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Research Article

Ocular and Systemic Vascular Adverse Events Following Intravitreal Bevacizumab Injection

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Abstract

During the last decade intravitreal bevacizumab has been widely used for controlling age related macular degeneration and retinal vascular disease. Since then, many reports were published reporting nonvascular ocular complications post bevacizumab injection with fewer reports about vascular ocular and systemic complications. The aim of this article is to review vascular complications, both ocular and systemic which should be considered when selecting this treatment modality, in order to reduce the rare chance of devastating events which can sometimes lead to blindness and even mortality. Ophthalmologists need to consider side effects of bevacizumab on systemic, retrobulbar and ocular circulation whenever visual loss is not attributable to progression of retinal or choroidal disease. Furthermore, ophthalmologist should be aware of possible systemic vascular complications involving the cardiovascular system, central nervous system, gastrointestinal tract, kidneys and lungs.

Keywords: Intravitreal bevacizumab; Ocular adverse events; Vascular adverse events; Systemic adverse events

Abbreviations

AMD: Age Related Macular Degeneration; DR: Diabetic Retinopathy; RVO: Retinal Vein Occlusion; CRVO: Central Retinal Vein Occlusion; BRVO: Branch Retinal Vein Occlusion; OIS: Ocular Ischemic Syndrome; ATE: Arterial Thromboembolic Events; VEGF: Vascular Endothelial Growth Factor; SAEs: Serious Adverse Events; CVA: Cerebrovascular Accident; DME: Diabetic Macular Edema; CDI: Color Doppler Imaging; PSV: Peak Systolic Velocity; EDV: End-Diastolic Velocity; PCA: Posterior Ciliary Arteries; BFV: Blood Flow Velocity; OA: Ophthalmic Artery; CRA: Central Retinal Artery; RI: Resistant Index; CRAO: Central Retinal Artery Occlusion; BRAO: Branch Retinal Artery Occlusion; NAION: Nonarteritic Anterior Ischemic Optic Neuropathy; LP: Light Perception; NLP: No Light Perception; IOP: Intraocular Pressure; RE: Right Eye; LE: Left Eye; MI: Myocardial Infarction

Terminology

Half-life time: How long it takes for the body to get rid of half of the dose of medicine.

Introduction

Intravitreal injection of anti-Vascular Endothelial Growth Factor (VEGF), became the standard of care in many common retinal diseases including Age related Macular Degeneration (AMD) [1] and retinal vascular diseases such as Diabetic Retinopathy (DR) [2], Retinal Vein Occlusions (RVO) and Ocular Ischemic Syndrome (OIS) [3]. Due to short intravitreal half-life of bevacizumab [4], repeated injections are needed to inhibit angiogenesis and to maintain control of activity of sub retinal new vessels in AMD as well as leaking from retinal capillaries in retinal vascular diseases [5-8]. Few reports were published describing devastating ocular and systemic vascular complications post intravitreal bevacizumab injection [9-24].

The aim of this article is to review vascular complications, both ocular and systemic which should be considered when selecting this treatment modality, in order to reduce the rare chance of devastating events which can sometimes lead to blindness and even mortality.

Methods

The MEDLINE database was searched for the past 10 years using the keyword "intravitreal bevacizumab". 2958 results were obtained. The articles list was analyzed and 339 articles were chosen, which were thought to be related to this review about ocular and systemic intravitreal bevacizumab side effects. After reviewing abstracts of the 339 chosen articles, 102 of them were found to be directly related to the subject. Full texts of the latter articles were obtained and used in this review.

Results and Discussion

Intravenous bevacizumab is widely used in treatment of many solid cancers [9,25]. Several adverse events have been reported with its intravenous administration including Arterial Thromboembolic Events (ATE), myocardial infarction, stroke, hypertension, gastrointestinal perforations, and kidney disease [10,26-31]. Recently, these observations have been extended to patients receiving intravitreal VEGF inhibitors [32].

Anti-VEGF agents became one of the main treatments of AMD and retinal vascular diseases [1-3]. Due to high cost of FDA approved anti-VEGFs, off-label intravitreal bevacizumab is often used in practice all over the world as it is very low in cost and as effective as other approved anti-VEGFs [5-7].

The incidence of serious ocular and systemic adverse events was approximately below 1 per 100 injections for intravitreal bevacizumab, intravitreal ranibizumab, and intravitreal pegaptanib. Most mild ocular adverse events were below 5 per 100 injections [33].

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Ocular and systemic nonvascular bevacizumab adverse events

Adverse nonvascular ocular events following intravitreal bevacizumab [34] included: Endophthalmitis [35-41], non infectious intraocular inflammation [26,42-44], rhegmatogenous retinal detachment [26,45]. Tractional retinal detachment [46], macular hole [47], intraocular pressure elevation [48-52], subconjunctival hemorrhage [7], massive subretinal hemorrhage [12,53], retinal pigment epithelium tear [54-56], intravitreal foreign body [57], Lens trauma [58,59], corneal complications [60-62], wound leak [63].

Meyer CH et al. [20] reported 2 cases of transient structured visual hallucinations in 2 patients with exudative AMD, one day and three days after intravitreal bevacizumab injection. Both patients experienced structured hallucinations including trees, faces, and water for approximately 15 to 30 minutes. Authors hypothesized that reduced retinal edema and realignment of the photoreceptors may cause this phenomenon and trigger hallucinatory episodes.

Ocular and Systemic bevacizumab vascular adverse events

As the commonly used intravitreal anti-VEGF agents were found to transit rapidly into the bloodstream after administration [64,65], concern about their systemic side effects was raised by retina specialists [64,66]. It was reported that small doses used for eye disease seem to be safe, but these agents are very potent, and there are several lines of evidence that imply that these small doses could potentially have a systemic effect [66,67].

Since treatment trials are designed primarily to assess the prevention of vision loss caused by ocular conditions, they are inadequate for detecting rare, but potentially serious, systemic side effects [64,68]. A number of clinical trials have demonstrated an association between anti-VEGF therapies and increased cardiovascular events [32]. There is an increased risk of arterial thromboembolism, but not of venous thromboembolism, in patients with metastatic carcinoma treated with chemotherapy and systemic bevacizumab. Patients with cancer are at increased risk of a thrombotic event, which rises further when bevacizumab is administered [10,13].

In a retrospective study of 1173 patients receiving intravitreal bevacizumab injections [69], the reported systemic events included acute blood pressure elevations (0.59%), cerebrovascular accidents (0.5%), myocardial infarctions (0.4%), iliac artery aneurysms (0.17%), and death (0.42%) [69]. WY Ng et al. [23] analyzed 1011 individuals treated with intravitreal bevacizumab for AMD and found that the incidence rate of myocardial infarction, stroke and death in their cohort of AMD patients was low and not significantly higher than the age adjusted incidence rate of these events in Singapore population.

CATT trial found an increased risk of systemic Serious Adverse Events (SAEs) in the bevacizumab treated patients versus the ranibizumab treated group [70]: all-cause mortality was 2.8% in ranibizumab versus 2.9% in bevacizumab (P = 1.00), arterio-thrombotic events: 2.2% in ranibizumab versus 1.7% in bevacizumab (P = 0.68), Stroke: 1.2% in ranibizumab *versus* 1.2% in bevacizumab (P = 1.00).

Although a meta- analysis published 2 years ago of nine AMD trials did not confirm increased incidence in SAEs following bevacizumab injection [71], Avery RL performed a more current update of this analysis and confirmed the original finding of a significant risk with bevacizumab [67]. This finding is consistent with the pharmacokinetic data that show much higher systemic exposure from bevacizumab than ranibizumab, as well as a much more pronounced reduction in plasma and serum VEGF with bevacizumab [65,67,72-74].

Two years data from the IVAN trial [75], demonstrated a statistically significant increase in risk of systemic adverse events (including cardiovascular) with bevacizumab compared with ranibizumab. These findings may, in part, be explained by the systemic absorption of these agents, determined by the presence of an Fc fragment on bevacizumab and aflibercept, facilitating recycling and systemic absorption, whereas ranibizumab lacks an Fc receptor and accordingly has a shorter systemic half-life. Avery et al. have previously demonstrated marked reductions in plasma VEGF levels following bevacizumab and aflibercept injections, but with minimal reduction following ranibizumab injections, with corresponding systemic absorptions 70 fold higher for bevacizumab and 13 fold higher for aflibercept compared with ranibizumab [65]. Taken together, these data suggest that systemic absorption of intravitreal VEGF inhibitors may determine their adverse cardiovascular effects, particularly in those patients at high baseline risk [75].

Given the higher baseline risk for ATEs in patients with diabetes [32,76], most Diabetic Macular Edema (DME) trials have excluded patients with recent Cerebrovascular Accidents (CVAs) or Myocardial Infarctions (MIs). Several recent meta-analyses of patients treated for DME have not shown a statistically significant increased risk of ATEs or death across all treatment regimens, but one did raise concerns about a dose-dependent increased risk of death in a subset of patients [67,77-79].

Other reported bevacizumab vascular systemic side effects included rupture of abdominal aortic aneurysm [80].

Pathogenesis of bevacizumab vascular adverse events

Several studies showed reduced systemic VEGF levels after intravitreal anti-VEGF injections. Elevated levels of anti-VEGF drugs in the bloodstream were correlated with the decreased VEGF levels [65,67,72-74]. Systemic and ocular side effects of intravitreal anti-VEGF injections are mainly vascular, related to the inhibition of Vascular Endothelial Growth Factor (VEGF) [10,14,81,82]. Concerns about its side-effects on the retrobulbar and systemic circulatory system were raised [10,14].

Mete et al. [83] studied the effect of intravitreal bevacizumab in AMD on retrobulbar blood flow using Color Doppler Imaging (CDI) at 1 day post injection. They found that Peak Systolic Velocity (PSV) and End-Diastolic Velocity (EDV) of Posterior Ciliary Arteries (PCA) were significantly decreased, whereas Blood Flow Velocity (BFV) of Ophthalmic Artery (OA) and Central Retinal Artery (CRA), as well as Resistant Index (RI) of OA, PCA and CRA did not show any statistically significant difference at 1 day post injection.

Bonnin et al. [84] also analyzed the effect of intravitreal bevacizumab in AMD patients on retrobulbar blood flow, at 4 weeks post injection and found a decrease in mean BFV of CRA, PCA and OA.

Tolku et al. [85] found a decrease in BFV of CRA and PCA and increased RI of CRA and PCA with no significant change in the BFV of OA at the end of 1st week after intravitreal bevacizumab for AMD. These parameters returned to preoperative values at the end of 1st month post injection.

In spite of some differences between the 3 previous studies [83-85] regarding effect of intravitreal bevacizumab in AMD patients on retrobulbar blood flow in PCA, CRA and OA, all of them confirmed the effect of intravitreal bevacizumab on decreasing the blood flow in PCA in the early post injection period starting from 1 day till 4 weeks post injection. These changes in choroidal circulation may be attributed to different factors including:

- VEGF is involved in several cellular signaling pathways that are important in the regulation and maintenance of the microvasculature [86].
- VEGF acts as a vessel dilator by stimulating nitric oxide synthesis and influencing the auto regulation in microcirculation [87]. Bevacizumab leads to retinal vasoconstriction [88], similar to the vasoconstriction seen after intravitreal triamcinolone (95% for retinal artery diameter and 89% for retinal vein diameter) [89].
- It was hypothesized that VEGF has a protective and a regenerative effect on endothelial cells [90,91].
- Bevacizumab may induce arterial thromboembolism by exposing subendothelial procoagulant phospholipids by inhibiting VEGF-induced endothelial regeneration [82], and by reducing the production of nitric oxide and prostacyclin, thus predisposing to thromboembolic events [81]. This may lead to thrombus formation and occlusion of choriocapillaris lumen and decrease in blood flow velocities with increase in RI of choroidal vessels.
- Peters et al. [92] studied ultra structural effects of intravitreal bevacizumab in the primate eye, and found significant changes in the choriocapillaris as early as 24 hours after injection which normalized or partly normalized at day 14.
- Bevacizumab may reduce the number of fenestrations in normal choriocapillaris in rat eyes [93]. This reduction may be the reason for increased resistance to blood flow on CDI noticed as increased RI and decreased BFV in PCA.

Bevacizumab ocular vascular side effects are more prominent in elderly patients [81,82], due to evolving compromise in retrobulbar blood flow rates with age [94]. In addition, Dimitrova et al. [95] reported a reduction in choroidal perfusion is in patients with AMD. Avunduk et al. [96] found a significantly lower average blood flow velocity in the ophthalmic and central retinal arteries of patients with ischemic Central Retinal Vein Occlusion CRVO compared with their fellow eyes and also compared with patients with non-ischemic CRVO.

Retinal artery occlusion following intravitreal bevacizumab

The International Intravitreal bevacizumab Safety Survey analyzed the rates of optionally announced adverse events from 7113 injections given to 5228 patients and found a single report of central retinal artery occlusion CRAO [97].

Mansour A.M et al. [17] recorded in their Collaborative multi-center retrospective case series study published in 2010, four cases of CRAO and one case of branch retinal occlusion BRAO following intravitreal bevacizumab.

Von Hanno et al. [13] reported one case of retinal artery occlusion after intravitreal bevacizumab injection to reduce macular edema secondary to CRVO. Their patient developed macular BRAO 2 days after injection, as he experienced further vision loss to finger counting. Fundus exam revealed BRAO just superior to the fovea. The macular edema almost resolved within 1 week post injection and did not recur; final VA was 0.6. As visual loss occurred within days of injection, it is therefore unlikely that the arterial occlusion was secondary to the rise in IOP usually seen immediately after the procedure. Authors postulated [13] that an eye with CRVO has a variable degree of ischemia. This causes oxidative stress and, consequently, the inhibition of VEGF may be unfavorable for endothelial cells in terms of their ability to survive and regenerate. This may in turn facilitate arterial thrombosis by both the activation of platelets and the initiation of a coagulation cascade [98]. They concluded [13] that anti-VEGF therapy may be associated with an increased risk of retinal arterial occlusion in eyes with CRVO.

Retinal vein occlusion following intravitreal bevacizumab

Mansour A.M et al. [17] recorded in their Collaborative multi-center retrospective case series study published in 2010, one case of CRVO and one case of BRVO following intravitreal bevacizumab.

Hemorrhagic macular infarction following intravitreal bevacizumab

Furino C et al. [18] reported a case of dramatic deterioration of CRVO condition 3 weeks after intravitreal injection of bevacizumab secondary to hemorrhagic macular infarction.

Nonarteretic Anterior Ischemic Optic Neuropathy (NAION) following intravitreal bevacizumab

Hosseini H et al. [16] reported a case of 72-year-old woman who had vision loss in her right eye to Light Perception (LP) related to exudative AMD and an episode of NAION 10 years earlier. She had active subfoveal choroidal neovascularization in her left eye with visual acuity finger counting at 1 m. The left eye was treated with intravitreal bevacizumab injection. Four weeks later, visual acuity became finger counting at 2 m in the left eye, with decreased activity of the neovascular complex. Additional intravitreal bevacizumab injection was done. One week after second injection, she reported visual loss in the left eye. Examination revealed visual acuity of LP in both eyes. Left fundus exam revealed optic disc edema with peripapillary hemorrhages. Authors proposed that impaired auto-regulation of optic nerve microcirculation due to VEGF inhibition might be the cause of NAION. Ameri et al. showed that a sudden drop in VEGF concentration may cause closure of normal capillaries [99].

Ganssauge M et al. [15] reported another case of NAION following intravitreal injection of bevacizumab of a 51-year-old male with pseudoxanthoma elasticum who presented with NAION 2 weeks after treatment with intravitreal bevazicumab for choroidal neovascularization secondary to angioid streaks.

The above reported 2 cases draw the attention to the fact that risk of NAION should be taken into consideration when using intravitreal

bevacizumab in the treatment of retinal vascular diseases. Given the widespread use of intravitreal anti-VEGF agents, a possible effect of VEGF blockade on optic nerve circulation require further exploration [16].

Acute ocular ischemic syndrome associated with acute stroke following intravitreal bevacizumab

Huang ZL et al. [14] reported a case of diabetic 55 year old patient with unilateral rubeosis who suffered acute OIS and acute stroke 3 days after intravitreal injection of bevacizumab. Best corrected visual acuity before injection in the treated left eye was 6/60. He had underlying left carotid artery stenosis combined with bilateral preproliferative diabetic retinopathy. His visual acuity became no light perception in the left eye, with a dilated, unresponsive pupil and deepened chamber angle but no obvious rubeosis. The patient had high Intraocular Pressure (IOP 51 mm Hg) in the left eye. The fundus showed diffuse retinal hemorrhages, cherry-red spot and pale but nonedematous optic disc. Fluorescein angiography demonstrated delayed choroidal flush and artery perfusion (50 seconds after fluorescein injection). Ultrasound imaging of the carotid and ophthalmic arteries showed a total occlusion of the left internal carotid artery and a retrograde flow of the ophthalmic artery, favoring a diagnosis of left-side OIS with stealing phenomenon. Brain magnetic resonance angiography showed total left internal carotid artery occlusion. The final visual acuity was No Light Perception (NLP) in the treated eye. Authors concluded that acute ocular ischemic syndrome may be associated with intravitreal injection of bevacizumab in patients with compromised ocular and systemic vascular conditions, such as carotid insufficiency and poorly controlled diabetes mellitus. Their case has alerted to the possibility of acute vision loss and stroke after intravitreal injection of bevacizumab.

Massive choroidal hemorrhage and contralateral sympathetic ophthalmia following intravitreal bevacizumab

Brouzas D et al. [11] reported a case of 75-year-old male with no previous history of ocular surgery, which had an intravitreal injection of 1.25 mg bevacizumab in the right eye RE because of exudative AMD. The patient had mild hypertension, and was not on anticoagulants. Ten days after injection, he manifested acute loss of vision with severe pain in the RE. On presentation, his best-corrected visual acuity was NLP in the RE and 0.3 in the left eye LE. Examination of the RE revealed congestive conjunctiva, corneal edema, elevated intraocular pressure (55 mmHg) and collapsed anterior chamber. An extensive choroidal detachment was evident in close contact with the lens. The intraocular pressure of LE was 14 mmHg and fundus examination of the LE revealed extensive confluent soft drusen at the posterior pole. Intravenous administration of carbonic anhydrase inhibitor and hyper osmotic agent failed to reduce the intraocular pressure and to alleviate the pain. An emergency sclerotomy with reconstruction of the anterior chamber with viscoelastic was performed two days later. Four months later, RE proceeded to phthisis bulbi. Five months post injection, the patient complained of mild pain, photophobia, and visual acuity deterioration in his fellow left eye. His best-corrected visual acuity in the LE was 1/20, and the fundus examination revealed extensive confluent drusen at the posterior pole with edema of the optic disc and flare and cells in the vitreous. The diagnosis of sympathetic ophthalmia was suggested. Since the patient had a subtotal gastrectomy for uncontrollable bleeding from peptic ulcer 15 years ago, activated by an excessive salicylates intake, only topical and peribulbar steroids were used. Ten days later, the patient experienced significant visual improvement. Three months later, his best-corrected visual acuity in LE was 2/10. Later patient was controlled by intravitreal triamcinolone acetonide injections every three months with a good response. His IOP became elevated and was managed with an Ahmed valve implantation. 11 months later, his best corrected vision was 1/10. Authors concluded that serious ocular complications after intravitreal bevacizumab cannot be excluded, including massive choroidal hemorrhage in the treated eye and sympathetic ophthalmia of the fellow eye.

Kidney toxicity following intravitreal bevacizumab

With the wide use of intravenous anti- angiogenesis drugs in cancer treatment, several renal related complications including proteinuria, hypertension and thrombotic microangiopathies have been reported [22]. Because of intravitreal bevacizumab absorption to the systemic bloodstream, there is risk of kidney injury in patients with previous kidney disease, as the kidney vasculature is reliant on VEGF [22].

Sato et al. [100] reported a case of nephrotic syndrome relapse (previously treated with prednisolone and remained in remission) after intravitreal bevacizumab in 16 years old girl. The patient was treated with intravitreal bevacizumab for myopic choroidal neovascularization. 9 days post injection the patient had relapse of her nephrotic syndrome with positive proteinuria caused by bevacizumab. Steroid was given again and proteinuria resolved. Authors concluded that special care should be taken in patients with nephrotic syndrome when treated with bevacizumab.

Ischemic colitis and gastrointestinal bleeding following intravitreal bevacizumab

Onoda Y et al. [101] reported a case of 78 year old woman with past history of surgical treatment for colon carcinoma. The day after intravitreal bevacizumab, the patient developed acute severe abdominal pain with massive lower gastrointestinal bleeding. Further investigations revealed the diagnosis of ischemic colitis. The authors concluded that alternative treatments should be used instead of intravitreal bevacizumab in patients with history of gastrointestinal cancer.

Alveolar hemorrhage following intravitreal bevacizumab

Seto et al. [102] reported a case of acute respiratory failure after intravitreal bevacizumab for BRVO. Chest CT scan and bronchoalveolar lavage fluid revealed alveolar hemorrhage. Authors suggested that intravitreal bevacizumab may be associated with diffuse alveolar hemorrhage and acute lung injury.

Conclusion

In case of any visual loss post intravitreal bevacizumab not attributed to reactivation of the underlying retinal or choroidal disease, one should think about the possible side effects of bevacizumab on systemic, retrobulbar and ocular circulation. Eyes have different risk profiles according to the underlying pathology which is treated by intravitreal bevacizumab. This should be considered in patients with compromised ocular and systemic vascular conditions, such as old patient's age, carotid insufficiency, poorly controlled diabetes mellitus, Ischemic CRVO, Ischemic ocular syndrome, previous MI,

previous stroke, early kidney disease and history of gastrointestinal cancer.

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