumab in the follow up period. The price of aflibercept is being quoted as £825 in the introductory leaflets to physicians in the UK. The economics and safety profile of intravitreal aflibercept may cause a significant shift in injectable treatment choices for neovascular AMD. The 2-year results and longer-term follow-up studies from these trials are likely to be interesting.

Role of anti-VEGF agents in diabetic retinopathy

Anti-VEGF agents have also been used for diabetic retinopathy. Use of intravitreal bevacizumab for PDR has

been proposed.[22–25] This is usually advocated as adjuvant therapy after maximal scatter laser photocoagulation. The preferred first line treatment for PDR remains pan-retinal laser photocoagulation. Targeted retinal laser photocoagulation after wide-field retinal angiography and multi-spot laser photocoagulation may change the treatment significantly by treating ischemic areas of the retina only.[26,27] Muqit et al recently reported results with wide field angiography and PASCAL laser to identify and treat ischemic areas in the retina.[26,27] With such techniques to reduce the VEGF drive, the need for anti-VEGF in PDR may be limited. A small number of patients may benefit from anti-VEGFs in this set of circumstances.

Anti-VEGF treatments have also been reported in patients with PDR due to undergo pars plana vitrectomy and delamination. Romano et al described this technique whereby intravitreal bevacizumab is administered to the affected eye 2 weeks before a planned vitrectomy and delamination.[28] They reported quicker surgical times as well as decreased incidence of peroperative bleeding. In eyes with tractional retinal detachments, anti-VEGF treatments may worsen the tractional retinal detachments or may convert it to a combined rhegmatogenous and tractional detachment.[29]

Anti-VEGF agents inclusive of bevacizumab, ranibizumab, and pegaptanib sodium have been used in eyes with diabetic macular edema (clinically significant macular edema).[30] The BOLT trial[30] reported significant improvements in patients receiving intravitreal bevacizumab and laser treatment (focal/grid laser photocoagulation). The DRCR studies showed significant improvement in eyes receiving intravitreal ranibizumab and laser compared to patients receiving either laser alone or laser combined with intravitreal triamcinolone injection.[31,32] In the DRCR studies, a small subgroup of pseudophakic eyes with diabetic macular edema receiving intravitreal triamcinone (IVTA) and laser appeared to have had better results compared to patients receiving laser and ranibizumab.[33] Results have been also reported with intravitreal bevacizumab for diabetic macular edema. Combination therapy of intravitreal bevacizumab and IVTA with focal laser have reported better outcomes than macular laser alone.[34,35]

Several other studies have reported good results with intravitreal anti-VEGF agents (bevacizumab) with IVTA and focal grid Argon laser treatment.[34–36]

The DRCR study results were based on laser treatment and monthly injections for 12 months similar to ANCHOR and MARINA. It remains to be seen if these effects are maintained by following a PRONTO-like regime with as required anti-VEGF injections after a loading course of three injections as well as Argon focal/grid laser treatment.

In the UK, ranibizumab is indicated for diabetic macular edema. However, it has not gained National Health Service funding, as it was not recommended by NICE on the basis of cost effectiveness.[37] However, similar to AMD, bevacizumab continues to be used on an off-label basis due to lower costs. Patients with diabetes and diabetic macular edema are likely to be younger and may be expected to live longer compared to patients with neovascular AMD. In the current economic climate, cost has become a significant consideration for many treating physicians as well as the Departments of Health in many countries. Although anti-VEGF treatment is effective for diabetic macular edema, it will be interesting to see whether this effect is maintained over the course of years in patients with diabetic retinopathy because of progressively increasing ischemic changes in diabetic retinopathy.

The long-term effect of anti-VEGFs in diabetic retinopathy is likely to ignite debate over health economics of treating diabetic macular edema in relatively younger patients with longer life expectancies than older patients with neovascular AMD.[38]

Aflibercept has also been used in early trials for diabetic macular edema. The DA VINCI study addressed different doses of aflibercept versus laser and reported 1 year outcomes showing superior outcomes for the aflibercept group versus laser.[39]

Given the current emergence of anti-VEGF agents it would be interesting to see studies comparing aflibercept, Lucentis, Avastin, Ozurdex® (Allergan, Irvine, CA, USA)/IVTA combined with focal or grid Argon laser photocoagulation for diabetic macular edema.

Role of anti-VEGF in retinal vein occlusions (RVO)

Anti-VEGF factors have also been used for the treatment of RVO. The conventional treatment of retinal vein occlusions is based upon the central RVO (CRVO) and branch RVO (BRVO) trials, which were published in the mid-1980s. This included addressing vascular risk factors, focal grid laser for BRVO with macular edema, and pan-retinal photocoagulation or sector photocoagulation in cases with retinal ischemia and iris/angle neovascularization. More recently, ranibizumab has been used for the treatment of branch RVO and central RVO with macular edema.[40] The BRAVO and CRUISE trials reported an improvement in central foveal

thickness along with improvement in vision.[41] Similar trials like the ROCC study also reported improved outcomes with respect to vision and decreased macular edema compared to sham treatment.[42]

The improvement in central foveal thickness appears to be maintained until the effect of the anti-VEGF remains. The improvement in visual acuity is maintained if resolution of macular edema is sustained. In the authors' opinion, if retinal collaterals develop and reduce the hydrostatic pressure in the retinal circulation, the reduction of foveal thickness may contribute to maintain reasonable visual function when the anti-VEGF is discontinued. Bevacizumab (off-label) and ranibizumab (licensed) continue to be used for macular edema secondary to RVO.

The SCORE trial used IVTA in 1 mg, 2 mg, and 4 mg concentrations in the eye. This trial showed an improvement in central foveal thickness and improvement in vision in patients with RVO.[43]

Recently, a prospective study comparing intravitreal bevacizumab (1.25 mg/0.05 mL) versus IVTA (4 mg/0.1 mL) reported significant visual improvement in both intravitreal bevacizumab and IVTA groups with no statistical difference between them.[43] However, the IVTA group had a higher incidence of raised intraocular pressure (IOP). The study concluded that the effects of both drugs were not permanent, and repeated injections were necessary for bevacizumab as well as triamcinolone. Kim and Park reported similar observations for BRVO and macular edema treated with triamcinolone 4 mg/0.1 mL and bevacizumab 1.25 mg/0.05 mL.[44] Both of these trials chose triamcinolone 4 mg/0.1 mL when a higher incidence of raised IOP may be expected. The risk of raised IOP may have been reduced if a lower dose of triamcinolone had been used as per the SCORE trial. It will be interesting to see if such a trial is conducted in the future.

Recently, intravitreal Ozurdex implants (dexamethasone 0.7 mg) have been gaining popularity as treatment for branch and central RVO with macular edema. Ozurdex appears to have a longer effect (up to 6 months) when compared to intravitreal anti-VEGF agents. In the UK, this is NICE approved as licensed treatment for nonischemic central RVO and macular edema and as adjunct therapy for branch RVO with macular edema after focal/grid laser or if laser treatment is not suitable.

The newer anti-VEGF agents like aflibercept have been used in the treatment trials of central RVO and macular edema. Favorable results have been reported up to 6 months follow up in the COPERNICUS study.[45]

Role of anti-VEGF agents in iris neovascularization

Anti-VEGF agents have also been used to augment glaucoma treatment in specific indications. This is mainly in cases of neovascular glaucoma (NVG) with iris neovascularization (NVI). Duch et al reported use of bevacizumab as an intracameral injection in the aqueous humor to try and control NVI as well as IOP. They reported prompt iris vessel regression and no operative difficulties with subsequent drainage/filtration surgery attributable to NVI.[46] Wakabayashi et al reported on a larger case series of patients with NVG or NVI treated with intravitreal bevacizumab.[47] They reported stabilization of NVI and reported better IOP control with early stage NVG without angle closure. They suggested an adjunctive role in advanced NVG.

In cases of ischemic RVO and PDR with NVI, treatment with panretinal photocoagulation along with intravitreal bevacizumab may be a sensible treatment strategy. Good results were reported by Ciftci et al[48] and Avery et al.[49]

Yazdani et al report a small randomized controlled trial with improved IOP outcomes in patients with NVI.[50] The intravitreal bevacizumab group (2.5 mg intravitreal bevacizumab) resulted in a significant decrease in IOP compared to the group receiving subconjunctival saline. No visual improvement was reported in either group.

Intravitreal bevacizumab has been used as an adjunct in glaucoma surgery. In a retrospective, interventional case series, Chen et al reported that adjunctive use of intravitreal bevacizumab in addition to trabeculectomy had significantly higher frequency and rapidity of regression of NVI, improved visual acuity, and fewer intraoperative and postoperative complications.[51] Intravitreal bevacizumab has also been successfully used to enhance the outcome of trabeculectomy with mitomycin C with respect to regression of NVI and control of IOP.[52] Intravitreal bevacizumab has also been reported as having a beneficial effect on regression of NVI due to ocular ischemic syndrome.[53]

Indications of anti-VEGF agents in choroidal neovascular membranes due to other causes

Choroidal neovascular membranes under the fovea can be caused by a number of diverse factors including myopic macular degeneration, punctate inner choroidopathy, serpiginous choroidopathy, multifocal choroiditis, etc.[54] A retrospective study of 15 patients treated with intravitreal bevacizumab for

inflammatory choroidal neovascularization showed transient improvement in best corrected visual acuity as well as in central foveal thickness. Repeated injections were necessary in the majority of the patients.[55] Mansour et al report 3-year visual outcome of intravitreal bevacizumab in inflammatory ocular neovascularization. Intravitreal bevacizumab sustained significant visual improvement of 2.7 lines and significant foveal flattening of 98 μm in a wide variety of inflammatory ocular diseases without major complications after a median of three injections.[56]

Moreover, a small cases series of two patients shows intravitreal bevacizumab to be effective for extra-foveal choroidal neovascularization due to ocular trauma.[57]

Case reports and case series show good responses for myopic macular degeneration treated with Lucentis as well as Avastin.[58]

Role of anti-VEGF agents in corneal neovascularization

Corneal neovascularization may accompany long standing corneal scars and may be found in instances of chronic herpetic keratitis, ocular surface disease, or conditions such as contact lens wear, chronic blepharitis, etc. Bevacizumab has been used to try and decrease corneal neovascularization and maintain corneal clarity.[59] Most surgeons favor the subconjunctival route for drug delivery. In a prospective case series, Benayoun et al showed that a single subconjunctival injection of bevacizumab (2.5 mg/0.1 mL) resulted in regression of corneal neovascularization from various ocular surface disorders suggesting that it can be safely used to improve the success of corneal grafts.[60] Yeung et al combined subconjunctival and intracorneal use of bevacizumab. Patients received up to three injections of 2.5 mg of bevacizumab (1.25 mg/0.05 mL subconjunctival and 1.25 mg/0.05 mL intrastromal). Injections were safe and well-tolerated and all patients showed a reduction in neovascularized area.[61] Moreover, subconjunctival bevacizumab has been used in combination with PDT using verteporfin and showed a notable decrease in corneal neovascularization and evidence of vascular thrombosis.[62] Qian et al reported successful use of subconjunctival bevacizumab as an adjunctive treatment to enhance the outcome of superficial keratectomy for corneal neovascularization.[63] Anijeet et al report use of anterior segment fluorescein and indocyanine green angiography to accurately document corneal neovascularization and corneal clarity. Studies like these are likely to form an objective measure of corneal clarity and neovascularization against which any treatment outcome may be measured and compared.[64]

However, bevacizumab has also been used topically, on an experimental basis, as drops (5 mg/mL) and showed to be effective in the inhibition of corneal neovascularization and in the reduction of new vessels' diameter. Bevacizumab drops may be used but care should be taken when epithelial defects or neurotrophic keratopathy are present.[65]

Role of anti-VEGF agents in ocular oncology

Anti-VEGF agents have been used for certain conditions in ocular oncology. Retinal vascular tumors have been treated with verteporfin and PDT, external beam radiotherapy, and agents like intravitreal bevacizumab and ranibizumab. Choroidal hemangiomas have been treated with combinations of PDT and intravitreal bevacizumab.[66]

Bevacizumab has also been used for radiation retinopathy.[67] Variable success has been reported.[68] The author has used bevacizumab and ranibizumab in radiation retinopathy without encouraging results.

Intravitreal bevacizumab has also been used to treat macular edema in eyes with choroidal melanomas. This is usually as adjunct therapy after the melanoma has been eradicated by ruthenium plaque radiation or external beam radiation.[69] In the authors' experience, the visual acuity may improve in these patients where macular edema is the sole cause of decreased vision. However, if there is significant radiation retinopathy around the macular area, the results are likely to be disappointing.

Radiation induced optic neuropathy after treatment of choroidal tumors is characterized by optic nerve edema and subsequent optic disc pallor. Bevacizumab has been reported to improve or stabilize the vision in the short term after radiation induced optic neuropathy. Longer term reports of its efficacy appear to be disappointing. This may be because of the VEGF induced protective effects on the retinal ganglion cells may be neutralized by anti-VEGF agents.[70]

A case with use of intravitreal bevacizumab as local chemotherapy for metastatic choroidal tumors has been reported.[71] This may be considered as a temporary measure if established treatments are not suitable due to patient co-morbidities. The presumed mechanisms are the anti-angiogenic and anti-permeability effects of the bevacizumab on the newly established metastatic tumor mass and by compromising its blood supply.

Anti-VEGF agents have been used when neovascularization in the tumor is thought to be the main factor in spreading the disease.[72] This may be true in highly vascular tumors of

the eye. Kenawy et al reported treatment of vasoproliferative ocular tumors with intravitreal bevacizumab.[73] However, Rennie has suggested that the effect of bevacizumab on vasoproliferative tumors may not be long acting. Vasoproliferative ocular tumors have been treated with radioactive ruthenium plaques, PDT, and triple thaw conjunctival cryotherapy.[74] Apart from a few cases reported above, we are not aware of any large prospective studies involving intravitreal VEGFs in vasoproliferative tumor treatment.

Iris melanomas treated with plaque radiotherapy followed by intravitreal bevacizumab has given good results in controlling neovascular glaucoma following radiotherapy. Biancitto et al report good results based upon one case report with resolution of NVI and control of IOP without the need for anti-glaucoma medication.[75]

Ciliary body adenomas have also been treated with a combination of plaque radiotherapy and intracameral bevacizumab.[76]

Anti-VEGFs have been used in ocular oncology mainly for managing complications after radiotherapy and have a variable effect on maintaining visual acuity depending on the involvement of the optic nerve and macula.

Role of Anti-VEGF treatments in central serous chorioretinopathy

Central serous chorioretinopathy (CSR) is usually a self-limited condition causing variable visual disturbance in patients and is usually expected to resolve with time. Conventionally, a 3–6 months period is given before any treatment is attempted. Treatments include fluorescein angiogram guided Argon laser, PDT, and more recently, intravitreal bevacizumab. Treatment of CSR has been reported as a safe option using PDT in various small case series.[77–81] More recently, treatment with intravitreal bevacizumab has been reported with success.[82] Some clinicians have tried combinations of PDT and intravitreal bevacizumab with success giving good visual results and improvement in macular thickness as measured by optical coherence tomography.[83–87]

Role of Anti-VEGF treatments in ROP

During the last few years, reports of intravitreal bevacizumab in ROP have been emerging. Reports suggested a potential role in patients where initial laser treatment has failed or achieved suboptimal results. In these instances, 0.625 mg of bevacizumab was given in the eye through the intravitreal route with needle entry 0.5 mm away from the limbus directed posteriorly to avoid the more globular crystalline lens in neonates. Most reports suggest success in this rescue role.[88] A follow up of one of these reported cases shows good results with useful vision at 3 years but developing high myopia (−11 diopters in one eye and −1 diopter in the other). Children with ROP may develop large refractive errors with conventional treatment.[89] It is not clear if anti-VEGFs will have any additional effect on the refractive error. There have been concerns regarding ocular growth retardation in patients receiving bevacizumab. However, this may need to be monitored as more data from follow up studies emerge.

There is an increasing tendency in using intravitreal bevacizumab for the treatment of ROP. The BEAT-ROP study was a prospective, controlled, randomized, stratified, multicenter trial which assessed the intravitreal use of bevacizumab as

Table 1 Emerging roles for antiangiogenesis factors in management of ocular disease

Drug	Indication	Level of evidence	Comment
Bevacizumab	Neovascular AMD	RCT	IVAN,[14] CATT[13]
Ranibizumab	Neovascular AMD	RCT	ANCHOR,[11] MARINA[9]
Pegaptanib	Neovascular AMD	RCT	VISION[17]
Aflibercept	Neovascular AMD	RCT	VIEW 1 and 2[20]
Verteporfin	Neovascular AMD	RCT	TAP, VIP[96]
Bevacizumab	Diabetic maculopathy	RCT	BOLT[30]
Ranibizumab	Diabetic maculopathy	RCT	DRCR net studies[31–33]
Bevacizumab	Adjunct in diabetic delamination	Case series	
Bevacizumab	Proliferative diabetic retinopathy	Case series	
Ranibizumab	Retinal vein occlusions	RCT	BRAVO,[41] CRUISE[41]
Aflibercept	Retinal vein occlusions	RCT	COPERNICUS[45]
Bevacizumab	Iris neovascularization	Case series	
Bevacizumab	Adjunct in glaucoma surgery	Case series	
Bevacizumab	Corneal neovascularization	Case series	
Bevacizumab	Radiation retinopathy	Case series	
Bevacizumab	ROP	Case series	
Pegaptanib	ROP	RCT	
Verteporfin	CSR	Case series	References 77–84
Bevacizumab	CSR	Case series	References 85–87

Abbreviations: AMD, age-related macular degeneration; CSR, central serous chorioretinopathy; RCT, randomized controlled trial; ROP, retinopathy of prematurity.

monotherapy compared to conventional laser treatment for zone I or zone II posterior stage 3+ ROP. The study included 150 infants (total of 300 eyes) and showed that intravitreal bevacizumab monotherapy had a significant benefit for zone I but not zone II disease. Peripheral retinal vessels continued to grow after intravitreal bevacizumab, but were completely destroyed after conventional laser therapy.[90]

An evidence-based meta-analysis of studies from 2009–2011suggested that monotherapy with intravitreal bevacizumab may be a viable first-line treatment for select cases of zone I ROP and possibly for posterior zone II disease. Adjunctive treatment with bevacizumab may enhance outcomes in patients treated with laser photocoagulation or pars plana vitrectomy.

The possibility of reactivation of ROP after intravitreal bevacizumab monotherapy was studied by Hu et al in a retrospective study. They found that the effect of the drug may be transient and that recurrence can occur later in the course as compared to conventional laser therapy. They concluded that a long-term favorable structural outcome may require extended observation and retreatment and that laser may be a useful treatment for recurrences.[91]

Apart from bevacizumab, pegaptanib (Macugen) has also been used for stage 3+ ROP. A prospective, randomized, controlled multicenter clinical trial has shown pegaptanib (Macugen) associated with laser treatment to be more efficacious than laser treatment alone in stage 3+ ROP.[92]

Some authors express significant concerns regarding long-term safety of anti-VEGF agents in fetal eyes.[93] These concerns include possible development of extreme refractive errors and structural abnormalities.

Ruland et al suggest microphthalmia, persistent hyperplastic hyaloid vasculature, and lens abnormalities following overexpression of VEGF-A in animal models.[94] If this is the case in humans as well, then further indications for anti-VEGF agents may emerge in neonates with ocular abnormalities.

Conclusion

Anti-VEGF agents are now in widespread use for a wide number of indications (refer to Table 1). The current generation of anti-VEGF agents may require repeated injections for a sustained therapeutic effect depending upon the condition being treated. The ideal anti-VEGF agent would have a sustained duration of action, hence needing significantly less invasive procedures. Some progress in this direction seems to have been made with VEGF trap. Future developments may see sustained release formulations or a next generation of anti-VEGF agents.

Disclosure

The authors report no conflicts of interest in this work.

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