Pharmacovigilance in Intraocular Antiangiogenic Therapy

Marianne L. Shahsuvaryan

ABSTRACT

Context: Currently several antiangiogenic agents are being widely and successfully used for the treatment of eye diseases like neovascular macular degeneration, retinal vein occlusion and diabetic macular edema. The discovery of anti-VEGF (Vascular endothelial growth factor) agents has revolutionized the treatment of these conditions. Ophthalmology has witnessed an explosion in the number of intravitreal injections delivered to patients over the past 10 years, driven in large part by the introduction and rapid incorporation of therapy with anti-VEGF agents.

Objective: Taking into consideration that VEGF plays an important role not only in the pathophysiology of several sight-threatening retinal disorders such as age-related macular degeneration, retinal vein occlusion, diabetic macular edema and proliferative diabetic retinopathy, but also in the physiology of the eye, and that more data are becoming available in intraocular antiangiogenic therapy, chemical compound-related ocular side effects across multiple antiangiogenic agents should be analyzed critically.

Methods: A comprehensive literature search was conducted on Medline, PubMed, and Google Scholar databases in February 2015. Search temporal limits included articles published from 2005 to 2015 with the purpose of providing the most recent evidence. Studies were queried using the following keywords in various combinations: antiangiogenics in eye diseases, intravitreal pharmacotherapy by anti-VEGF, adverse effects, potential ocular hazards, bevacizumab, pegaptanib sodium, ranibizumab, aflibercept. The articles of high or medium clinical relevance were selected for review.

Results: Almost uniformly all trial evaluating ocular safety of antiangiogenic agents reveal the serious side effects including geographic atrophy, pigment epithelial tear, ocular hemorrhage despite the fact that the incidence is low. Ocular safety concern in intraocular pharmacotherapy by anti-angiogenic agents has a strong body of clinical evidence, resulting in plenty of peer reviewed clinical articles.

Conclusion: Currently available findings obviate the need to raise awareness about chemical compound-related ocular side effects in patients with eye diseases treated by antiangiogenic agents. Hopefully that noninvasive therapeutic options will become available soon.

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Key words: Pegaptanib sodium; Ranibizumab; Aflibercept; Bevacizumab; Intravitreal injections; Ocular side effects.


INTRODUCTION

Vascular endothelial growth factor (VEGF) plays an important role not only in the pathophysiology of several light-threatening retinal disorders such as age-related macular degeneration, retinal vein occlusion, diabetic macular edema and proliferative diabetic retinopathy contributing to increased permeability across both the blood-retinal and blood-brain barrier, but also in physiology of the eye. Within the posterior segment of the eye, VEGF is produced by retinal pigment epithelial cells, neurons, glial cells, endothelial cells, ganglion cells, Muller cells, and smooth muscle cells. VEGF appears to be essential for development and maintenance of functionally efficient retinal vasculature as well as for integrity of the
retinal pigment epithelium (RPE), Bruch’s membrane and choroidal endothelial cells[5]. Research conducted by Saint-Geniez et al[6] revealed an important role for endogenous VEGF in the maintenance and function of adult retina neuronal cells. Although VEGF affects all cells within the retina, its primary targets are vascular endothelial cells.

The discovery of anti-VEGF agents has revolutionized the treatment of aforementioned retinal diseases. Ophthalmology has witnessed an explosion in the number of intravitreal injections delivered to patients over the past 10 years, driven in large part by the introduction and rapid incorporation of therapy with anti-VEGF agents.

The term antiangiogenic therapy was born more than 35 years ago by J. Folkman, who hypothesized that cancer may be treated by abolishing the nutrients and oxygen-providing blood vessels[7] by agents that could block the angiogenic cascade. Monoclonal antibodies against VEGF were first developed as an intravascular treatment for metastatic colorectal cancer[7,8].

Consequently, several antiangiogenics have been developed for the treatment of sight-threatening retinal diseases, including neovascular age-related macular degeneration, retinal vein occlusions and diabetic macular edema in diabetic retinopathy.

There are 4 anti-VEGF agents that are either approved or in common use in ophthalmology, namely pegaptanib (Macugen, Pfizer), ranibizumab (Lucentis, Novartis), aflibercept or VEGF Trap-Eye (EYLEA, Bayer) and bevacizumab (Avastin, Roche).

**Pegaptanib**

Pegaptanib is a selective VEGF inhibitor, targeting only one isoform of the VEGF molecule, leaving other isoforms unaffected[9]. In 2004, pegaptanib (Macugen/Pfizer and OSI/Eyetech Pharmaceuticals, Inc.) was the first anti-VEGF agent to receive FDA approval for the treatment of neovascular age-related macular degeneration (AMD). The use of pegaptanib has declined with the release of newer anti-VEGF agents, such as ranibizumab (Lucentis™, Genentech, Inc., South San Francisco, CA, and Novartis Pharma AG, Basel, Switzerland), aflibercept (VEGF-trap eye, Eylea™, Regeneron Pharmaceuticals, Inc., and Bayer Pharma AG, Berlin, Germany) and bevacizumab (Avastin™, Genentech, Inc., South San Francisco, CA, and Roche, Basel, Switzerland).

**Ranibizumab**

Ranibizumab (Lucentis™, Genentech, South San Francisco, CA, USA) is a humanised antigen binding fragment of a murine full length monoclonal antibody directed against human vascular endothelial growth factor - VEGF A. Ranibizumab binds all active isoforms of VEGF-A and is thus considered a non-selective VEGF-A inhibitor[10].

**Afiblercept**

Afiblercept or VEGF Trap-Eye (EYLEA, Bayer) is a fully human fusion protein, consisting of soluble VEGF receptors 1 and 2, that binds all forms of VEGF-A along with the related Placental Growth Factor (PIGF). VEGF Trap-Eye is a specific and highly potent blocker of these growth factors. Afiblercept acts as a decoy receptor binding-free VEGF[11].

**Bevacizumab**

Bevacizumab (Avastin, Roche), is a full-length, humanized monoclonal antibody directed against all the biologically active isoforms of vascular endothelial growth factor (VEGF) – A. Bevacizumab binds to the receptor-binding domain of all VEGF-A isoforms[12].

Bevacizumab is FDA-approved for the treatment of colorectal cancer. However, because the agent costs substantially less per dose than ranibizumab, it has been widely used off-label since 2004 to treat several retinal diseases.

Currently more data are becoming available due to wide antiangiogenic agents use for the treatment of eye diseases, and safety data review for intravitreal injection of common anti-VEGF agents was conducted[13].

VEGF plays an important role in adult homeostasis. It is essential for postnatal angiogenesis and other non-angiogenic functions, such as the modulation of tissue repair and organ regeneration, vascular homeostasis by regulating key vascular proteins[12,13], and inflammation.

Taking into consideration that VEGF plays an important role in the physiology of the eye, ocular safety data across multiple antiangiogenic agents should be analyzed critically and chemical compound-related ocular side effects will be highlighted.

**CHEMICAL COMPOUND-RELATED OCULAR SIDE EFFECTS**

**Clinically proved effects**

**Geographic atrophy**: Geographic atrophy (GA) occurs with natural history of AMD, which marks progression of disease, but on the other hand according to the results of the MARINA trial[14] and further in the CATT trial[15], it was revealed that ranibizumab causes deterioration of vision in treated patients. When ranibizumab and bevacizumab have been compared at two years[16] researchers evidenced more prominent harmful effect on retinal pigment epithelium cells in case of ranibizumab.

In the CATT trial[15,16] it has been shown that frequency of geographic atrophy was higher in monthly treated patients subgroup. Evidences from clinical trials evaluating effectiveness of different antiangiogenic agents-Ranibizumab and bevacizumab in AMD therapy suggest significantly increased frequency of developing geographic atrophy in the range of 20-29% of cases, specifically 20% in the CATT Trial[15], and 28% and 29% in IVAN and HARBOR trials respectively[17-19].

Evaluating impact of treatment schedule in CATT[15] and IVAN[17] trials it has been demonstrated that monthly injections predispose to geographic atrophy comparing to as-needed (pro re nata-PRN). The HARBOR trial asseccing the risk factors for geographic atrophy[18,19] indicated that absence of subretinal fluid in the study eye and atrophic changes in the fellow eye could serve as a predictors for aforementioned complication.

The latest findings by Schlütze et al[20] evidenced that in neovascular AMD progressive RPE atrophy and GA developed in the majority of eyes treated by ranibizumab over two years.

**Retinal pigment epithelial tear**

Tears of the retinal pigment epithelium occur with natural history of AMD associated with choroidal neovascularization, but at the same time could be a consequence of thermal laser therapy, photodynamic therapy and intraocular pharmacotherapy by antiangiogenics[21].

The general consensus is that retinal pigment epithelial tear is the ocular side effect of intraocular antiangiogenic pharmacotherapy and is not related with any specific anti-VEGF drug[22-24].

The latest findings by Leon et al[25] evidenced that in 40% of AMD cases the RPE tears occurred within two years of anti-VEGF
injections. In 86.6% of cases the RPE tear was associated with pigment epithelial detachment (PED), and in 46.6% the RPE tear occurred in the central area of the retina and involved the fovea. In all cases visual acuity decreased at the end of the follow-up period (24 weeks) independently of the type or the topographical location of the lesion.

In conclusion, though RPE tears can occur spontaneously with natural history alone, the risk of RPE tears with antiangiogenic therapy is enhanced by preexisting large and high pigment epithelial detachments.

Ocular hemorrhage

Few studies have focused on ocular hemorrhage following the use of intravitreal injections of antiangiogenic agents[26–30]. Based on Ladas et al[26] findings subconjunctival hemorrhage has been documented approximately in 10% of injections recipients, and was more common in patients simultaneously receiving aspirin[29]. For bevacizumab it has been documented a case of a massive choroidal hemorrhage following intravitreal injection[27]. According to the reports of Karagiannis et al[28] and Madore et al[29] massive subretinal hemorrhage has been evidenced after switching from bevacizumab to ranibizumab and only in bevacizumab injections[28,29].

The latest research conducted by Azar et al[30] also revealed that macular hematoma may follow intravitreal anti-VEGF injection for exudative AMD with large occult neovascularization, especially if a large RPE tear is found. In contrast to earlier study[29] in authors’ opinion the occurrence does not seem to be linked to anticoagulation treatment or the presence of vitreomacular traction.

The long-term data from the randomized, double-blind study evaluating the effectiveness and safety profile of the latest anti-VEGF agent aflibercept in treatment of macular edema secondary to central retinal vein occlusion (CRVO) also evidenced that the most frequent ocular serious adverse event from baseline to week 100 was vitreous hemorrhage.

**IMPACT ON OCULAR BLOOD FLOW**

Anti-VEGF therapy may therefore have adverse effects on ocular blood flow. Von Hanno et al[31] presented two cases of retinal artery occlusion after intravitreal injection of bevacizumab (Avastin) and ranibizumab (Lucentis) respectively and concluded that the therapeutic principle may be associated with an increased risk of retinal arterial occlusions.

Increased risk of ocular blood flow disturbances was noted specifically in case of bevacizumab injections–retinal venous occlusions[32], anterior ischemic optic neuropathy[33], development or exacerbation of ocular ischemic syndrome, decrease in retrobulbar blood flow[37].

Leung et al[38] presented a series of three patients of the nearly 200 patients with CRVO who suffered apparent macular infarction within weeks of intravitreal administration of bevacizumab. The authors stated that this has not been described in the natural history of the disease and is associated with poor visual outcomes.

Few studies have focused on macular ischemia, after intravitreal injection of anti-VEGF agents[36,40].

In Manousaridis and Talk[40] opinion worsening of macular ischemia in the long term cannot be definitely excluded, particularly in eyes with significant ischaemia at baseline and after repeated intraocular anti-VEGF injections. The decision to offer prolonged anti-VEGF treatment in cases of significant coexisting macular ischaemia should not be based only on measurements of macular thickness; instead repeat fluorescein angiograms should be performed.

For bevacizumab in CRVO also it has been demonstrated that ischemic retinal injury may be severe adverse vascular reaction[41].

In conclusion, available findings demonstrated significant impact of antiangiogenics on ocular blood flow.

**Tractional retinal detachment**

Few studies have focused on the development or progression of tractional retinal detachment after intravitreal injection of bevacizumab before vitrectomy for advanced proliferative diabetic retinopathy[42–44].

It is recognized that intravitreal injection of anti-VEGF agents should be used with extreme caution in extensive neovascularization secondary to diabetic retinopathy or retinal vein occlusion, and the patient should be followed closely for the possible need for vitrectomy.

The general consensus is that ocular complications are higher in patients treated by anti-VEGF agents[45,46].

**IMPACT ON LONG-TERM EFFICACY**

Tachyphylaxis/tolerance

The worldwide use of intravitreal application of anti-vascular growth factor and the realisation that regular applications over long periods of time are necessary to maintain vision in these eyes, has revealed the problem of tolerance/tachyphylaxis[47]. In 2008, two papers suggested for the first time possible tachyphylaxis/tolerance with chronic ranibizumab[47] and bevacizumab treatment[48]. Binder S[46] recommended different options to prevent tachyphylaxis/tolerance: (1) to increase the dosage or shorten treatment intervals if tolerance has developed; (2) to pause treatment if tachyphylaxis has occurred; (3) to combine drugs with different modes of action; or (4) to switch to a similar drug with different properties (bevacizumab and ranibizumab differ in molecular size, affinity and absorption).

**EXPERIMENTALLY PROVED EFFECTS**

Impact on retinal pigment epithelium

Malik et al[49] in the experimental study evaluated the safety profiles of antiangiogenics on human retinal pigment epithelium cells. The researchers concluded that bevacizumab and ziv-aflibercept showed mild mitochondrial toxicity at clinically relevant doses, in contrast to ranibizumab.

Impact on photoreceptors and choriocapillaris

Avci et al[50] obviated a significant increase in apoptotic activity in rabbit photoreceptor cells after bevacizumab and pegaptanib sodium injections.

Kurihara et al[51,52] in the experimental study revealed an essential role of VEGF-A in regulating choroid vasculature and cone photoreceptors, responsible for central and color vision and evidenced that VEGF inhibition causes damage and loss of endothelial cells of the choriocapillaries and severe vision loss secondary to cone cell death in mice.

Sene et al[53] also emphasized the critical role of chronic VEGF suppression as a cause of the loss of prosurvival and neurotrophic capacities of VEGF ending by vision loss.

Multiple experimental studies were conducted on rat[26,29], rabbit[55] and primate eye[56] to evaluate bevacizumab impact on choriocapillaris.

The general consensus[54,57] is that intravitreal injection of...
bevacizumab causes a loss of choriocapillaris endothelial fenestrations and therefore VEGF is required for the maintenance of the choroidal homeostasis[57].

**Impact on ciliary body**

The role of VEGF-A in ciliary body homeostasis was explored by Ford *et al*[26] in the experimental study.

Authors discovered that inhibiting anti-VEGF might have a harmful effect on the ciliary body, as a tissue responsible for producing aqueous humor, by degeneration of capillary beds, particularly fenestrated capillaries found in the ciliary body. Sugimoto *et al*[27] reconfirmed by electron microscopy decrease of endothelial cell fenestrations in the choriocapillaris and ciliary body after intravitreal injections of bevacizumab.

**CONCLUSION**

The discovery of anti-VEGF agents has revolutionized the treatment of neovascular macular degeneration, retinal vein occlusion and diabetic macular edema. Ophthalmology has witnessed an explosion in the number of intravitreal injections delivered to patients over the past 10 years, driven by the introduction and rapid incorporation of therapy with antiangiogenics. At the same time taking into consideration that VEGF plays an important role not only in the pathophysiology of several sight-threatening retinal disorders, but also in the physiology of the eye, there is a growing body of evidences on ocular side effects in intraocular antiangiogenic therapy. Currently available findings obviate the need to raise awareness about chemical compound-related ocular side effects in patients with eye diseases treated by antiangiogenic agents. Hopefully that noninvasive therapeutic options will become available soon.

**CONFLICT OF INTERESTS**

The author has no conflicts of interest to declare.

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Peer reviewer: Yoshihiko Usui, Department of Ophthalmology, Tokyo Medical University Hospital, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo, Japan 160-0023.