



Intravitreal Anti-Vascular Endothelial Growth Factor Complications

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Abstract

The use of antiangiogenic drugs (anti-VEGF) has been described in several retinal diseases, so their use has become a common practice in most eye centers around the world. Since its application involves an invasive procedure, several complications have been described associated with their use, including from subconjunctival hemorrhage to devastate endophthalmitis. In this systematic review we describe the reported association between the different anti-VEGF agents and this rate of complications reported. The study was conducted in the PubMed database with those articles that discuss the adverse effects associated with intravitreal injection of anti-VEGF agents were selected. The conclusions obtained were that complications can occur during and after the procedure with either Anti-VEGF agent, so it is recommended to follow a security protocol during application.

Keywords

Intravitreal injection, Antiangiogenic, Adverse effects, Bevacizumab, Ranibizumab, Aflibercept

Introduction

In recent years, the role of angiogenesis and vascular permeability has been established in various retinal pathologies as critical mechanisms for tissue regeneration. The vascular endothelial growth factor (VEGF) is the primary regulator of angiogenesis [1]. VEGF-A belongs to the family of VEGF growth factors (A, B, C and D) and is currently accepted as one of the most important growth factors in the induction of angiogenesis. There are six isoforms of VEGF-A: 121, 145, 165, 183, 189 and 206, produced by RPE cells, ganglion cells, Müller cells, pericytes, endothelial cells, glial cells and neurons [2].

Different treatments targeting VEGF (anti-VEGF) and inhibiting angiogenesis have been developed for intravitreal administration, changing the paradigm for the treatment of several retinal diseases [1]. Some of these anti-VEGF treatments include:

Anti-VEGF drugs

1) Pegaptanib (Macugen, Eyetech Pharmaceuticals, Melville, NY / Pfizer, New York, NY); ribonucleic acid pegylated aptamer that binds with high affinity to the VEGF 165 isoform.

2) Bevacizumab (Avastin, Genentech, Inc., San Francisco, CA, USA) is a recombinant humanized monoclonal immunoglobulin that inhibits all isoforms of VEGF-A. It was designed to oncological diseases, however, several studies have shown its usefulness "off label" in retinal pathologies.

3) Ranibizumab (Lucentis, Genentech, USA, Inc., San Francisco, CA, USA / Novartis Ophthalmics, Basel, Switzerland); fragment of chimeric monoclonal antibody with high affinity to all isoforms of VEGF-A, approved in 2006 by the FDA to treat neovascular age related macular degeneration (ARMD) [3].

4) VEGF Trap-Eye / Aflibercept (EYLEA®-Regeneron Pharmaceuticals, Inc., Tarrytown, New York, NY, and Bayer Healthcare Pharmaceuticals, Berlin, Germany); fuse VEGF receptors 1 and 2 with a fragment of IgG. Acts on all the isoforms of VEGF-A and VEGF-B and Placental growth factors 1 and 2 (PlGF) [4].

Several randomized clinical trials showed that these drugs have positive results in diseases such as age related macular degeneration, diabetic macular edema, cystoid macular edema, macular edema secondary to vein occlusion, diabetic retinopathy, choroidal neovascularization, neovascular glaucoma, intraocular tumors, retinopathy of prematurity, and others [1,5].

Intravitreal application of antiangiogenic drugs is an invasive procedure that requires following a safety protocol during application. Nevertheless, the number of adverse effects has increased due to the increase number of injections currently used. Among them, two types of complications have been described, 1) associated with the injection occasioned by the introduction of the needle to eyeball and 2) associated with the action of the pharmacodynamics of the drug [5].

Material and Methods

We conducted a systematic review of the PubMed database according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement guidelines by Liberaty A et al. [6] Predefined search terms were used to identify articles published, and after a screening of the results obtained, we include 51 selected by their relation to adverse effects associated with the use of intravitreal antiangiogenic agents like anti-VEGF. The search terms were:

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intravitreal injection, complications, antiangiogenic, adverse effects, bevacizumab, ranibizumab, aflibercept.

Complications associated with the injection

Endophthalmitis: Acute endophthalmitis is one of the most aggressive complications secondary to any ocular invasive procedure; it's produced by the contamination during the application of injection. To reduce the risk of infection, the procedure must be performed in special areas such as halls cures or prepared places where there is not a high volume of incoming and outgoing patients. A meta-analysis by McCannel [7] in 2011 reported an incidence of 52 cases per 105.536 injections (0.049%) [7].

There are several risk factors and standardized security measures for the procedure. In terms of patient preparation, studies recommend the use of 10% povidone iodine in the eyelid area and 0.5% in the conjunctival sac prior to the procedure. Although it is reported that topical preoperative antibiotics decrease the bacterial flora on the ocular surface, there is no evidence of reduction in the risk for endophthalmitis [8].

In the review by McCannel [7], the bacterial identification from the samples of endophthalmitis secondary to intravitreal injection was *Staphylococcus coagulase negative* in 65.4%, *Streptococcus* in 30.8% and 3.8% *Bacillus cereus*. In contrast to other studies the presence of streptococcus is higher than reported in cases of endophthalmitis secondary to other surgical procedures like endophthalmitis vitrectomy study (9.0%), endophthalmitis associated with cataract surgery in clear cornea (8.2%) and reports of endophthalmitis post-vitrectomy without any case associated to streptococcus.

The evidence indicates that the increased incidence of *Streptococcus* intravitreally is due to oropharyngeal transmission by tiny fluge droplets expelled during talking, coughing or sneezing by health personnel at the moment of the injection, so is recommended to avoid performing these actions during the procedure and to use surgical mask [7]. Other factors that should be also avoided during the procedure involve the injection in the presence of infection with discharge or blepharitis and the contact of the needle with lid margin or lashes.

Moreover, the application of antibiotics immediately after the injection is controversial, by one side reports show protection against infection [9], but largest series about proves that this action do not always diminishes the risk of endophthalmitis. In fact, some authors report that the immediate application of antibiotic, in combination with its use for 5 days post-injection is associated with endophthalmitis and increase resistance of microorganisms to antibiotics in ocular surface [10].

In contrast to the empiric treatment with intravitreal antibiotics frequently a combination of vancomycin 0.1mg/0.1ml and ceftazidime 2mg/0.1ml [11], established by the guidelines of the Endophthalmitis Vitrectomy Study [12], there are no specifications for endophthalmitis treatment after intravitreal injection of anti-VEGF.

Daphna et al. [11] suggest the use of intravitreal antibiotics when there is a clear view of the retina in cases of suspected endophthalmitis, and they also agree with Kuhn and Gini who recommend that immediate vitrectomy surgery should be performed in an attempt to reduce bacterial overload and potentially improve outcome for cases in which no retinal details can be seen (caused by anterior chamber inflammatory reaction or severe vitreous haze) [9,11,13].

Intraocular inflammation: Acute intraocular inflammation is associated with all types of anti-angiogenic drugs; the reported incidence is 0.33% to 2.9%, however among different agents Anti-VEGF the incidence is variable [1]. Is believed that this inflammatory process is associated with immune response of the host and the presence of preservatives or contamination of the drug during the preparation, for example bevacizumab, where multiple doses of the same road are prepared, and occurs a contamination, the risk of inflammation increases in each patients receiving injection prepared

from the same bottle. Ranibizumab and aflibercept single doses presentation and preservatives-free reduces the risk. In the case of aflibercept, is believed that occurs protein denaturation associated with the higher viscosity of the molecule; the aflibercept injection is prepared with a 19 G needle, little bubbles are difficult to remove from the syringe form. The denaturation can occur in these hydrophobic-hydrophilic interfaces, while the protein is guiding their hydrophobic groups in the non-aqueous layer. The denaturation process can be accelerated by the stress exerted when is injected with a 32G needle versus 30 G, because the diameter of the inner lumen is 33% lower [14].

Clinical aspects such as presentation time, pain and severity of the disease help in the differentiation from inflammatory or infectious case. The reported average time for the presentation goes to 2.55 days (range 1-6) in endophthalmitis and even less than 1 day in acute inflammatory condition. Pain is present in both conditions, however, during endophthalmitis is steadily and is more intense.

The severity of the disease is higher in cases of endophthalmitis, often associated to keratic precipitates, hypopyon and anterior synechiae. Despite of the clinical differences, the recommendation in a case is always to suspect of endophthalmitis and initiate intensive treatment with close monitoring and antibiotics [5,11].

Increased intraocular pressure: Increased intraocular pressure (IOP) is a frequent complication associated with the increase in the volume of the vitreous cavity. There are several reports showing an increase, not sustained IOP subsequent to intravitreal injections of anti-VEGF. These reports show that IOP return under 25mmHg one hour after the injection without using drugs. It has been shown that this transient increase in IOP is more common in phakic patients with a history of glaucoma or in those who the return to baseline IOP is delayed [15].

Yannuzzi et al. [16] reported an incidence of sustained elevation IOP by 1-5%, , other series reported from 0.5 to 13% [15]. Good et al. [17] reported an increased risk in the eyes that received only bevacizumab (9.9%) compared to eyes receiving ranibizumab (3.1%) [17]. However, in the statistical analysis, the authors could not conclude if bevacizumab had a higher risk of IOP. It is hypothesized that Bevacizumab, being a higher molecular weight protein (148k-Da) may obstruct the trabecular meshwork [3]. Other authors hypothesized that aflibercept could lead to a lower incidence of sustained IOP elevation because requires fewer injections, nevertheless there is insufficient data to support this premise [18].

Hoang et al. [19] found that the sustained increase in IOP was associated with the number of injections, they reported that those who had received more than 29 injections had 16.1 more probabilities of sustained IOP than those with less than 12 injections [19]. There are not previous studies evaluating the impact of the injection technique and needle gauge on the sustained elevation of IOP, several studies have investigated the effects of the injection technique in short term. Hohn and Mirshahi examined the impact of a straight scleral incision compared with tunneled in patients who received injections of ranibizumab. The tunneled incisions had an average of 11mmHg greater increase in mean IOP straight scleral incisions [16,20]. Reported differences in the size of the needles conclude that smaller gauge needles (30 or 32 G) are associated with higher peak ocular hypertension when compared to 27 gauge, they explained by the presence of more vitreous reflux associated with thicker gauges.

Other associations focus in the amount of injected volume and the injection rate. When you inject 0.05 ml in less than 1 second, increase 5 times sustained IOP, probably secondary to damage to the trabecular meshwork [16].

Some studies report less increased IOP if compression in the eye is applied prior to injection, even if performed with a cotton swab [21].

Patients with increased IOP were adequately managed with topical medication. Bocco et al. [22] reported acute hypertension and

transient loss of light perception in four patients treated with Anti-VEGF injection. Three of these patients were successfully treated with acetazolamide, and in one patient, anterior chamber puncture was necessary [22,23].

Subconjunctival hemorrhage: This is perhaps the most common complication in 64.75% to 72% of the cases. The development is associated with the rupture of capillary and vessels during the procedure, is located only in the quadrant where the injection was performed, not usually associated with other symptoms. Some studies report an association between the size of the hemorrhage and the use of aspirin; it's been proposed to discontinue their use three days before injection to recover it one day later [24]. Studies as MARINA [25], ANCHOR [26], and the series of Mason et al. [27] no association between the uses of anticoagulants (aspirin, clopidogrel, warfarin) with another ocular hemorrhagic event has related, but an increase in the risk of a thromboembolic event if the drug is stopped, they recommend to individualize each case [28]. Despite concerns among the patients about the appearance of hemorrhage, usually is reabsorbed between 9-15 days after injection.

Rhegmatogenous retinal detachment (RRD): This complication is rare, with a reported incidence of 0.013%, certain factors are associated like the site of the injection; it should be between 3.5 - 4mm posterior to the limbus, if its applied after this, you may damage the vitreous base, ora serrata or cause a retinal tears. Is suggested to use lighter to 30 gauges, because thicker sizes do not necessarily reduce the pain and they can cause more strength and force application that could reduce precision in the injection. The needle should be directed to the center of the eye, in the center of an angle formed between the posterior capsule of the lens and the retinal surface. The needle depth suggested is one third to half of the needle size. You should take special care in anxious patients and make sure to put topical anesthesia in order to reduce the risk of inadvertent movement. Introducing tunneled needle is suggested to promote wound closure and prevent backflow of drug and as well as vitreous incarceration, traction and tear formation.

It has also been described an association between the underlying disease and the risk of DRR, patients with CMV retinitis, macular hole, diabetic retinopathy and vitreous hemorrhage have higher risk of retinal detachment and patients with age related macular degeneration, vitreous liquefaction and posterior vitreous detachment have low risk [28].

In patients with myopia, is recommend to search for predisposing lesions (such as lattice or asymptomatic holes) and treat them prior to the application of Anti-VEGF injection [28].

Crystalline damage: The lenticular state is an important factor in determining the site of intravitreal injection. Most surgeons recommend a distance of 4.0mm from the limbus in phakic eyes and 3.5mm in pseudophakic and aphakic eyes. The needle should be directed towards the center of the vitreous cavity or, towards the posterior pole. The injection can be performed under microscopy, direct visualization or under indirect ophthalmoscope, according to surgeon preference. You should take special care to avoid damaging the lens [29].

Jonas et al. [30] reported a low incidence of rapid cataract formation (traumatic cataract) 0.06% in 5403 injections, however, because conditions such as AMD require multiple injections, the procedure may become routine and lens damage is actually reduced [30]. This complication is associated with some factors as inexperience of the surgeon, uncooperative patients or misdirection of the needle. When the posterior capsule is damage, cataract surgery becomes a challenge for the surgeon. There are signs that can guide during this condition like to observe the path of the needle in the crystalline, loss of convexity of the anterior capsule, the presence of cataract or observation of a break in the B mode ultrasound [31].

Felcida et al. [32] reported one case of traumatic cataract after Bevacizumab injection. The application was made in the inferior

temporal quadrant of the left eye with 30 gauge needle. The surgeon referred the patient moved during the procedure. The patient had decreased visual acuity, rapid progression of cataract and an image suggestive of lens nucleus dislocation in B-mode ultrasound. When cataract surgery was performed, they noted a tear in the posterior capsule from the meridian of 4 to meridian of 7. The authors of this report suggest exploring by indirect ophthalmoscopy at the end of each injection [32].

Complications associated with anti-VEGF agents

Retinal pigment epithelium tears (RPE Tears): RPE tears are present in 2-3% of patients with AMD and increases to 10-15% in patients with detachment of the retinal pigment epithelium (PED). Spontaneous RPE tears have been described since 1981, almost associated with a PED. The most important risk factor for developing an RPE tear is the basal diameter of PED and its vertical height [33].

Anne E. Fung and colleagues reported the first estimate of RPE tears after Anti-VEGF injection, with a rate of 0.06%, however, did not report the time between injection and tearing, the nature of the injury or if associated with a PED [34].

In 2007, Clement Chan and colleagues reported an RPE tear rate of 2.1% (21 eyes of 1010 injected). All cases were associated with a vascularized PED (125 cases), resulting in a rate of 16.8%. The time between injection and tearing of the RPE was approximately one month (range 4 days - 3 months). No statistical difference was observed between visual acuity before and after RPE tear; this is probably due to continued regression of neovascularization [35].

Konstantinidis et al. [36] observed four RPE tears in 72 consecutive patients (5.6%) with predominantly classic CNV and seven eyes of 55 patients (12.3%) with DEP and occult CNV, all treated with ranibizumab. Both groups of patients showed improvement in visual acuity after injection of ranibizumab (despite having developed the tear) [31]. Iris Moroz et al. [37] studied predictors in OCT to RPE tear developed after injection of bevacizumab in 143 consecutive patients with neovascular AMD, including 24 eyes with serous PED. Six eyes developed RPE tear after the first injection, they all had a preexisting DEP (4.2% overall and 25% among PED). The six patients who developed the tear showed a wavy appearance or interruption in the continuity of the layer RPE [37].

Cunningham and colleagues examined the incidence of RPE tears in ANCHOR, MARINA and PIER studies reporting a 2.4% in the group that receive the injections, compared to 1.6% in the control group. It also found that 16 of the 21 cases of tear (76%) were associated with DEP. Notably, all patients who developed RPE tears continued treatment with ranibizumab and had better visual acuity than control patients at 24 months follow-up group, which makes clear the benefit of treatment against the risk of developing RPE tear [38].

The studies suggest that the incidence of tearing of the RPE in all patients treated with AMD is 2-6% and 12-25% in patients who have associated DEP. Also, patients receiving injections of anti-VEG are more likely to develop this complication than patients without treatment, probably due to accelerated involution causing Anti-VEGF therapy [33].

The exactly pathogenesis of RPE tears remains unknown. The suggested mechanism of RPE tears is the inhibition of VEGF that causes a decline in intercellular adherence or the increased pressure of the serous fluid exerting cohesive forces on the RPE. As already mentioned RPE tears may occur spontaneously in the natural course of the disease or associated with an injection of anti-VEGF agent. At first, Aflibercept was described as an option for patients with higher risk such as those with PED, however, Saito et al. [39] reported the first case of RPE tear and confirmed by subsequent fluorangiography and OCT after use of aflibercept in a patient with neovascular AMD [39].

Subretinal hemorrhage: There are reports of extensive subretinal hemorrhage after injection of bevacizumab at a dose of 1.25mg much as 2.25mg, as well as the series of Karagiannis reporting this

bleeding in 3 of 36 patients who were switched from bevacizumab to ranibizumab because of poor treatment response. These reports were performed in patients with age related macular degeneration, is also frequently in cases with extensive choroidal neovascularization. The mechanism of this complication remains unknown, is believed to be due to a rapid contraction of the neovascular membrane, although it may be a result of the natural evolution of the disease [40,41].

Tractional retinal detachment: Despite the effectiveness demonstrated in ocular neovascularization, Anti-VEGF agents can produce tractional retinal detachment (TRD) in patients with proliferative diabetic retinopathy. The hypothesis of this mechanism talks about acceleration in the closure of the neovessels replacing them by fibrous tissue and the fibrous tissue contraction can cause TRD and vitreous hemorrhage. Another suggested mechanism is the mechanical deformation of the eye during the injection causing vitreous incarceration at the site of the wound, causing vitreoretinal traction [3].

Torres-Soriano et al. [42] reported a rate of 1.45% TRD in a period of 1-6 weeks after injection and may be associated with the injection or with the natural history of the disease. Arevalo et al. [43] found that in 82% of cases, the TRD is presented in the first 5 days after injection, but some reports make the association in a range up to 2 months. In some cases, the Anti-VEGF therapy has surgical purposes; reduce risk of trans and postoperative bleeding, as less surgical time, however, the general recommendation is to perform a vitrectomy no longer than 1 week of injection, to reduce the risk of TRD [44].

The tractional retinal detachment induced by anti-VEGF treatment has been reported not only in proliferative diabetic retinopathy but also in retinopathy of prematurity (ROP) and Coats disease. There are studies supporting the use of bevacizumab in ROP, however, in advanced stages, there is a danger of TRD due to contraction of fibrotic tissue associated with neovascularization. Similarly, in Coats disease, there is a risk of developing vitreoretinal traction with consequent retinal detachment [45,46].

Rare ocular complications: There are reports of uncommon complications associated with intravitreal anti-VEGF as anterior ischemic optic neuropathy, retinal vein occlusion, occlusion of the central retinal artery, paralysis of the sixth cranial nerve, and exacerbation of ocular ischemic syndrome [5].

Systemic complications: Anti-VEGF agents are widely used in the treatment of many solid cancers, have several adverse events reported with systemic administration of anti-VEGF monoclonal antibodies, including thromboembolism, myocardial infarction, stroke, hypertension, gastrointestinal perforations, and kidney disease. Levels of anti-VEGF were detected measurable in the systemic circulation in patients treated with intravitreal injections, so its possible the presence of systemic effects [5,47].

Although first clinical trials of ranibizumab showed no increase in risk, other studies suggest a potential increased rate of systemic diseases associated with injection of ranibizumab, especially in elderly patients. The intraocular injection of ranibizumab has been linked to the presence of non-ocular bleeding events, including bruising, gastrointestinal bleeding, vaginal bleeding and subdural hematomas.

The rates of deaths from any cause, myocardial infarction and cerebrovascular events are not significant. Whereas the details of adverse effects with the use of bevacizumab are limited, data on the systemic safety of intravitreal bevacizumab is less conclusive compared to ranibizumab clinical trials. Intravitreal bevacizumab injections could be associated with an increased risk of non-ocular hemorrhage [5,48].

In a retrospective study of 1173 patients who received injections of bevacizumab, the reported systemic events were acute elevation of blood pressure (0.59%), stroke (0.5%), myocardial infarction (0.4%), iliac artery aneurysms (0.17%) and five deaths [49].

When analyzing risk factors, it was an 11% risk of death from

any cause and a 57% increased risk of hemorrhagic stroke with bevacizumab, without statistically significant differences between the risks of any heart attack or stroke [50].

In a study by Schmucker et al. [51] higher proportion of patients reported serious systemic infections and gastrointestinal disorders with bevacizumab than with ranibizumab; arterial thromboembolic events were similar between two groups.

Van der Reis et al. [23] evaluated and compared the incidence of systemic side effects associated with pegaptanib, ranibizumab and bevacizumab and concluded that there is insufficient evidence to show differences in safety between drugs [45].

It is necessary to pay special attention to women of childbearing age, especially to diabetic retinopathy or diabetic macular edema, as the average age of these patients is lower than AMD, and there is potential risk of teratogenicity, carcinogenicity and impairment of fertility with the use of Anti-VEG. Counselling of patients is therefore essential to ensure that adequate contraception is being used and that possible systemic side-effects are understood [3].

Conclusions

Many complications have been associated with all types of anti-VEGF agents in general, most of them can be avoided if a security protocol is followed during application, and this will reduce the incidence of complications. We strongly recommend due to the actual absence of a guideline, to the standardization of the procedure so the risk-benefit balance will be positive against the risk of developing any of these complications.

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