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Review Article

CARDIOVASCULAR EVENTS RISK PROFILE IN ANTIANGIOGENIC INTRAOCULAR PHARMACOTHERAPY

Shahsuvaryan ML.

Yerevan State Medical University, 26 Sayat-Nova Avenue, Yerevan, 0001, Republic of Armenia

Corresponding Author: Dr. Marianne Shahsuvaryan, 26 Sayat-Nova Avenue,Yerevan, 0001, Republic of Armenia

Abstract

Background: Currently several anti-angiogenic agents are being widely and successfully used for the treatment of eye diseases like neovascular macular degeneration, retinal vein occlusion and diabetic macular edema. Taking into consideration that these patients may present with a different spectrum of underlying diseases and potentially higher risk profiles, systemic safety data across multiple anti-angiogenic agents should be analyzed critically. **Methods:** A comprehensive literature search was conducted on Medline, PubMed, and Google Scholar databases in June 2014. Search temporal limits included articles published from 2005 to 2014 with the purpose of providing the most recent evidence. Studies were queried using the following keywords in various combinations: anti-angiogenics in eye diseases, intravitreal pharmacotherapy by anti-VEGF, adverse effects, potential systemic hazards, bevacizumab, pegaptanib sodium, ranibizumab, aflibercept. The articles of high or medium clinical relevance were selected for review. **Results:** Almost uniformly all trial evaluating systemic safety of anti-angiogenic agents reveal the serious side effects including cardiovascular events, despite the fact that the incidence is low. Systemic 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 cardiovascular risk profile in patients with eye diseases treated by anti-VEGF. Early detection is crucial so that intraocular injections can be stopped before severe accident occurs.

Keywords: adverse effects, aflibercept, intraocular pharmacotherapy, pegaptanib sodium, potential systemic hazards, ranibizumab.

INTRODUCTION:

The term anti-angiogenic 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 [1] by agents that could block the angiogenic cascade. Monoclonal antibodies against Vascular Endothelial Growth Factor (VEGF) were first developed as an intravenous treatment for metastatic colorectal cancer [2,3].

Therapy by Vascular Endothelial Growth Factor Inhibitors (anti-VEGF) is a clear break through,which has dramatically changed treatment and management of sight-threatening retinal diseases, including neovascular age-related macular degeneration, retinal vein occlusions and diabetic macular edema in diabetic retinopathy. Taking into consideration that these patients may present with a different spectrum of underlying diseases and potentially higher risk profiles, systemic safety data across multiple anti-angiogenic agents should be analyzed critically.

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METHODS

A comprehensive literature search was conducted on Medline, PubMed, and Google Scholar databases in June 2014. Search temporal limits included articles published from January 2005 to June 2014 with the purpose of providing the most recent evidence. Studies were queried using the following keywords in various combinations: anti-angiogenics in eye diseases, intravitreal pharmacotherapy by anti-VEGF, adverse effects, potential systemic hazards, bevacizumab, pegaptanib ,ranibizumab, aflibercept. The articles of high or medium clinical relevance were selected for review.

RESULTS

The rising popularity of anti-VEGF drugs came along with concerns about its safety in clinical use. Anti-VEGF agents given intraocularly spread into the systemic circulation and have the potential to cause systemic adverse.

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 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 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 [5].

Aflibercept 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 (PlGF). VEGF Trap-Eye is a specific and highly potent blocker of these growth factors. Aflibercept acts as a decoy receptor binding-free VEGF [6].

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 [7].

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.

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Potential Systemic Hazards of Anti-VEGF Therapy

Intraocular injections of anti-angiogenic agents could cause the cardiovascular effects (thrombosis, hemorrhage, hypertension, proteinuria), as well as the less frequent cerebrovascular accidents, myocardial infarction, transient ischemic attacks, deep vein thrombosis, pulmonary embolism, thrombophlebitis [8,9].

Singerman et al. [4] in two double-masked randomized studies evaluated the safety of up to 3 years of pegaptanib sodium therapy in the treatment of neovascular AMD and concluded that serious adverse events were rare. The authors found no findings in relation to vital signs or electrocardiogram results suggesting a relationship to pegaptanib treatment. Results of other randomized trial [10] of pegaptanib sodium for macular edema secondary to branch retinal vein occlusion (BRVO) revealed a trend towards a higher risk of stroke among patients with a history of heart disease.

Pegaptanib (Macugen) is associated with a lower risk of stroke than either Lucentis or

Avastin [11]. The most probable reason for this finding relates to selective binding just one strain of VEGF.

Campbell et al. [12] assessing the risk of systemic adverse events associated with intravitreal injections of vascular endothelial growth factor inhibiting drugs in the nested case-control study have found that intravitreal injections of bevacizumab and ranibizumab were not associated with significant risks of ischaemic stroke, acute myocardial infarction, congestive heart failure, or venous thromboembolism.

The International Intravitreal Bevacizumab Safety Survey gathered adverse events from doctors around the world via the internet [13] and showed all ocular and systemic side effects to be under 0.21% including different ocular abnormalities and also blood pressure elevation, transient ischaemic attack, cerebrovascular accident and death. Fung. et al. [13] concluded that self-reporting of adverse events after intravitreal bevacizumab injections did not show an increased rate of potential drug-related ocular or systemic events and these short-term results suggest that intravitreal bevacizumab seems to be safe.

The reliance on self reported information on bevacizumab use represents a potential limitation of this study. On the other hand, findings reviewed in 2006 were insufficient to evaluate the systemic safety of bevacizumab. More data are becoming available on this agent. It is recognized that the widespread off-label use of bevacizumab, because of its relative inexpensiveness compared to ranibizumab, raises concerns, particularly when systematic reviews of clinical trials comparing the clinical effectiveness of the two drugs [14] suggesting increased frequency of systemic serious adverse events (SAE) [15,16] and representing a disadvantage of bevacizumab . The results from pooled analysis of two large comparative effectiveness trials for neovascular age-related macular degeneration [17-20] suggest that systemic SAEs were more common in the bevacizumab-treated patients, despite the fact that the risk of death or arteriothrombolic events (ATEs) was similar between the drugs.

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Few studies are focused on safety profiles of ranibizumab in retinal vein occlusion. Clinical evaluation of ranibizumab based on two double-blind randomised trials comparing ranibizumab versus placebo in a total of 795 patients revealed that the incidence of heart failure and transient ischaemic attacks was higher during the second year of ranibizumab therapy than during the first year of treatment [21].

For central retinal vein occlusion – CRUISE study [22] it has been demonstrated that death from unknown cause was found in 0.8%, myocardial infarction -0.8%, cerebrovascular events in the 2.4% in ranibizumab group.

An incidence of non-ocular serious adverse events for patients suffered from branch retinal vein occlusion and treated by ranibizumab –BRAVO study [23] was equal to 9.1%, non-ocular hemorrhage was reported in 2.3%. Pielen et al. [24] conducted a systematic review on this matter and concluded that in general, the incidence of systemic adverse events and rates of death (0-3%) were low and did not significantly differ between treatment groups in the multicenter trials [22,23,25,26]. In authors opinion [24] it is likely that information on ocular and systemic adverse events varied between trials due to very detailed reporting within most multicenter trials (including additional information available as online supplements) and, on the other hand, the overall notification of "no ocular and systemic adverse events" in a single-center trial. Individuals presenting with considerable systemic diseases in their recent past medical history are most often excluded. Certainly, in all trials numbers of participants are still too low to be calculated to detect small differences in rare systemic events. Dubey et al. [27] proved that non-ocular adverse event profile of ranibizumab in patients with diabetic macular edema (DME) is similar to that observed in patients with neovascular age-related macular degeneration or retinal vein occlusion.

There is some evidence that intraocular anti-VEGF injections due to systemic absorption may result in injury in organs that are reliant on VEGF, such as the kidney. Pellé et al. [28] reported the first case of a patient who developed an acute decrease in kidney function, nonimmune microangiopathic hemolytic anemia with schistocytes, and thrombocytopenia after 4 intravitreal injections of ranibizumab. Light microscopy of a kidney biopsy specimen showed segmental duplications of glomerular basement membranes with endothelial swelling and several recanalized arteriolar thrombi. Early detection is crucial so that intravitreal injections can be stopped before severe kidney disease occurs. In Sorenson and Sheibani [29] opinion perhaps baseline and renal function during treatment (serum creatinine and urinary protein levels, blood pressure) should be carefully monitored to ensure that the improved visual acuity is not at the expense of renal function. A recent meta-analysis asseccing the non-ocular serious adverse events potentially related to anti-VEGF agents in retinal vein occlusion indicated rare the Antiplatelet Trialists' Collaboration Arterial Thromboembolic Events (APTC ATEs) including myocardial infarction, ischemic stroke, vascular deaths [30]. Avery [31] evidenced that analysis of large populations will be critical to identify if there is a systemic risk to intravitreal agents, as individual trials are not powered to detect differences in uncommon events. There may be subsets of patients, such as patients with diabetes, the elderly or those with recent ATEs such as stroke, who may be at increased risk after intraocular anti-VEGF injection.

The latest approved agent is aflibercept. Its greater VEGF binding affinity (140 times that of ranibizumab) coupled with larger molecular size (twice that of ranibizumab) and a longer duration of action may allow for a less-frequent dosing schedule than with either bevacizumab or ranibizumab with good efficacy [27,32]. Concerns have also arisen regarding the safety of aflibercept. It could cause non-ocular haemorrhages and arterial thromboembolic events [33,34].

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Only recently, aflibercept has been investigated in patients with CRVO in the COPERNICUS (Controlled Phase 3 Evaluation of Repeated Intravitreal Administration of VEGF Trap-Eye in Central Retinal Vein Occlusion: Utility and Safety) trial [26]. According to the results of this trial no deaths were reported in the aflibercept 2 mg group during the first 12 months. However, 2 deaths (2.7%) occurred in the sham/aflibercept group . Both deaths had a vascular cause (myocardial infarction and cardiac arrhythmia). Non-lethal myocardial infarction was documented in 1 patient of each group (0.9% and 1.7%).
The results from the most recent trial on aflibercept in age-related macular degeneration [35] suggest that although adverse events were carefully noted, there is always a possibility that some systemic effect may not have been captured in this retrospective study.
Further clinical trials and comparative studies with aflibercep are needed to establish the systemic safety profile of this agent.

In summary, almost uniformly all trial evaluating systemic safety of anti-angiogenic agents reveal the serious side effects including cardiovascular events, despite the fact that the incidence is low. **The most probable reason for incidence rate relates to** the absence of stratified analysis by age myocardial infarction , stroke risk. Systemic 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

A several anti-angiogenic agents are being widely used for the treatment of eye diseases like neovascular macular degeneration, retinal vein occlusion and diabetic macular edema. Taking into consideration that these patients may present with a different spectrum of underlying diseases and potentially higher risk profiles, systemic safety data across multiple anti-angiogenic agents have analyzed critically. Currently available findings obviate the need to raise awareness about cardiovascular risk profile in patients with eye diseases treated by anti-VEGF. Early detection is crucial so that intraocular injections can be stopped before severe accident occurs.

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