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Review Article

Ophthalmic Vigilance in Antiangiogenic Pharmacotherapy

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Abstract

Background: Vascular endothelial growth factor (VEGF) plays an important role 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. The discovery of anti-VEGF 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.

Currently several anti-angiogenicagents are being widely and successfully used for the treatment of eye diseases. However, there is some evidence that intravitreal Antiangiogenic injections may result in injection-related ocular side effects. This mandates awareness on the matter.

Keywords: *Antiangiogenic agents; Pegaptanib Sodium; Ranibizumab; Aflibercept; Bevacizumab; Intravitreal injections; Ocular side effects*

Introduction

Dr. Folkman introduced the term “anti-angiogenic therapy” more than 35 years ago, whohypothesized that cancer may be treated by abolishing the nutrients and oxygen-providing blood vessels [1] by agents that could block the angiogenic cascade. Monoclonal antibodies againstVascular Endothelial Growth Factor (VEGF) initially were indicated for metastatic colorectal cancer therapy by intravenous route [2,3], but lately a few new agents were specially developed for use in sucheye diseases as a age- related macular degeneration, specifically Neovascular form, retinal vein occlusions and diabetic retinopathy with macular edema .

At present the following Antiangiogenic are used in ophthalmology:

1. Pegaptanib (Macugen, Pfizer),
2. Ranibizumab (Lucentis, Novartis),
3. Aflibercept or VEGF Trap-Eye (EYLEA, Bayer)
4. Bevacizumab (Avastin, Roche)

Pegaptanib is a selective VEGF inhibitor, targeting only one isoform of the VEGF molecule, leaving other isoforms unaffected [4]. 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 (Lucentis™; Genentech, South San Francisco, CA, USA) is a non-selective VEGF-A inhibitor [5], since binds all isoforms of VEGF-A.

Aflibercept or VEGF Trap-Eye (EYLEA, Bayer) is a strong blocker of all forms of VEGF-A with the related Placental Growth Factor (PlGF) [6]. Bevacizumab (Avastin, Roche), is a nonselective anti-VEGF agent binding all isoforms of anti-VEGF-A [7] officially indicated for oncology use in colorectal cancer, which makes off-label expansion into ophthalmology due to price affordability comparing to ranibizumab from 2004.

Over the past decade a huge amount of intravitreal injections was done, mostly due to pharmacotherapy by Antiangiogenics. At present anti-VEGF agents represent standard care in retinal eye diseases. Accummulated evidence shed a light on injection-related ocular side effects. This mandates awareness on the matter.

Injection-Related Ocular Side Effects

Infectious Endophthalmitis

Each intravitreal injection poses a risk of infection. The most devastating complication of intravitrealangiogenics injection is endophthalmitis.

Bacterial endophthalmitis

Retrospective reviews looking at bevacizumab, Pegaptinib, and ranibizumab have found rates of endophthalmitis per injection of 0%, 0.02%, 0.077%, and 0.16% [8-11]. Severe intraocular inflammation was noted in 0.03% per injection in the 4 randomized trials of ranibizumab [12], in 0.09% in a 12-month study of bevacizumab [13], and up to 1.5% in ranibizumab and bevacizumab injections based on retrospective review of [8].

The large-scale longitudinal case-control study of 6,154 individuals undergoing anti-VEGF treatment for Neovascular AMD also revealed that at 2-year follow-up, the rates of endophthalmitis per injection (0.09%; $p < 0.01$), uveitis (0.11%; $p < 0.01$), were significantly higher in the anti-VEGF treatment group comparing to controls with Neovascular AMD who did not undergo anti-VEGF treatment [14].

There is a relatively high proportion of culture-positive cases that have the virulent Streptococcal species as the causative organism [15,16]. Simunovic., *et al*. [16] revealed that in these cases endophthalmitis is associated with earlier presentation and poorer visual outcomes when compared with endophthalmitis following cataract surgery. General consensus is that many of these Streptococcal cases have dismal functional results, with visual acuity often dropping to hand motions or worse level and many cases leading to evisceration or enucleation [15-17].

The likely explanation for contamination process during injection is the respiratory flora from the patient, the medical assistant or the injecting physician. [18,19]. Aforementioned indicates a no-talking policy during the injection process and the use of face masks, but currently it is not uniform type of care [20]. At the beginning it was highlighted not really evidenced importance of topical antibiotic therapy before and after injection directed to decrease the rate of endophthalmitis [21].

Lessons learned from Kim and Toma practice [22,23] are that this approach not only did nothing to reduce the risk of infection, it also created more antibiotic-resistant bacteria for those cases that did develop despite the use of antibiotics. Based on the findings preventive therapy by antibiotics is not advised [24].

Endophthalmitis after Bevacizumab injections at present off-label intravitreal bevacizumab is only available through compounding pharmacies; there is a potential risk for contamination of bevacizumab during the aliquoting process, during transportation from the pharmacy to the physician's office or during storage of the drug [25].

Physicians should permanently monitor pharmacy-supplier to be sure in sterility of prepared drugs. Unfortunately, outbreaks of blinding cases of endophthalmitis have occurred when deviation from established protocols has led to widespread contamination of bevacizumab lots [17,26].

Fungal Endophthalmitis

Not only bacterial, but also fungal endophthalmitis cases were presented by Sheyman., *et al*. [27] after intravitreal injection of bevacizumab and triamcinolone prepared in pharmacy.

Due to a number of infections, the Department of Veterans Affairs discontinued the use of Roche's Avastin for wet age-related macular degeneration [28].

In conclusion, although endophthalmitis cannot be prevented in all cases, certain risk reduction strategies have been proposed, including the use of an eyelid speculum, povidone iodine, avoidance of needle contact with the eyelid margin or eyelashes, and avoidance of routine post-injection antibiotics [24].

Results of research conducted by Day., *et al*. [14] evidenced that pharmacotherapy by antiangiogenics increases the rate of endophthalmitis on 0.09% per injection, uveitis on 0.11%, and vitreous hemorrhage per injection on 0.23%.

With Cox proportional hazards modeling, the anti-VEGF treatment group had a 102% higher risk of severe ocular complications overall, and a 4% increased risk per injection, both of which were statistically significant ($p < 0.01$).

Sterile inflammation- Sterile endophthalmitis

Sterile endophthalmitis (also known as "pseudoendophthalmitis") is described as any acute intraocular inflammation without infection that resolves without antibiotic treatment, unlike true endophthalmitis. Frequency of sterile endophthalmitis after anti-VEGF intravitreal injections fluctuates from 0.033% to 2.9% [29-34].

It is important to differentiate infectious endophthalmitis from sterile endophthalmitis, as the management and prognosis are different in each case. Sterile endophthalmitis typically manifests 24 hours to 7 days after injection [30,31,34-38], is painful or painless.. Severe inflammation in the anterior chamber and vitreous cavity manifests bypain .Another accompanying symptoms are blurred vision and floaters [31].

Visual acuity at presentation is substantially reduced compared with preinjection acuity and typically returns to preinjection acuity after resolution of the inflammation [30,31]. The average time to resolution of inflammation ranges from 2 to 12 weeks [31,35,37] and recovery of visual acuity occurs between 7 and 9 weeks [31]. Visual rehabilitation is not related with duration of inflammation manifestation [30].

In addition, history of prior intravitreal anti-VEGF injections does not increase the risk or severity of ocular inflammation in subsequent injections [31,39]. Topical steroid therapy is indicated for the treatment of sterile endophthalmitis.

Agrawal., *et al*. [40] highlighted the sterile inflammation is an adverse event of intravitreal anti-VEGF injection that should be included in the patient consent in all anti-VEGF agents.

At present the etiology is unclear. The likely explanations include degradation of the agent with increased immunogenicity [41,42] due to unfollowing the protocols - the medication should berefrigerated at 2 to 8 degrees C (36 to 46 degrees F), protected from the light, stored in the original carton until used, and used within 8 hours of being opened [43] or Bacterial endotoxin contamination has been reported in the pharmaceutical production phase of antibody preparation [44].

Acute intraocular inflammation is most frequently following bevacizumab [45], possibly due to the less stringent purification process of the medication [45].

Ocular Hypertension

An ocular hypertension can occur transiently immediately following the bolus injection of 50 to 100 microliters of an anti-VEGF drug. What is more concerning is the potential for significant and sustained elevations in intraocular pressure elevation. This documented in 3.5 percent to 11 percent of patients receiving chronic anti-VEGF agents [46-48]. The etiology of this process is an open question.

Supposed explanation could be a drug impact on the trabecular meshwork, hydrostatic damage to the trabecular meshwork, increased outflow resistance or combined influence, or due to some other unidentified mechanism.

The key point here is to recognize the possibility of the risk (especially in patients with pre-existing risk factors for glaucoma), to monitor the IOP and optic nerve and to make the appropriate adjustments to the injection protocol when delivering subsequent anti-VEGF injections (e.g., lowering the volume of drug injection, using a larger-bore needle, which likely causes less pressure during injection and prevents hydrostatic damage to the trabecular meshwork or increasing the injection interval) [49].

Other injection-related quietly uncommon complications

They manifest by the following: retinal tears, retinal detachment, vitreous hemorrhage and traumatic iatrogenic cataract [21].

At the same time the latest findings from two-year results from the COPERNICUS study Intravitreal aflibercept injection for macular edema due to central retinal vein occlusion [50] revealed that the most frequent ocular serious adverse event from baseline to week 100 was vitreous hemorrhage (6.8%).

Conclusion

Over the past decade a huge amount of intravitreal injections was done , mostly due to pharmacotherapy by antiangiogenics in neovascular macular degeneration, retinal vein occlusion and diabetic macular edema.

Taking into consideration that each intravitreal injection of anti-VEGF agents may potentially cause injection-related ocular side effects, currently available findings mandate the need to raise awareness of ophthalmologists about facing complications in patients with eye diseases treated by anti-VEGF. Early detection is crucial for appropriate management.

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