VEGF Inhibitors for AMD and Diabetic Macular Edema

Vascular endothelial growth factor (VEGF) is a principal mediator of neovascularization in wet age-related macular degeneration (AMD) and diabetic macular edema. It induces angiogenesis and increases vascular permeability and inflammation. VEGF inhibitors reduce leakage from blood vessels, prevent proliferation of new abnormal vessels, decrease swelling of the retina, and improve visual acuity in patients with neovascular (wet) AMD and diabetic macular edema. These drugs are given as periodic intravitreal injections with topical anesthesia.

Ranibizumab (Lucentis – Genentech) is a recombinant, humanized, monoclonal anti-VEGF antibody fragment. It has been approved by the FDA for treatment of wet AMD, diabetic macular edema, and macular edema following retinal vein occlusion.

Bevacizumab (Avastin – Genentech) is the full-length monoclonal antibody from which ranibizumab is derived. It has been approved by the FDA for intravenous treatment of various malignancies and has been used off-label as an intravitreal injection for treatment of wet AMD, diabetic macular edema, and macular edema following retinal vein occlusion. Divided into aliquots and repackaged by compounding pharmacies, it costs much less than ranibizumab, pegaptanib, or aflibercept, which are all available in ready-to-use formulations, but the repackaging process has introduced some safety risks. Ranibizumab and bevacizumab appear to have similar effects on visual acuity in patients with wet AMD.

Aflibercept (Eylea – Regeneron), a fusion protein, is FDA-approved for treatment of wet AMD, diabetic macular edema, and macular edema following retinal vein occlusion. In 2 controlled trials in patients with wet AMD, it appeared to be similar to ranibizumab in effectiveness. A large 1-year study sponsored by the NIH and conducted by the Diabetic Retinopathy Clinical Research Network randomized 660 adults with diabetic macular edema to intravitreal aflibercept 2 mg, bevacizumab 1.25 mg, or ranibizumab 0.3 mg every 4 weeks. In patients with mild initial visual acuity loss (visual acuity letter score 69-78), there were no significant differences in mean visual acuity at 1 year between the 3 groups. In patients with a visual acuity letter score <69, the mean improvement was significantly better with aflibercept (18.9 letters) than with ranibizumab (14.2) or bevacizumab (11.8).

Pegaptanib sodium (Macugen – Valeant), a selective VEGF inhibitor, is approved by the FDA only for treatment of wet AMD. It appears to be less effective than ranibizumab or bevacizumab.

Adverse Effects – The adverse effects of VEGF inhibitors have been largely related to the injection procedure rather than to the drug itself; they include conjunctival hemorrhage, acute intraocular pressure rise, traumatic cataract, uveitis, and retinal detachment, all occurring in <2% of patients.

Endophthalmitis – Intravitreal injection of VEGF inhibitors carries a risk of intraocular infection or endophthalmitis. The overall risk of endophthalmitis with intravitreal injections of VEGF inhibitors appears to be low, but repackaging of bevacizumab without proper aseptic technique has led to endophthalmitis and loss of vision in some patients.

One retrospective review of patients who received a total of 11,710 intravitreal injections of a VEGF inhibitor found that clinically suspected endophthalmitis occurred in 5 cases. In one trial in 1185 patients, endophthalmitis developed in 0.7% of patients treated with ranibizumab and in 1.2% of those treated with bevacizumab. A retrospective case-control study in 6154 VEGF-treated patients and an equal number of matched controls with neovascular AMD found that the incidence of endophthalmitis was 0.09% per injection, and the total incidence was 0.62% in patients...
Table 1. Intravitreal VEGF Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulations</th>
<th>Neovascular AMD Dosage</th>
<th>DME Dosage</th>
<th>Cost¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflibercept – Eylea</td>
<td>2 mg/0.05 mL single-use vial</td>
<td>2 mg q4 wks x 3 doses, then 2 mg q8 wks</td>
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<td>Pegaptanib⁵ – Macugen</td>
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<td>Ranibizumab – Lucentis</td>
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<td>25 mg/mL; 4, 16 mL vials</td>
<td>1.25 mg q4 wks</td>
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AMD = Age-related macular degeneration; DME = Diabetic macular edema
1. Medicare allowable charges for one intravitreal injection for treatment of DME.
2. Not FDA-approved for treatment of DME.
3. Approximate WAC for one intravitreal injection for treatment of AMD (administration cost not included). WAC = wholesaler acquisition cost, or manufacturer’s published price to wholesalers; WAC represents a published catalogue or list price and may not represent actual transactional prices. Source: AnalySource® Monthly. March 5, 2015. Reprinted with permission by First Databank, Inc. All rights reserved. ©2015. www.fdbhealth.com/policies/drug-pricing-policy.
4. Not FDA-approved for treatment of AMD or DME.
5. Cost of a 4-mL single-use vial is $663.75. A compounding pharmacy can divide the vial into small aliquots. Actual retail prices may vary.


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