A
ger-related macular degeneration (AMD) is the leading cause of irreversible blindness in adults older than age 50 years. In the United States, approximately 11 million people have AMD. AMD is characterized by 2 distinct types—wet (neovascular or exudative) or dry (atrophic) condition, each with specific characteristics.

In patients with wet AMD, abnormal blood vessel growth (ie, choroidal neovascularization) occurs under the retina and macula. These new blood vessels can bleed and leak fluid, causing the macula to bulge or to lift from its usually flat position. This leads to the central vision being distorted or destroyed, causing loss of vision and potential blindness. Although only a minority of patients with AMD have wet AMD, these patients are significantly more likely to have severe vision loss from the disease.

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The treatment for wet AMD has traditionally included laser photocoagulation and photodynamic therapy with verteporfin for injection (Visudyne), which helps to direct the laser to the affected area. However, because laser treatment of wet AMD has clinical limitations, researchers have developed novel agents that can maintain vision for longer periods without the need for repeated exposure to laser therapy.

Today, the treatments for wet AMD include drugs that inhibit the vascular endothelial growth factor (VEGF), a protein that stimulates abnormal blood vessel growth. VEGF inhibitors that are indicated for the treatment of wet AMD include ranibizumab (Lucentis) and aflibercept (Eylea). Bevacizumab (Avastin), another VEGF used for AMD, is not indicated for the treatment of wet AMD. These agents are periodically injected into the eye (ie, intravitreal) to reduce VEGF levels.

FDA Approves New Dosing Schedule for Eylea

On August 17, 2018, the US Food and Drug Administration (FDA) approved a new, longer dosing schedule with 12-week intervals for aflibercept injection (Eylea; Regeneron) for the treatment of patients with wet AMD. Aflibercept, a VEGF inhibitor that is injected intravitreally, was initially approved in 2011 for dosing intervals of every 4 weeks, or every 8 weeks after the initial 3 monthly doses for patients with wet AMD.

Based on this approval, the updated prescribing information for aflibercept now states that “Although not as effective as the recommended every 8 week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. Patients should be assessed regularly.”

In addition, aflibercept was previously approved by the FDA for the treatment of macular edema after retinal vein occlusion, diabetic macular edema, or diabetic retinopathy in patients with diabetic macular edema.

Mechanism of Action

Aflibercept is a VEGF inhibitor that acts as a soluble decoy receptor to bind VEGF-A and placental growth factors. VEGF-A activates the VEGFR-1 and VEGFR-2 pathways, which are tyrosine kinase receptors present on the surface of endothelial cells. This activation results in the neovascularization and vascular permeability of endothelial cells.

Dosing and Administration

In patients with wet AMD, the recommended aflibercept dose is 2 mg (0.05 mL), administered by intravitreal injection every 4 weeks (every 28 days) for the first 12 weeks, then continuing with 2 mg (0.05 mL) via intravitreal injection once every 8 weeks.

Intravitreal aflibercept may be dosed as often as 2 mg every 4 weeks (approximately every 25 days), but the efficacy did not improve in most patients when this more frequent dosing (ie, every 4 weeks instead of every 8 weeks) was implemented.

Some patients may need a dosing schedule of every 4 weeks after the first 12 weeks. Although not as effective
Pivotal Clinical Trials: VIEW1 and VIEW2

The safety and efficacy of aflibercept were assessed in 2 randomized, multicenter, double-masked, active-controlled VIEW1 and VIEW2 studies in patients with wet AMD. A total of 2412 patients received treatment and were evaluated for efficacy in the 2 studies. In each study, patients with wet AMD were randomly assigned to 1 of 4 dosing regimens: (1) aflibercept 2 mg administered every 8 weeks after 3 initial monthly doses; (2) aflibercept 2 mg administered every 4 weeks; (3) aflibercept 0.5 mg administered every 8 weeks; and (4) ranibizumab 0.5 mg administered every 4 weeks.

Although the VIEW1 and VIEW2 studies were each 96 weeks in duration, after 52 weeks the patients no longer followed a fixed dosing schedule. Between week 52 and week 96, the patients continued to receive aflibercept at the dosage strength to which they were initially randomized on a modified 12-week dosing schedule. The doses were given at least every 12 weeks, with additional doses as needed. There was no active control arm in either VIEW1 or VIEW2 from week 52 to week 96.

The primary efficacy end point in both studies was the proportion of patients who maintained vision, defined as losing fewer than 15 letters of visual acuity after 52 weeks compared with baseline. After 52 weeks, the group that received aflibercept 2 mg every 8 weeks after 3 initial monthly doses and the group that received 2 mg every 4 weeks were clinically equivalent to the group that received ranibizumab. Efficacy data from the VIEW1 and VIEW2 studies are shown in the Table.

Table: Efficacy of Afibercept for Wet AMD in the VIEW1 and VIEW2 Studies, at Week 52

<table>
<thead>
<tr>
<th>Efficacy parameter</th>
<th>VIEW1</th>
<th>VIEW2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aflibercept 2 mg every 8 wks&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Aflibercept 2 mg every 4 wks</td>
</tr>
<tr>
<td>Patients maintaining visual acuity (&lt;15 letters of BCVA loss), %</td>
<td>94</td>
<td>95</td>
</tr>
<tr>
<td>Difference, aflibercept group minus the ranibizumab group, %</td>
<td>0.6 (95.1% CI, –3.2 to 4.4)</td>
<td>1.3 (95.1% CI, –2.4 to 5.0)</td>
</tr>
<tr>
<td>Difference&lt;sup&gt;b&lt;/sup&gt; in LS mean of vision from baseline, N (%)</td>
<td>92 (31)</td>
<td>114 (36)</td>
</tr>
<tr>
<td>Patients who gained at least 15 letters of vision from baseline, N (%)</td>
<td>96 (31)</td>
<td>91 (29)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Aflibercept group minus the ranibizumab group.
<sup>b</sup>LS mean, least squares mean.

As the recommended dosing regimen of every 8 weeks, patients may receive 1 dose of aflibercept every 12 weeks after 1 year of effective therapy.

Adverse Events

The safety population includes 2711 patients who received intravitreal aflibercept in phase 3 clinical trials. Among these patients, 2110 received the recommended 2-mg dose of aflibercept.

Serious adverse reactions related to the injection procedure, including endophthalmitis and retinal detachment, occurred in less than 0.1% of patients who received injections.

The most common (≥5%) adverse reactions in patients receiving aflibercept intravitreally were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and increased intraocular pressure.

Contraindications

Intravitreal aflibercept is contraindicated in patients with ocular or periocular infections, in patients with active intraocular inflammation, and in patients with known hypersensitivity to aflibercept or to any of its excipients.

Use in Specific Populations

No adequate data are available regarding fetal development risk associated with aflibercept use in women who are pregnant, the presence of aflibercept in human milk, the effects on breastfed infants, or the effects on milk production.

Women of reproductive potential should use effective contraception during treatment with aflibercept and for 3 months after the final dose.
The safety and effectiveness of aflibercept have not been established in children.¹

There were no differences in safety or efficacy between patients aged ≥65 years and younger patients who received aflibercept intravitreally in clinical studies.²

**Warnings and Precautions**

The prescribing information for intravitreal aflibercept includes warnings regarding endophthalmitis and retinal detachments, increase in intraocular pressure, and thromboembolic events (ie, nonfatal stroke, nonfatal myocardial infarction, or vascular death, including death of unknown cause). Patients using aflibercept should be monitored for these adverse events and managed appropriately.³

**Conclusion**

Wet AMD is the major cause of blindness in older adults. The expanded FDA indication for intravitreal aflibercept, a VEGF inhibitor, now allows dosing at longer, 12-week intervals after 1 year of effective treatment with this medication. This new option offers enhanced convenience and flexibility in scheduling for patients with wet AMD and their physicians and may improve outcomes for patients. ■

**References**

7. Eylea (aflibercept) injection, for intravitreal injection [prescribing information]. Tarrytown, NY: Regeneron Pharmaceuticals; August 2018.