Pegaptanib sodium for ocular vascular disease

Dhananjay Shukla, MS; Perumalsamy Namperumalsamy, MS; Mauro Goldbaum, MD; Emmett T Cunningham Jr, MD, PhD, MPH

Pegaptanib sodium (Macugen™) is a selective RNA aptamer that inhibits vascular endothelial growth factor (VEGF)165, the VEGF isoform primarily responsible for pathologic ocular neovascularization and vascular permeability, while sparing the physiological isoform VEGF121. After more than 10 years in development and preclinical study, pegaptanib was shown in clinical trials to be effective in treating choroidal neovascularization associated with age-related macular degeneration. Its excellent ocular and systemic safety profile has also been confirmed in patients receiving up to three years of therapy. Early, well-controlled studies further suggest that pegaptanib may provide therapeutic benefit for patients with diabetic macular edema, proliferative diabetic retinopathy and retinal vein occlusion. Notably, pegaptanib was the first available aptamer approved for therapeutic use in humans and the first VEGF inhibitor available for the treatment of ocular vascular diseases.

Key words: Age-related macular degeneration, aptamer, diabetic macular edema, pegaptanib, vascular endothelial growth factor


Studies of the pathophysiology of neovascular diseases of the eye, such as age-related macular degeneration (AMD) and diabetic retinopathy (DR), have demonstrated a central role for vascular endothelial growth factor (VEGF; also known as VEGF-A) in the pathogenesis of these disorders. VEGF acts as a master regulator and promoter of angiogenesis1 and is also the most potent known promoter of vascular permeability.2 Ocular VEGF concentrations were found to be elevated in the eyes of patients suffering from neovascularizing conditions and preclinical studies showed that VEGF was both necessary and sufficient for the development of ocular neovascularization.3

These studies provided compelling evidence for the use of VEGF inhibitors in treating AMD patients. To date, two VEGF-targeting therapies have received regulatory approval for the treatment of neovascular AMD – pegaptanib sodium (Macugen™; OSI-Eyetech, Inc. and Pfizer, Inc.) approved in December 2004 and ranibizumab (Lucentis™; Genentech, Inc.) approved in June 2006. Pegaptanib is an RNA aptamer that inhibits the VEGF165 isoform while sparing VEGF121. In contrast, ranibizumab is a Fab antibody fragment that binds to and inhibits all VEGF isoforms.4 This review focuses entirely on pegaptanib (for more detailed reviews see Ng et al.3; Cunningham et al.5).

Development of Pegaptanib

Pegaptanib was developed in the 1990s using the SELEX (selective evolution of ligands by exponential enrichment) technique. The result was a 29-nucleotide aptamer, with a chemically modified RNA backbone that increases nuclease resistance and a 5’ terminus that includes a 40kD polyethylene glycol moiety for prolonged tissue residence [Fig. 1].3 Pegaptanib was shown to bind VEGF165 with high specificity (kD = 200 pM) and inhibited VEGF165-induced responses, including cell proliferation in vitro and vascular permeability in vivo, while not affecting responses to VEGF121. Pegaptanib proved to be stable in human plasma for more than 18h, while in monkeys pegaptanib administered into the vitreous was detectable in the vitreous for four weeks after a single dose.3

Preclinical Findings

In rodent models,VEGF164 (the rodent equivalent of human...
VEGF acts as a potent inflammatory cytokine, mediating both ischemia-induced neovascularization and diabetes-induced breakdown of the blood-retinal barrier (BRB). In these experiments, intravitreous pegaptanib was shown to significantly reduce pathological neovascularization, while leaving physiological vascularization unimpaired and was also able to reverse diabetes-induced BRB breakdown. Moreover, VEGF proved to be dispensable for mediating VEGF’s role in protecting retinal neurons from ischemia-induced apoptosis. These data suggested that intravitreous pegaptanib could provide a safe and effective treatment against both ocular neovascularization and diabetes-induced treated retinal vascular damage.

**Clinical Studies**

**Neovascular AMD**

Pivotal clinical trial data have demonstrated that pegaptanib is both effective and safe for the treatment of neovascular AMD. These data were derived from two randomized, double-masked studies known jointly as the V.I.S.I.O.N. (VEGF Inhibition Study in Ocular Neovascularization) trials. A total of 1186 subjects with any angiographic subtypes of neovascular AMD were included. Patients received intravitreous injections of 0.3 mg, 1 mg or 3 mg pegaptanib or sham injections every six weeks for 48 weeks. Subjects with predominantly classic lesions could also have received photodynamic therapy with verteporfin (PDT; Visudyne™, Novartis) at investigator discretion. After one year, the 0.3 mg dose conferred a significant clinical benefit compared to sham treatment as measured by proportions of patients losing <15 letters of visual acuity (VA); compared with 55% (164/296) of patients receiving sham injections, 70% (206/294) of patients receiving 0.3 mg of pegaptanib met this primary endpoint (P < 0.001). In contrast to PDT, clinical benefit was seen irrespective of angiographic AMD subtype, baseline vision or lesion size and led to the clinical approval of pegaptanib for the treatment of all angiographic subtypes of neovascular AMD. The 1 mg and 3 mg doses showed no additional benefit beyond the 0.3 mg dose. Treatment with 0.3 mg pegaptanib was also efficacious as determined by mean VA change, proportions of patients gaining vision and likelihood of severe vision loss. In an extension of the V.I.S.I.O.N. study, patients in the pegaptanib arms were rerandomized to continue or discontinue therapy for 48 more weeks. Compared to patients discontinuing pegaptanib or receiving usual care, those remaining on 0.3 mg pegaptanib received additional significant clinical benefit in the second year. Further subgroup analyses suggested that pegaptanib treatment was especially effective in those patients who were treated early in the course of their disease.

Pegaptanib showed an excellent safety profile. All dosages were safe, with most adverse events attributable to the injection procedure rather than to the study drug itself. In the first year, serious adverse events occurred with <1% of intravitreous injections and no new safety signals have been identified in patients receiving pegaptanib for two and three years.

The frequencies of serious ocular adverse events for all three years are presented in Table 1. In addition, no systemic safety signals have emerged over this period. These conclusions have also been confirmed in assessments of systemic parameters following intravitreous injection of 1 mg and 3 mg pegaptanib.

**Diabetic macular edema (DME)**

Safety and efficacy of pegaptanib were assessed in a randomized, sham-controlled, double-masked, Phase 2 trial enrolling 172 diabetic subjects with DME affecting the center of the fovea. Intravitreous injections were administered at baseline and every six weeks thereafter. At Week 36, 0.3 mg pegaptanib was significantly superior to sham injection, as measured by mean change in VA (+4.7 letters vs. -0.4 letters, P = 0.04), proportions of patient gaining ≥10 letters of VA (34% vs.10%; P = 0.003), change in mean central retinal thickness (68µm decrease vs. 4 µm increase, P = 0.02) and proportions of patients requiring subsequent photocoagulation treatment (25% vs. 48%, P = 0.04).

In addition, a retrospective subgroup analysis revealed that pegaptanib treatment led to the regression of baseline retinal neovascularization in eight of 13 patients with proliferative diabetic retinopathy (PDR) whereas no such regression occurred in three sham-treated eyes or in four untreated fellow eyes. Early results from a small, randomized, open-label study suggest that adding pegaptanib to panretinal photocoagulation conferred significant clinical benefit in patients with PDR.

**Macular edema secondary to central retinal vein occlusion (CRVO)**

VEGF has been implicated in the pathophysiology of CRVO. Accordingly, in a trial that enrolled subjects with CRVO of <6 months duration, 98 subjects were randomized (1:1:1) to receive intravitreous pegaptanib (0.3 mg or 1 mg) or sham injections every six weeks and panretinal photocoagulation if needed. At Week 30, treatment with 0.3 mg pegaptanib was superior in terms of mean change in VA, proportions of patients losing ≥15 letters from baseline, proportions with a final VA of ≥35 letters and reduction in center point and central subfield thickness.

**Investigational studies with pegaptanib**

Encouraging findings have been reported in small case series investigating the use of pegaptanib for the treatment of neovascular glaucoma, retinopathy of prematurity and familial exudative vitreoretinopathy. In addition, given its positive safety profile, now validated over three years in clinical trials and two and a half years of postmarketing experience, pegaptanib is being studied as a maintenance treatment for familial exudative vitreoretinopathy.

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**Table 1: Serious ocular adverse events, rates (% per injection)**

<table>
<thead>
<tr>
<th>Events</th>
<th>Year 1 (N=7545 injections)</th>
<th>Year 2 (N=4091 injections)</th>
<th>Year 3 (N=3227 injections)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endophthalmitis</td>
<td>0.16</td>
<td>0.10</td>
<td>0.06</td>
</tr>
<tr>
<td>Traumatic cataract</td>
<td>0.07</td>
<td>0.02</td>
<td>0</td>
</tr>
<tr>
<td>Retinal detachment*</td>
<td>0.08</td>
<td>0.17</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Eleven rhegmatogenous and three exudative*
anti-VEGF inhibitor following induction with nonselective anti-VEGF agents such as ranibizumab or bevacizumab, which bind all VEGF isoforms\(^2,25\) and appear to be associated with an increased, albeit small, risk of stroke.\(^26\)

**Conclusions**

Pegaptanib is both safe and clinically effective for the treatment of all angiographic subtypes of neovascular AMD. Early, well-controlled trials further suggest that pegaptanib may provide therapeutic benefit for patients with DME, PDR and RVO. The roles that pegaptanib will ultimately play as part of the ophthalmologist’s armamentarium remain to be established. The recent results with ranibizumab demonstrating the potential for significant vision gains in AMD\(^27,28\) have been impressive, but issues of safety remain to be definitively resolved.\(^26\) Combinatorial regimens may ultimately prove to be most effective in balancing safety with efficacy.\(^24\) Similarly, more established approaches, such as photodynamic therapy with verteporfin, may provide greater clinical benefit when combined with anti-VEGF therapy,\(^29\) so that there is likely to be considerable space for empiricism in determining the best approach for a given patient. Nonetheless, the overall trend is highly positive, with the anti-VEGF agents affording many more options than were available only a few years ago. Such successes highlight the importance of VEGF in the pathogenesis of ocular vascular disorders and support the use of anti-VEGF agents as foundation therapy in patients with these conditions.

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**References**


23. Hughes MS, Sang DN. Safety and efficacy of intravitreal


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