Bevacizumab

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Bevacizumab (Avastin; manufactured in the United States by Genentech/Roche) is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits vascular endothelial growth factor (VEGF), reducing the growth of new blood vessels. VEGF is a biochemical signal protein that promotes angiogenesis throughout the body and in the eye.

Bevacizumab	
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Contents

Background

VEGF is a member of the platelet-derived growth factor (PDGF) family. The VEGF gene family is constituted of VEGF-A, VEGF-B, VEGF-C, VEGF-D and placenta growth factor (PlGF), located on chromosome 6p12.[1] The binding of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel growth and thus plays a key role in angiogenesis. Physiology of new vessel growth and development are an extremely complex and coordinated process that requires a cascade of receptor activation. In this process, VEGF represents an initial and critical rate-limiting step in physiological angiogenesis.[2] [3] [4] The critical role of VEGF in angiogenesis has been highlighted by the loss of a single VEGF allele resulting in defective vascularization.[5]

There are nine VEGF-A isoforms: $VEGF_{121}$, $VEGF_{145}$, $VEGF_{148}$, $VEGF_{162}$, $VEGF_{165}$, $VEGF_{165b}$, $VEGF_{183}$, $VEGF_{189}$ and $VEGF_{206}$.[6] The most abundant isoform found in the eye is $VEGF_{165}$.[7] [8] $VEGF_{165}$ is a secreted heparin-binding homodimeric 45-kDa glycoprotein with a significant fraction bound to the cell surface.[9] VEGF activates endothelial cells by binding VEGFR-1 (Flt-1) and VEGFR-2 (KDR) endothelial cell receptors, which in turn activates intracellular signal transduction cascades.[9] VEGFR-2 is thought to be principally responsible for VEGF signaling in angiogenesis.[9]

VEGF-A levels have been found greatly elevated in the vitreous of patients with choroidal neovascularization (CNV) in age-related macular degeneration (AMD), 10 among other eye diseases. Choroidal neovascularization may be instigated by several events, such as accumulation of lipid metabolic byproducts, oxidative stress, reduction in choriocapillaris blood flow, and alterations in Bruch's membrane.[10] [11] [12] Hypoxia has been shown to be a major inducer of VEGF gene transcription. As a response to metabolic distress, the retinal pigment epithelium (RPE) and the retina produce various factors, particularly VEGF, which induce CNV proliferation. VEGF has been shown to be a chemo-attractant for endothelial cell precursors, causing CNV in mouse models.[13] VEGF also prevents endothelial cell apoptosis.[14] Additionally, VEGF promotes metalloproteinases production by endothelial cells, causing tissue degradation that facilitates invasion by new vessels.[15] [16] VEGF is a powerful agonist of vascular permeability, which causes vascular leakage and macular edema.[17] VEGF is thought to cause increased vascular permeability by formation of fenestrations in microvascular endothelium.[18][18][19] Furthermore, VEGF was shown to up-regulate leukocyte adhesion to ICAM-1 in mice, thereby promoting vascular permeability and capillary non-perfusion.[20] On this basis, inhibition of VEGF activity is key to treatment of macular edema and prevention of progressive capillary non-perfusion, especially in diabetic retinopathy and retinal vein occlusions.

Mechanism of Action (proposed)

Bevacizumab binds to soluble VEGF and inhibits the binding of VEGF molecules to its receptors on the surface of endothelial cells. Bevacizumab is a nonspecific VEGF inhibitor with two binding sites per molecule.[5][21][21] Bevacizumab prevents all VEGF-A isoforms from binding to endothelial cell receptors.[5][21][22] [23] Reduction in activity of VEGF inhibits angiogenesis and vascular permeability.

Indications and Uses

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Bevacizumab use in ophthalmology is off-label, meaning it is not FDA approved for ocular use. In USA more than 20% of the used drugs are off-label. It is most commonly used to treat CNV (in AMD and other diseases), diabetic macular edema (DME), and macular edema due to retinal vein occlusions. Interest in bevacizumab for ocular use began due to the molecular similarity it shares with ranibizumab (Lucentis; Genentech), which is FDA approved for AMD, DME, and macular edema due to retinal vein occlusions. The debate over the use of bevacizumab versus ranibizumab will be discussed in the Considerations section.

Off-label use does carry risk for both the practitioner and the patient. Off-label use may raise the risk of lawsuit should a patient have a negative outcome from its use. From the patient's perspective, there may be a theoretical lack of safety data for off-label use as compared to FDA approved drugs. As part of the FDA approval process, sponsors submit detailed information about safety and efficacy as shown in large randomized multi-center clinical trials done for specific indications. The approval process involves the FDA carefully examining extensive databases of studies in toxicologic evaluations, animal studies and clinical trials.[24] Off-label drugs do not receive this structured rigorous evaluation process on an official basis by the FDA in particular disease states.[25]

However, the off-label use of medication is extremely prevalent and is a vital part of prescribing practices across medicine. Many patients benefit when they receive medications under circumstances not approved by the FDA. Typically, the makers of generic drugs have little financial incentive to attempt the costly process of FDA approval for a new indication, despite wide off-label use. In fact, off-label uses are often the standard of care for some health conditions. In many areas of oncology, pediatrics, geriatrics, and obstetrics, patients could not obtain treatment without off-label prescribing. When medical and scientific evidence validate off-label uses (both safety and efficacy) and use is accepted by the medical community, physicians may consider use of these medications in the best interest of their patients.[25] Both practitioners and patients should weigh the risks and benefits of using medication in an off-label manner and patients should always be informed of their treatment options.[26][27] Bevacizumab is one of many such drugs with a long history of safety and efficacy, albeit without FDA approval for ocular use. Based on its affordability, the world health organization has put bevacizumab and not ranibizumab in WHO model list of essential drugs. http://www.who.int/medicines/publications/essentialmedicines/EML2015_8-May-15.pdf

Colorectal Cancer
Bevacizumab is FDA approved in metastatic colorectal cancer, with intravenous 5-fluorouracil–based chemotherapy as first- or second-line treatment. It also is used with fluoropyrimidine- irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab-containing regimen.

Lung Cancer
Bevacizumab is FDA approved for use in non-squamous non-small cell lung cancer, in conjunction with carboplatin and paclitaxel for first line treatment of unresectable, locally advanced, recurrent or metastatic disease.

Brain Cancer
Bevacizumab has a FDA indication for glioblastoma, as a single agent for adult patients with progressive disease following prior therapy.

However, the indication of metastatic breast carcinoma for intravenous bevacizumab was removed by the FDA as it did not improve the survival or the quality of life when compared to the possible life-threatening complications if the intravenous drug.

Administration and Dosing
In ophthalmology, bevacizumab is typically given by transconjunctival intravitreal injections into the posterior segment, although it has been used in the form of topical drops or sub-conjunctival injection. Intravitreal injections for retinal pathologies are typically administered at 4-6 week intervals, although this varies widely based on disease and response. The typical dose is 1.25mg in 0.05ml in adults,and half that dose in babies. While other doses (2.5mg) have been evaluated in large trials, no significant benefit has been shown over the 1.25mg standard dose,[28] although some advocate "super-doses" in certain situations.[29]

Preparation
Bevacizumab is a clear to slightly opalescent, colorless to pale brown, sterile solution for intravenous infusion. Its pH is 6.2. It is supplied in 100 mg and 400 mg preservative-free, single-use vials with a volume of 4 mL or 16 mL of bevacizumab (25 mg/mL).[22]

Bevacizumab is only commercially available in the 4ml and 16ml intravenous formulation. Intravitreal aliquots are typically compounded from these large vials. The American Academy of Ophthalmology risk management guidelines recommend preparing individual syringes. Typically compounding pharmacies provide this service.

Several studies have shown no bacterial growth and minimal degradation at three months of refrigerated bevazicumab compounded into syringes.[30][31][32] Although rare, there have been reported cases of bacterial endophthalmitis associated with contaminated batches of compounded bevacizumab and this continues to be an issue of concern.[33] [34] [35]

Another issue is counterfeit or spurious batches of Avastin which have been noted to cause cluster endopthlmitis.

Efficacy in Ophthalmic Pathology
Bevacizumab is considered efficacious for treatment of CNV and macular edema by the ophthalmologic community. As this drug has not been FDA approved for ophthalmic indications, classic clinical trials do not uniformly exist, however convincing data has been published for the most commonly treated pathologies.

Age-related Macular Degeneration (neovascular with CNV) – The sham injection/untreated arm of the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA)[36] trial showed vision loss of 14.9 letters from baseline over 24 months, which is often quoted as the natural history of neovascular AMD. While the Comparison of Age-related Macular Degeneration Treatments Trials (CATT)[37] did not have an untreated arm, it was perhaps the most well-structured clinical trial involving bevacizumab and showed a 7.8 letter gain from baseline with monthly adminisration. The Inhibit VEGF in the Age-Related Choroidal Neovascularization trial (IVAN)[38] echoed this positive result.

Diabetic Macular Edema (DME) – The Pan-American Collaborative Retina Study Group (PACORES)[39] trial compared monthly intravitreal bevacizumab with macular focal-grid laser photocoagulation (standard of care at that time) and showed an anverage of 11.86 letters gained with bevacizumab and 3.66 letters gained with focal grid laser over 24-months.

Macual Edema due to Retinal Vein Occlusion - The untreated macular edema arm (Group M) of the Central Vein Occlusion Study (CVOS)[40] trial lost approximately 5 letters from baseline. The PACORES trial for central vein occlusion,[41] which did not have a untreated arm but had similar inclusion criteria, showed 19 letters of improvement from baseline over 12 months with monntly/as-needed intravitreal bevacizumab.

Various other papers have been published showing the efficacy of intravitreal bevacizumab in control of myopic CNV, proliferative diseases, and various other eye diseases.

Adverse Affects and Safety
General
Bevacizumab has 3 black box warnings; gastrointestinal perforation, surgery and wound healing complications, and severe or fatal hemorrhage, hemoptysis, gastrointestinal bleeding, CNS hemorrhage, and vaginal bleeding. It is unknown whether intravitreal bevacizumab is associated with the same black box safety issues however these types of complications are not included in the known complications following intravitreal used of bevacizumab. The risk of these severe adverse effects are thought to be very low as the intravitreal dose is 300–500 times less than the intravenous dose and is administered less frequently.[5][21] However, we do know that systemic/serum levels of VEGF are reduced with intravitreal administration (IVAN), but the significance of this is not yet clear. Furthermore, some studies suggest a fellow eye effect.[42]

Ophthalmic

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Bevacizumab has been used in the eye without significant intraocular toxicity.[43] Transient elevation of intraocular pressure (IOP) after intravitreal injection is common and typically normalizes rapidly without intervention.[44] However, some believe this may cause long term increases in IOP, leading to glaucoma.[45] It is generally thought that these potential manageable complications are outweighed by the benefit of these injections.

Acute intraocular inflammation (or 'sterile endophthalmitis') is a more serious ocular adverse event, but rarely occurs. At 24-months, the CATT trial reported only two cases of 'pseudo-endophthalmitis,' one case in the bevacizumab group and one case in the ranibizumab group.

Bacterial endophthalmitis is rare but is the most serious and vision threatening complication of intravitreal bevacizumab and is associated with the procedure rather than the medication.[46] At 24-months, the CATT trial reported 11 total cases of bacterial endophthalmitis, yielding an infection rate of 0.9%, with 7 cases in the bevacizumab groups and 4 cases in the ranibizumab groups (no statistical difference). However much larger retrospective reviews show the rate of infection to be between 0.022% and 0.16%.[47] One such large review, looked at over 26,000 injections of both bevacizumab and ranibizumab and showed an over all infection rate of 0.02%. Interestingly, both the bevacizumab and ranibizumab groups had 2 cases of endophthalmitis for a 0.02% infection rate for each group.[47]

Meta-analysis of clinical trials show serious ocular adverse effects to be less than 1.2% for bevacizumab.[48]

Systemic

The occurrence of serious systemic adverse effects are rare with intravitreal bevacizumab. The exact systemic risk attributable to intravitreal bevacizumab is unknown. Firstly, due to the fact that large scale randomized placebo-controlled studies have not been conducted on this drug, it is not possible to obtain pure safety data to answer this question. Secondly, even the best studies that collected safety data on bevacizumab did so in non-uniform ways and published the data in non-comparable generalities and vary widely. For instance, the IVAN trial showed serious adverse effects (SAE) to be 12.5% in the bevacizumab group while the CATT trial showed SAE rate of 40%. The Bevacizumab or Laser Therapy (BOLT)[49] trial, which compared bevacizumab versus macular laser, showed approximately 5% SAE in the bevacizumab group and 10% in the laser group. Furthermore, in the IVAN study, the data trended toward bevacizumab being the safer therapy, while the CATT trial trended toward the opposite.

Interestingly in the IVAN study, there was a clear trend toward fewer systemic SAEs with continuous monthly treatment versus as-needed treatment, although the significance of this is unknown.

Considerations and Comparison

There is a large debate over the use of bevacizumab versus ranibizumab for ocular pathology. Some key areas of comparison are listed here.

Ranibizumab is a Fab of an antibody and is about one-third the size of bevacizumab, which is a full length antibody (48 vs 149 kilodaltons). Theoretically, a smaller molecule size may allow better retinal penetration after intravitreal injection. Studies in rabbits and monkeys demonstrated that smaller antibody moieties such as Fabs have better tissue penetration than full-length antibodies.[50] However, in the CATT and IVAN trials, no difference in treatment effect was shown between these two drugs in AMD. Recently, the SCORE2 study showed "no difference" in the mean visual acuity between bevacizumab and aflibercept (non-inferiority trial at 6 months (primary outcome point).

Ranibizumab has a higher affinity to binding VEGF than does bevacizumab, however bevacizumab has two binding sites per molecule, while ranibizumab only has one. It has been shown that at clinical doses, bevacizumab and ranibizumab are equally potent at binding VEGF.[5][21][22][23][51][52]

The incidence of serious systemic adverse effects are rare with both intravitreal bevacizumab and ranibizumab.[46] The large head-to-head clinical trials show no statistical difference in serious artheriorthrombotic events or all-cause-death between bevacizumab and ranibizumab[38][53] In the 24-month CATT and IVAN reports, there was a trend toward ranibizumab having less systemic adverse effects, although not statistically significant. However, in 24-month CATT trial, the category of "One or more serious adverse events" showed a statistically significant outcome of ranibizumab having less such events (31.7% versus 39.9%), representing the only statistically significant difference in safety outcome in these trials. A 'serious systemic event' was defined as death from any cause, arteriothrombotic event, nonfatal myocardial infarction, nonfatal stroke, death from vascular causes, venous thrombotic event, transient ischemic attack and hypertension. [51][54][55]

Bevacizumab has a longer systemic half-life than ranibizumab (20h vs. 4h). This means that bevacizumab may persist longer in the eye than ranibizumab. However, the CATT and IVAN trials showed no difference in treatment effect between these two drugs in AMD. However, due to the longer half-life, bevacizumab also persists longer systemically in the serum,[56][57] which may be an explanation for the increased systemic adverse effects seen in the CATT trial in the bevacizumab groups, if indeed this was a real effect.

An other explanation for possible differences in systemic adverse effects may be rates of systemic absorption. Animal and human studies have shown that systemic absorption does occur.[56][58] The IVAN trial, which examined VEGF levels in serum showed a reduction from 173 to 151 pg/ml (15% reduction) in the ranibizumab group and a reduction from 203 to 83 pg/ml (60% reduction) in the bevacizumab group. This might be explained by the longer half-life of bevacizumab.

Large well-structured clinical trials, such as CATT and IVAN, indicate that both medications are equally effective in the treatment of CNV in AMD. Furthermore, both drugs are effective in DME and vein occlusions and both are commonly used by clinicians although head to head trials have not yet been published. There is little debate that both drugs are effective within the ophthalmic community. The debate still remains unsettled as to the true difference in systemic adverse effects between the two drugs, with the focus being 1) the added risk from the necessity to compound bevacizumab and 2) the inherent systemic risk of each compound.

Bevacizumab was available and used intravenously for cancer treatment before the approval of ranibizumab. Off-label use of the intravenous formulation of bevacizumab was compounded for the intravitreal route in the treatment of ocular disorders around mid-2005.[59][60] Ranibizumab was not approved until June 2006.

Complicating matters in this debate is the fact that ranibizumab is more than 50 times more expensive than bevacizumab. The cost for one dose of intravitreal bevacizumab as reimbursed by Medicare is $64.62, while one dose of ranibizumab is reimbursed $1,986.29.[61]

The cost difference is a potential reason why the manufacturer of both the drugs, Roche are against the intraocular use of the cheaper drug Avastin. The financial benefit of the company may have prevented the company to apply for an FDA approval for intraocular use of Avastin which has been shown to be equally effective, safe and affordable than the much costlier alternative Lucentis.

Additionally, there is a significant net revenue differential between the two drugs due to the 6% mark-up allowed for in-office medication administration.

Overall, it is still unclear if either ranibizumab or bevacizumab offers a treatment or safety advantage to the patient.

Additional Resources

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