Mini Review

Anti-vascular endothelial growth factor drugs safety and efficacy in ophthalmic diseases

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ABSTRACT

Macular degeneration is the leading cause of blindness in developed countries. In the treatment of neovascular age-related macular degeneration, vascular endothelial growth factor (VEGF) has emerged as a key target for therapy. The intravitreal injection of anti-VEGF drugs has been widely employed to reduce the disease progression and improve the visual outcomes of the affected patients. However, each intravitreal inoculation poses a risk of several complications as infection, inflammation, endophthalmitis, intraocular inflammation, increase of intraocular pressure and vitreous hemorrhage. This short review evaluates the efficacy and the incidence of adverse drug reactions related to intravitreal administration of the main anti-VEGF drugs actually available: Bevacizumab, ranibizumab and aflibercept.

Key words: Adverse drug reactions, aflibercept, age-related macular degeneration, bevacizumab, choroidal neovascularization, ranibizumab

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of blindness in the population older than 50 years and consists of an alteration in the central part of the retina, the macula.[1] Two different forms of macular degeneration may be distinguished: Dry (non-exudative) AMD and wet (exudative) AMD. Dry AMD, the less serious of the two, occurs in about 85% of patients diagnosed with macular degeneration and refers to the condition in which, due to advancing age, the retina accumulates waste material, which leads to amorphous deposits termed as drusen and the retinal pigment epithelial cells degenerate leading to loss of central vision.[2] No specific treatment is available, although, a diet implemented with carotenoid has been proved to slow the lesions progression and the visual impairment.[3] The wet AMD accounts for only 15% of all macular degeneration, but causes up to 90% of blindness in individuals diagnosed with AMD. Wet AMD refers to the condition, in which new blood vessels grow from the choroid (the layer between vascularized retina and sclera). This process is known as "choroidal neovascularization," and causes uplift of the macula from its normal position resulting in blurred and distorted vision. The macular damage develops rapidly and without treatment, vision loss may be rapid and severe.[3]

In the wet AMD, the main purpose of drug treatment is the elimination of new-formed vessels under the retina and the reduction of macular edema. An important drug treatment used

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for this purpose is the intravitreal injections of anti-vascular endothelial growth factor (VEGF). Here, we report a brief review of the efficacy and safety of such drugs.

ANGIOGENESIS AND VEGF

Angiogenesis has been defined as a process of blood vessel growth and expansion by sprouting and remodeling into a highly organized vascular network.[4] This process normally occurs in adults during menstrual cycles and in the placenta during pregnancy. Several diseases (such as cancer, diabetes and inflammatory disorders) have been associated with angiogenic rearrangement. Among pro-angiogenic factors, VEGF regulates endothelial cell proliferation and migration.

VEGF is a dimeric glycoprotein of 36-46 kD, which acts as an angiogenic cytokine inducing mitosis.[5] The VEGF gene family includes six different isoforms, namely VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E and placental derived growth factor.[6] These genes are located on chromosome 6 and share many sequences with the platelet derived growth factor gene. A host of hormones can up-regulate VEGF, such as estrogens, insulin, corticotropin, thyrotropin, steroidal hormones and a number of circulating growth factors.

Three VEGF receptor subtypes have been identified (VEGFR1-3). Induction of angiogenesis is mainly mediated by VEGFR2, which activates phosphatidylinositol 3 kinase/akt murine thymoma viral oncogene homolog (Akt) and Raf-mitogen-activated protein kinase kinase-extracellular pathways,[7] conversely VEGFR1 seems to play a role in adult angiogenesis by inducing endothelial cell protease.[8] Ligand binding activates VEGFRs, triggering a downstream intracellular signaling cascade that promotes endothelial cell proliferation, survival, activation, invasion, migration and permeability.[9] Both VEGFR-1 and VEGFR-2 are located in the vascular endothelium, neurosensory retina and retinal pigment epithelium cells.[10] The key role of VEGF in angiogenesis explains the use of anti-VEGF drugs in treatment of wet AMD.

MATERIALS AND METHODS

A computer-aided search of PubMed and Cochrane library databases was performed; data were collected to review the efficacy and safety of intravitreal injections of anti-VEGF in the treatment ophthalmic diseases. The upper limit date for the search was April 30, 2013, without lower limit.

Secondary search included articles cited in reference lists identified by the primary search. Records were first screened by title/abstract before full-text articles were retrieved for eligibility evaluation. Remaining articles were then subject to a citation search before a final hand-search of all reference lists.

INTRAVITREAL USE OF ANTI-VEGF DRUGS

VEGF is believed to be a key factor in the development and progression of choroidal neovascularization.[11] In recent years, anti-VEGF drugs (e.g., bevacizumab and ranibizumab) have been used in the treatment of choroidal neovascularization and several studies have demonstrated the validity of intravitreal injection of such drugs.[12,13]

The first Food and Drug Administration (FDA) approved anti-VEGF therapy for neovascular AMD was pegaptanib. Pegaptanib is an RNA aptamer that binds human $VEGF_{165}$ with high affinity and specificity.[14] The drug, however, did not bind other active VEGF isoforms such as $VEGF_{121b.}$[14]Bevacizumab, the most popular agent treating choroidal neovascularization among all the anti-VEGF drugs, is a humanized monoclonal antibody with strong anti-angiogenic activity.[12] It is used in cancer therapy to stop the growth of the neovascular network in the context of metastatic colorectal cancer and was first approved by the US FDA in 2004.[15] Possible "off label" applications, refer to the treatment of neovascular macular degeneration and vascular diseases of the retina, which are characterized by a marked edematous and exudative component such as diabetic retinopathy[16] and occlusion of the central retinal vein.[17]

Another anti-VEGF drug is ranibizumab, a monoclonal antibody fragment derived from bevacizumab. It is smaller than bevacizumab and was introduced to enhance the affinity for VEGF-A.[18] FDA approved it for the treatment of neovascular AMD. However, bevacizumab has been extensively used off-label for this indication, mostly for economic reasons; in fact, it is much cheaper than any other anti-VEGF agent commercially available.[19] Recently, the results of two large-scale trials comparison of AMD treatments trials (CATT and IVAN trial), demonstrated that bevacizumab is non-inferior to ranibizumab with regards to visual improvement.[20,21]

A recent anti-VEGF drug used for the treatment of this ophthalmic affection is aflibercept. It is a human recombinant fusion protein that binds all VEGF-A isoforms, VEGF-B and placental growth factor (PlGF).[22] Aflibercept has been developed for the treatment of cancer and eye disorders. The eye formulation is obtained with purification steps and modification to allow comfortable, nonirritating intravitreal injection. Aflibercept binds PlGF and animal studies have shown that PlGF contributes to the development of experimental choroidal neovascularization.[23] Another differentiating feature of aflibercept is represented by the binding affinity for VEGF, which is stronger than ranibizumab and bevacizumab. This allows an effective blocking of VEGF, even at low concentrations, which may translate into a longer duration of action and extended dosing intervals and also reduce the number of intravitreal injections. These encouraging results coupled with the apparent safety of the drug, fueled the demand for human clinical trials.

CLINICIAL STUDIES AND ADVERSE DRUG REACTIONS (ADRs)

CATT[20] study conducted by the National Institutes of Health reported the near equivalence of ranibizumab and bevacizumab used for neovascular AMD. The CATT study concluded that ranibizumab and bevacizumab had similar effects on visual acuity over a 2-year period. The study also showed similar ADRs' profiles at 2-years, but with a slightly higher frequency for bevacizumab-related systemic adverse events.

The CATT trial showed almost similar treatment efficacy of the two drugs with a significant cost difference. The CATT study quoted the average cost of drug per patient in favor of bevacizumab.

IVAN trial[21] was a multi-centered, randomized trial comparing the efficacy of bevacizumab and ranibizumab in AMD. The results suggest that ranibizumab and bevacizumab are equivalent with regards to visual improvement. There was no difference between the drugs respect to serious systemic adverse effects.

View 1 and View 2[24] trials for aflibercept report good visual outcomes comparing aflibercept and ranibizumab. After an initial loading phase of monthly injections for 3 months, intravitreal injections of aflibercept every 2 months appeared to be non-inferior to ranibizumab.

CLEAR-IT 2 1-year data showed good visual and anatomic outcomes with aflibercept. After one injection per month for 3 months, on average one to two more injections were needed per eye on an as-required basis and average time for reinjection was reported as 129 days.[25]

ANTI-VEGF AND ADRS

Anti-VEGF, when used intravitreally, are associated with ocular adverse events. These events include endophthalmitis, intraocular inflammation, increase of intraocular pressure, vitreous hemorrhage, retinal detachment, retinal pigment epithelial tears and cataract[26,27] [Table 1].

Many studies have demonstrated that systemic levels of VEGF are lower in patients treated with bevacizumab than in those treated with ranibizumab. However, experimental observations have shown that treatment with bevacizumab may be associated with a higher risk of serious adverse effects, especially arterial thromboembolic events, due to its greater systemic penetrance.

Table 1: ADRs of Anti-VEGF drug

Systemic event
Arterial-thrombotic event
Venus-thrombotic event
Transient ischemic attack
Hypertension
Cardiac disorder
Infection
Nervous System disorder
Benign or malignant neoplasm
Other system organ class
Ocular event
Endophthalmitis
Pseudo-endophthalmitis
Rhegmatogenous retinal detachment
Retinal tear
Uveitis
Vitreous hemorrhage

VEGF=Vascular endothelial growth factor; ADRs=Adverse drug reactions

Systemic ADRs

The role of anti-VEGF in the development of systemic adverse events remains unclear. However, the risk of development of systemic adverse events may be higher with bevacizumab than with ranibizumab. In fact, ranibizumab has a higher affinity for VEGF than bevacizumab and as an antibody-binding fragment, it lacks the domain necessary to activate complement-mediated cytotoxicity or to interact with Fc receptors on immune cells.[28] Therefore, bevacizumab is more able to induce immunologic activation than ranibizumab. Next, the systemic concentration after intravitreal anti-VEGF injection appeared to be higher for bevacizumab (59.8-86.5 ng/mL) than for ranibizumab (0.3-2.36 ng/mL).[20] Thus, bevacizumab administration may represent a higher risk of systemic adverse events. The results of CATT study indicate that patients treated with bevacizumab had more frequently systemic events than ranibizumab.

Systemic administration of anti-VEGF drugs has been associated with arterial-thrombotic complications.[29] Arterial-thrombotic ADRs were more common among patients treated with bevacizumab, but this difference was not statistically significant. The majority of these ADRs were hospitalizations, mostly for reasons unrelated to the anti-VEGF therapy. However, despite these observation, intravitreal administration of bevacizumab, in accordance with the data accumulated in previous studies, suggest that the risk for arterial-thrombotic ADRs associated with bevacizumab therapy is low. Gastrointestinal disorders (e.g., gastrointestinal hemorrhage, nausea) were rare.[30]

Overall, it was concluded that there is no sufficient evidence to prove that there is a difference in rates of adverse events between these anti-VEGF drugs.

Ocular ADRs

Although intravitreal anti-VEGF drugs have improved the final visual outcome of AMD, the relatively high frequency of injections required, increases the risk of endophthalmitis,

rhegmatogenous retinal detachment, retinal tear, uveitis and vitreous hemorrhage [Table 1]. However, ocular complications in anti-VEGF treatment are still rather rare and are actually lower than those reported after other types of intravitreal injections.[31] Some studies have reported cases of pseudo-endophthalmitis with culture-negative severe intraocular inflammation that is believed to be a reaction to a non-infectious substance.[32]

The risk of ocular complications was also significantly higher for people undergoing anti-VEGF injection when compared with patients with neovascular AMD who did not receive anti-VEGF treatment.

CONCLUSION

Although the risk for the development of systemic adverse events may be higher with bevacizumab than with ranibizumab or aflibercept from a theoretical viewpoint, clinical studies demonstrate that there is no difference between the drugs in terms of the risk of systemic adverse events among patients who receive intravitreal injections.[20,21]

Anti-VEGF therapy has changed the efficacy of treatment but not without drawbacks. Although severe ADRs were rarely observer/reported, every intravitreal injection sets patients at risk of endophthalmitis, intraocular inflammation, vitreous hemorrhage, retinal tear, retinal detachment and iatrogenic cataract. Recent studies have also suggested a sustained increase of intraocular pressure induced by repeated injections of anti-VEGF agents.[33]

There are three FDA-approved therapies for wet AMD:

- Aflibercept at the dose of 2 mg every 4 weeks for 3 months, followed by 2 mg every 8 weeks;[34]
- Ranibizumab is currently dosed at 0.5 mg monthly;[35]
- Bevacizumab, the most-used therapy for wet AMD because of its relatively low cost and comparable efficacy to ranibizumab, dosed at 1.25-2.5 mg/monthly.[36]

All three therapies are considered to have equal efficacy across the board based on studies and clinical data that have been evaluated,[37] but they differ from an economic point of view. In fact, a single treatment of ranibizumab costs USD 1,950. If a patient is on ranibizumab for 1 year, the cost of therapy is USD 23,400 (12 doses).[38] A single dose of aflibercept costs approximately USD 1,850 and the yearly cost averages USD 14,800 (8 doses). Bevacizumab is the cheapest treatment costing USD 50 per dose/treatment. A yearly treatment of one bevacizumab dose per month would cost about USD 600.[18]

Finally, the necessity of a smaller number of administrations of aflibercept may contribute to fewer side effects.

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