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REVIEW

Anti-vascular endothelial growth factor indications in ocular disease

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Abstract

The purpose of this systemic review was to investigate the indications of anti-vascular endothelial growth factor (anti-VEGF) in the treatment of ocular diseases. For this, a comprehensive literature research was performed exploring the current use of anti-VEGF in a variety of retinal or anterior segment diseases and highlighting the visual outcome for these patients. The anti-VEGF therapy is now commonly used for a wide range of pathologies like age-related macular degeneration, retinal vein occlusion or diabetic retinopathy. Pathological processes such as abnormal neovascularization, ocular angiogenesis and macular edema which can greatly reduce visual acuity are now targeted by anti-VEGF treatment, having a major impact on vision.

Keywords: anti-VEGF therapy, ranibizumab, bevacizumab, aflibercept, age-related macular degeneration

Introduction

The use of anti-vascular endothelial growth factor (VEGF) agents for the treatment of ocular disorders has been introduced for over 10 years and represents one significant advancement in modern medicine. Anti-VEGF therapy has been introduced in the treatment of vascular and exudative diseases of the retina, currently being licensed for age-related macular degeneration, diabetic retinopathy, retinal vein occlusion and myopic choroidal neovascularization. Expanding indications now include a vast number of possible ocular diseases but clinical trials must still prove their efficacy. Anti-VEGF agents like ranibizumab, bevacizumab and aflibercept have sparked a dramatic shift in the treatment of the main causes of blindness around the world.

VEGF and angiogenesis

VEGF is a key factor in the process of angiogenesis by promoting proliferation and vascular endothelial cell migration [**1**]. It increases vascular permeability and vasodilation required in physiological processes like lesion healing, but is also involved in pathological neovascularization found in ocular diseases with irreversible vision loss [**2**]. Principal causes of blindness in infants and elderly like retinopathy of prematurity, diabetic retinopathy and age-related macular degeneration which have VEGF as an angiogenesis promoter, which makes it a

highly considerable therapeutic target. VEGF is a 40 kDa dimeric glycoprotein that is produced by hypoxic stimulation in different cells of the retina: vascular endothelium, retinal pigment epithelial cells, Müller cells [**3**]. There are seven members of the VEGF family (A-F and placental growth factor) and four isoforms that are believed to play an important role in the human eye: VEGF-121, VEGF-165 (responsible for pathological ocular neovascularization), VEGF-189 and VEGF-206 [**4**].

Anti-VEGF drugs

The first antiangiogenic therapy used for ocular neovascularization and approved by the FDA in 2004 was **pagatanib** (Macugen). It is a RNA aptamer which binds to VEGF-A 165 isoform responsible for vascular permeability and pathological retinal neovascularization. Studies showed a reserved efficacy due to the short half-life of VEGF-A 165 compared with other isoforms found in the eye. The structural specificity was considered to limit systemic vascular events [**5**].

Its usage was restricted after appearance of **bevacizumab** (Avastin) as an off-label intravitreal anti-VEGF for the treatment of exudative age-related macular degeneration (AMD). Bevacizumab is a monoclonal antibody (149kDa) that binds to all isoforms of VEGF-A, approved by FDA for adjunct treatment of colorectal cancer. Systemic administration of bevacizumab resulted in improved visual acuity, OCT and angiographic imaging, which led to the development of intravitreal administration with very good results [**6**].

Ranibizumab (Lucentis) which is a Fab fragment of the humanized monoclonal antibody (48kDa) with affinity to all isoforms of VEGF was developed for intraocular usage only. This truncated alternative molecule was created theoretically as having a better retinal penetration due to its smaller size. A number of clinical trials studied the effect of ranibizumab in the treatment of neovascular AMD. They showed improvement of visual outcomes for all types of choroidal neovascularization and provided evidence of superior efficacy over standard treatment of the time [**7**] [**8**].

Approved by the FDA in 2011, **aflibercept** (Eylea) is a recent anti-VEGF therapy for the treatment of neovascular AMD. It is a soluble fusion protein which has an extracellular VEGF-binding domain derived from the VEGF receptors 1 and 2 that acts by blocking the biological effect of VEGF. Aflibercept has an increased affinity for VEGF-A, VEGF-B and placental growth factor 1 and 2 [**9**]. It also has a much higher VEGF-binding affinity than ranibizumab that can last up to 10-12 weeks, double the period of time of bevacizumab and ranibizumab. Aflibercept has improved pharmacokinetics and decreased frequency of usage (every 2 months) which can be cost saving. Studies on aflibercept showed good results in the treatment of AMD. The bimonthly therapy was equal to the monthly ranibizumab treatment in preventing loss of vision and had similar safety profiles and visual outcomes. Treatment with aflibercept showed a better anatomical outcome with retinal pigment epithelial detachment [**10**] [**11**].

Indications of anti-VEGF therapy

1. Wet age-related macular degeneration

AMD is the most common form of vision loss in elderly patients in developed countries [**12**]. Neovascularization secondary to wet AMD is responsible for most AMD-related severe vision loss. Intravitreal injections with anti-VEGF aim to stop the growth of these abnormal vessels and improve sight. Comparing to the control, patients who received one of the anti-VEGF treatments (ranibizumab, bevacizumab, aflibercept), were more likely to gain 15 letters or more of the visual acuity and after one year of follow-up to have 20/200 vision or better [**13**].

For ranibizumab, monthly doses of 0.5 mg can produce the optimal visual outcome although an as needed (pro-re-nata PRN) regime after 3 months loading doses can give similar visual improvement for the one year follow-up [**14**]. Stabilization of visual acuity and decreased number of injections could be obtained also by a regime that involves monthly treatment until the macula is dry and then increasing the period between applications [**15**]. Bevacizumab, which is the cheaper off-label alternative to ranibizumab, showed similar safety and efficacy in monthly or PRN regime of 1.25 mg dosing. The best corrected visual acuity (BCVA) for both anti-VEGF agents was equal after 2 years follow-up. The monthly versus PRN regimes were found similar in one clinical study but with better outcome for monthly dosing in the second one

[**16**] [**17**]. For aflibercept, 2 mg every two months (after loading phase) showed equivalent results in visual acuity as ranibizumab over a period of 2 years [**18**]. The big advantage is the need for fewer injections. Patients treated with anti-VEGF have morphological improvement regarding the thickness of central retina and the size of neovascularization compared with the non-treated group. Nevertheless ranibizumab showed a greater decrease in central retinal thickness compared to bevacizumab. The most important ocular adverse reactions after intravitreal injections were increased intraocular pressure and ocular inflammation. At one and two-years follow-up a small number of patients experience ocular adverse reactions, like endophthalmitis, retinal detachment, vitreous hemorrhage or systemic adverse events such as myocardial infarction, stroke, ischemic cardiopathy (<1% of total number of patients). Also patients treated with ranibizumab more often develop cataract compared with control group. Reported minor adverse events include subconjunctival hemorrhage, transient increased intraocular pressure, post-injection pain and mild ocular inflammation. In trials endophthalmitis had a reported frequency of less than 1%. Around 18% of the bevacizumab and 14% of the ranibizumab treated patients experience at least one adverse reaction. Serious systemic adverse events occur with the same frequency in the anti-VEGF patients and control group [**13**].

Other treatments like Fovista (anti-PDGF BB) which inhibits platelet-derived growth factor from binding to pericytes can increase the efficacy of anti-VEGF medication. Preliminary studies showed that Fovista conjuncted with ranibizumab on monthly injections for a period of 6 months was 60% more effective than ranibizumab alone [**19**]. Also topical anti-VEGF agents are being tested for the treatment of wet AMD which would eliminate the burden of intravitreal injections on regular basis.

2. Diabetic retinopathy (DR)

DR affects around 28 million people in the world [**20**]. About one in three patients with diabetes have DR (three out of four developed it over a period of 10 years). From the forms of DR, the proliferative one and diabetic macular edema (DME) are among one-third of the patients with DR. 5% of the mild, 20% of the moderate and 50% of the severe forms of non-proliferative DR can progress in one year into the proliferative form [**21**]. For a long time, laser photocoagulation has been the standard treatment for DME and proliferative diabetic retinopathy (PDR), though laser therapy has significant adverse effect due to the destructive nature on the retina. Although intraocular injections with steroids have been used for over a decade to reduce DME and improve vision, these beneficial effects are also associated with significant side effects like cataract and ocular hypertension.

The expanding indications for anti-VEGF therapy as intravitreal injections now include DME and PDR. Clinical trials have shown that anti-VEGF treatment is better than laser regarding the preservation and improvement of vision in DME patients. When compared with laser therapy alone, ranibizumab was more effective in monotherapy or combined with laser. From those that used ranibizumab injections, 46% of the patients improved vision versus 18% with laser only [**22**]. The best visual outcome in patients that have received ranibizumab and laser treatment was achieved by initiation of intravitreal injections followed by postponed laser therapy 6 months later. The DRCRnet (Diabetic Retinopathy Clinical Research Network) proposed that the mean number of intravitreal injections in the first three years to maintain vision gained in DME treatment was 9, 3 and respectively 2 injections/year [**22**]. Guidance by NICE (National Institute for Health and Care Excellence) suggested that for DME a dose up to 0.5 mg of intravitreal ranibizumab should be used on monthly basis until maximum VA is reached (stable VA for three consecutive months). FDA approved the lower dose of 0.3 mg [**23**].

When comparing ranibizumab and bevacizumab in DME treatment, these anti-VEGF agents have shown similar efficacy in reduction of central subfield thickness based on optical coherence tomography. Ranibizumab was associated with greater improvement in BCVA compared to bevacizumab at some study visits, but differentiated results on visual outcome were not conclusive [**24**]. Studies regarding the need for vitrectomy in PDR-vitreous hemorrhage, have shown no significant short-

term benefit of intravitreal ranibizumab in reducing the need for vitrectomy. Nevertheless positive outcomes included improved visual acuity, increased panretinal photocoagulation completion rates and reduced recurrent vitreous hemorrhage rates [**25**].

Aflibercept was also approved for the treatment of sight impairment as a result of DME. The recommended dose of intravitreal aflibercept for DME is 2 mg. In the first year treatment should be initiated with one injections/month for 5 consecutive months, followed by one intravitreal injection every 2 months with the possibility of extension based on anatomic and visual outcome [**26**].

There is high quality evidence shown in clinical trials that anti-VEGF agents have an important benefit compared to other treatments for DME, that exerted the revision of therapeutic guidelines which now recommend its use as first-line treatment in some instances [**27**].

3. Retinal vein occlusion (RVO)

RVO is the second most common cause of retinal vascular disease that causes vision loss after diabetic retinopathy [**28**]. Branch RVO is 2-3 times more frequent than central RVO. It occurs at arteriovenous crossing sites while central RVO is due to external compression of the central retinal vein. The leading cause of vision loss is macular edema [**29**]. There is no effective treatment for patients with macular edema from central RVO, as laser therapy was not effective in this situation [**30**]. Until recently, macular grid laser was the treatment of choice for macular edema due to branch RVO.

Currently ranibizumab, bevacizumab and aflibercept have been successfully applied in treating macular edema due to RVO. All anti-VEGF agents have shown better BCVA results at 12 months than steroids in both branch and central RVO. Best visual outcomes at one year are found after aflibercept (2 mg every 4 weeks for 6 months followed by PRN scheme) and bevacizumab (1.25 mg every 6 weeks) for central RVO, and ranibizumab (0.5 mg monthly for 6 months followed by PRN) for branch RVO [**31**]. One trial that compared bevacizumab 1.25 mg in combination to grid photocoagulation to bevacizumab in monotherapy as treatment for branch RVO showed better results in the combination group [**32**].

Anti-VEGF therapy for macular edema in RVO can bring visual acuity improvement that is clinically significant in double the number of patients than those treated with laser or triamcinolone (25% responders for 1 mg or 4 mg triamcinolone versus 50-60% for anti-VEGF therapy). Another important aspect is that the effect of anti-VEGF medication depends on the moment the treatment starts. It is assumed that the time between occlusion and treatment is a critical factor for the therapeutic effect, as the anti-VEGF impact is more pronounced if begins early after macular edema onset [**31**] [**33**]. No significant ocular or systemic adverse reactions have been identified. By comparison, for steroid medication, cataract and glaucoma are main draw-backs while the high injection frequency is a disadvantage for anti-VEGF.

4. Other anti-VEGF indications

Myopic choroidal neovascularisation (MCNV) is characterized by the formation of abnormal blood vessels that can penetrate Bruch's membrane into the subretinal space and appear in the retina or under the retinal pigment epithelium. It is one of the complications of pathological myopia, occurring in approximately 10% of high myopic patients [34]. In patients that already have MCNV in one eye, the fellow eye can also develop MCNV in 35% of the cases in the next 8 years. Visual prognosis may vary in these patients depending on baseline VA, age, extension of chorioretinal atrophy and location and size of choroidal neovascularization. Prior to anti-VEGF therapy, treatment of MCNV was mainly based on laser photocoagulation and verteporfin photodynamic therapy [**35**].

There has been demonstrated superiority of anti-VEGF over photodynamic therapy. The only licensed anti-VEGF agent for the MCNV treatment is ranibizumab, although no difference was observed between ranibizumab and bevacizumab. Ranibizumab has shown good potential for vision improvement and preventing irreversible damage of retina. The estimated visual gain is two lines on average [**35**]. The usual treatment involves one initial anti-VEGF injection followed by PRN regime. Some studies have shown a slightly better visual outcome for 3+PRN injections than 1+PRN injections in one year [**36**]. The follow-up is recommended monthly for the first 2 months and then every 3

months for the first year. Recent proof confirms that anti-VEGF treatment should be the first-line therapy for MCNV [**35**].

Retinopathy of prematurity (ROP) is a significant cause of childhood blindness around the world secondary to vascular proliferation in the developing retina. VEGF has an important role in neovascular phase of ROP so anti-VEGF can be justified in selected cases. Oxygen-induced pathological retinal neovascularization in models have shown high intraocular levels of VEGF [**37**]. The current standard care for ROP is laser photocoagulation or cryotherapy. Treatment of ROP with intreavitreal bevaciumab has been reported in a prospective trial that compared it to conventional laser therapy. The study showed benefit for anti-VEGF in the treatment of stage 3 zone I or posterior zone II (regression of tunica vasculosa lentis, reduction of iris vessel engorgement, decreased plus disease, regression of peripheral retinal neovascularization) [**38**]. A study regarding intravitreal injection of ranibizumab has shown reactivation of ROP at 6 weeks after treatment whereas none of the eyes treated with bevacizumab experienced reactivation [**39**]. Although anti-VEGF has shown beneficial outcomes, the uncertainty regarding ocular and systemic side effects in premature infants (potentially harming the developing preterm infant because vascular growth factors play a critical role in organogenesis) should retain the clinician from using the therapy outside exceptional cases [**40**]. Photocoagulation and cryotherapy remains the standard care choice.

Neovascular glaucoma (NVG) is a type of secondary glaucoma that results from numerous causes of anoxia or retinal ischemia and can induce significant visual morbidity. The abnormal formation of blood vessels in the anterior segment leads to impaired drainage of aqueous. NVG is usually secondary to ischemic retinal vein occlusion, proliferative DR or retinal artery occlusion. Photocoagulation, cryotherapy and antiglaucoma medications have shown to control intraocular pressure in the majority of cases [**41**]. Anti-VEGF therapy has also been successful in treating NVG. Improvement of intraocular pressure and regression of neovascular vessels have been reported within 48 hours of intravitreal bevacizumab in patients with media opacities that could not have panretinal photocoagulation [42]. Good outcomes resulted in cases of combined therapy with anti-VEGF and panretinal photocoagulation versus photocoagulation alone in the treatment of NVG. There was a significantly higher rate and speed of neovascular regression in the combination group than in panretinal photocoagulation alone [43]. Intravitreal anti-VEGF can be useful in patients not able to undergo photocoagulation and severe cases of elevated intraocular pressure as adjuvant therapy [44].

Central Serous Retinopathy (CSR) is a condition of unknown cause characterized by leakage of subretinal fluid at the macula resulting in visual impairment and metamorphopsia. The majority of cases resolve spontaneously within 6 months. Anti-VEGF therapy has been reserved, alongside laser photocoagulation and photodynamic therapy as a possible treatment in case of persistent CSR. Studies have shown better BCVA and reduced central macular thickness in patients treated with anti-VEGF than placebo at one month, but the difference no longer existed at 3 and 6 months. The anti-VEGF can reduce the duration of symptoms and accelerate visual improvement but does not influence the final visual outcome [45].

Ocular tumors have also been treated with anti-VEGF. Systemic and intravitreal treatment with bevacizumab usually associated with chemotherapy has been reported to lead to choroidal metastases regression. The average number of injections used was 3.4 [**46**]. Intravitreal bevacizumab has been used in the treatment of peripheral and juxtapapillary retinal capillary hemangioblastoma and radiation-induced macular edema after radiotherapy for choroidal melanoma. Anti-VEGF in combination with other oncology treatment modalities may help improve visual acuity but only modestly in some cases [**47**] [48].Intravitreal injections of bevacizumab in patients with choroidal melanoma that have been misdiagnosed initially with choroidal neovascular membrane did not seem to stop the progression of the tumor. Moreover the drug led

to the formation of a fibrotic membrane over the underlying tumor that delayed the correct diagnosis [**49**].

Corneal neovascularization is a serious condition that can lead to compromised visual acuity and may determine inflammation and corneal scaring. In experimental animal models topical bevacizumab partially reduced neovascularization of the cornea [**50**]. Human studies have also confirmed the efficacy of topical bevacizumab in reducing corneal neovascularization. For patients unresponsive to anti-inflammatory therapy, topical bevacizumab induced a 61% reduction in mean vascularized area and a 24% reduction in vessel diameter [**50**] [**51**]. Subconjunctival bevacizumab administration has also shown significant reduction in neovascularization and decreased levels of tissue VEGF. In corneal transplantation, increased rates of graft survival after anti-VEGF treatment have been demonstrated. In patients with previous graft failure and subconjunctival, perilimbical and intrastromal injections of bevacizumab before surgery, 85.7% of the grafts remained transparent during the follow-up period [**52**].

Conclusions

Anti-VEGF treatments have a huge impact on serious disorders which represent a large proportion of irreversible vision loss. Currently available anti-VEGF agents like ranibizumab (approved by FDA), bevacizumab (off-label but cost-efficient) and aflibercept (latest drug approved by FDA with less frequent administration regime) have similar visual outcomes and safety profiles.

The anti-VEGF agents' injected intravitreally have mainly been studied in wet AMD aiming to stop growth of abnormal vessels and prevent further neovascularisation. The superiority remains unclear between ranibizumab, bevacizumab and aflibercept, all of them showing significant gain of visual acuity and improvement in morphological outcomes.

However their use has been approved and started to include other conditions like diabetic macular edema, retinal vein occlusion or myopic choroidal neovascularization. Anti-VEGF has also been utilized as off-licence basis for a large array of ocular diseases that range from retinopathy of prematurity, corneal neovascularization to neovascular glaucoma or ocular tumors.

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