Bevacizumab: Off-label use in ophthalmology

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Bevacizumab is a full-length, humanized monoclonal antibody directed against all the biologically active isoforms of vascular endothelial growth factor (VEGF-A). The antibody was initially designed and studied as an anti-angiogenic strategy to treat a variety of solid tumors. After approval by the US Food and Drug Administration, bevacizumab gained access into ophthalmology to treat various types of neovascular diseases. Since the first report in 2005 more than 100 publications share the experience with bevacizumab in ophthalmology. Two authors independently assessed the research results from Pubmed to April 2007. The reference list is a selection of key publications related to the issue. Currently, there is no well-designed randomized controlled trial yet to establish the efficacy and safety of intraocular bevacizumab for any ocular disease in spite of its assumed characteristics representing the most cost-effective VEGF inhibitor.

Key words: Bevacizumab, intravitreal injection, neovascular ocular disease

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More than 35 years ago a man had a dream. Judah Folkman hypothesized that cancer may be treated by abolishing the nutrients and oxygen-providing blood vessels. The term anti-angiogenic therapy was born and bevacizumab (AVASTIN®, Genentech, Inc.) became the first therapy approved by the US Food and Drug Administration (FDA) designed to inhibit angiogenesis in tumors.

Angiogenesis is a complex multifaceted process influenced by several factors. Inducers and inhibitors balance the angiogenic switch which finally turns the process on or off. Though the number of known factors is steadily increasing, vascular endothelial growth factor (VEGF)-A seems to play a very pivotal role and is the primary target of recent anti-angiogenic strategies. An extensive number of experimental studies have established that VEGF plays a central role in the development of several ocular pathologies characterized by neovascularization and increased vascular permeability.

The logical consequence was a therapeutic regimen specifically targeting VEGF. Though other VEGF inhibitors are being developed or already licensed to treat ocular diseases, the anticancer drug, bevacizumab, found its way into ophthalmology and clinical practice all around the world.

Description of Bevacizumab

Bevacizumab is a full-length, humanized monoclonal antibody directed against all the biologically active isoforms of VEGF-A.[1] It is a recombinant IgG1 antibody with a molecular weight of about 149kD that is produced in a Chinese Hamster Ovary mammalian cell expression system in a nutrient medium containing the antibiotic gentamicin.[2] AVASTIN® (bevacizumab) is a clear to slightly opalescent, colorless to pale brown, sterile solution with pH 6.2. It was originally designed for intravenous (IV) infusion and is supplied in 100 mg and 400 mg preservative-free, single-use vials to deliver 4 mL or 16 mL of AVASTIN® (25 mg/mL). The product is formulated in alpha-trehalose dihydrate, sodium phosphate (monobasic, monohydrate), sodium phosphate (dibasic, anhydrous), polysorbate and water for injection.[2]

Mechanism of Action

Bevacizumab binds to the receptor-binding domain of all VEGF-A isoforms. Consequently, it prevents the interaction between VEGF-A and its receptors (Flt-1 and KDR) on the surface of endothelial cells which starts the intracellular signaling pathway leading to endothelial cell proliferation and new blood vessel formation.[1]

Clinical Application

Bevacizumab was primarily developed for the treatment of a variety of solid tumors.[3-5] In 2004, the FDA approved bevacizumab for the treatment of metastatic colorectal cancer in combination with standard chemotherapy.[4] The recommended dose of bevacizumab for colorectal cancer is 5 mg/kg given once daily every two weeks as an IV infusion.

Though not formally studied or approved for any intraocular disease, Rosenfeld's pioneering work[6,7] and the unavailability of a related ocular drug, ranibizumab, led to rapid and wide use of bevacizumab all over the world. After initial studies were done with IV injections, this route of administration was not generally accepted due to higher costs and due to a more conceivable risk of systemic side-effects.[8,9]

Efficacy of intravitreal bevacizumab in experimental and clinical studies

Preclinical data suggested that full-length antibodies would not penetrate the retina and be useful for subretinal pathologies such as choroidal neovascularization (CNV) in age-related

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macular degeneration (AMD).[10] The publication of clinical cases demonstrating the impressive resolution of macular fluid in neovascular AMD and central retinal vein occlusion (CRVO), however, raised doubts about the previous assumption.[6,7] Meanwhile, several studies demonstrated that bevacizumab is able to penetrate the retina after intravitreal injection.[11,12] More published case series of bevacizumab treatment for different neovascular ocular pathologies indicated a positive anatomical and functional effect.[13-17] First clinical results indicate a promising efficacy profile for neovascular AMD.[18,19] Though only small numbers have been investigated yet, there seems to be no difference between distinct types of CNV.[13] Promising results have been shown also for myopic CNV[20-22], CNV secondary to angioid streak[23,24] and juxtafoveal telangiectasia.[25,26] Currently, only short-term results on efficacy and safety are available.[27,28] Further aspects, such as pretreatment and/or combination with other therapies and different treatment intervals are making our understanding more complicated.[29-33]

Safety of intravitreal bevacizumab in experimental and clinical studies

Bevacizumab was not intended and therefore not formally studied or approved for intraocular use. The need for a potent drug led to its off-label use, but also to an impressive research effort to exclude local and systemic side-effects. In clinical practice, local side-effects did not seem to differ compared to other intraocular drugs.[34-36] Rarely, intraocular inflammation was observed.[37] A small series of patients did not reveal an increase in flare.[38,39] In electrophysiological studies no negative side-effects were seen on the retina. In contrast, the results showed a recovery effect on photoreceptors even at the site of the CNV.[40] Most of the *in vitro*, *ex vivo* and *in vivo* experiments excluded short-term negative effects on ocular cells and histology.[41-45] A recent paper, however, discloses mitochondrial disruption in the inner segment of photoreceptors and apoptosis after high doses of intravitreal bevacizumab in the rabbit eye.[46] The electrophysiological investigation and light microscopy, in contrast appeared unaltered. This suggests that potential side-effects on the cellular level cannot be detected with the present diagnostic tools in clinical practice.

A potential side-effect that strikes the clinician is the apparently increased incidence of retinal pigment epithelium (RPE) tears (5 to 10%), most often after large and hemorrhagic pigment epithelium detachment.[47,48] It has been postulated that the fast resolution of fluid and/or contraction of the fibrous tissue may cause the rip.

Although the full-length antibody bevacizumab is larger in size and has therefore extended half-life (5.5 days) in the eye, it still leaves the ocular compartment and gets access to the systemic circulation.[49] This explains the biological effects observed in the contralateral eye after intravitreal application.[13] The risk of hypertension and thromboembolic events has been described for systemic application in cancer patients.[4] The risk of systemic side-effects in multiple applications remains unclear. Some patients displayed significantly elevated blood pressure levels after intravitreal injections[50,51] but there is no controlled collection of adverse events yet. Patients must be, therefore, meticulously informed about all potential risks of intraocular injection in general and about bevacizumab therapy in particular.[52,53]

Conclusions

Though data from controlled trials are lacking, bevacizumab appears to be safe and effective in the short term. The evidence for efficacy and safety is increasing, but the quality of the studies is still low compared to controlled multicenter trials for drug approval. The physician has to be aware of their responsibility towards the patient. This not only includes the risks associated with the off-label use, but also the cost problem and the availability of approved drugs for different ocular pathologies.

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