

Pegaptanib in the treatment of wet, age-related macular degeneration

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Abstract: Age-related macular degeneration (AMD) is a major cause of severe visual loss worldwide. Neovascular (wet) AMD accounts for 90% of the visual loss associated with the disorder and vascular endothelial growth factor (VEGF) has been shown to play a major role in neovascularization and vascular permeability, the major causes of visual loss in AMD, making it an ideal target for therapeutic intervention. To utilize this strategy, pegaptanib, an aptamer that specifically binds to and blocks VEGF₁₆₅, the VEGF isoform primarily responsible for abnormal vascular growth and permeability in AMD, was developed. Following encouraging preclinical trials, clinical trials showed that pegaptanib stabilized vision and reduced the risk of severe visual loss in the majority of patients with AMD, with some patients showing visual improvement. Pegaptanib has maintained a good safety profile with only occasional adverse effects. Even greater success was achieved when pegaptanib was used in combination with another therapeutic strategy, such as photodynamic therapy or bevacizumab, a pan isoform VEGF inhibitor. Further investigation of pegaptanib for the therapy of wet AMD, particularly in combination with other modes of therapy, should be encouraged.

Keywords: age-related macular degeneration, pegaptanib, vascular endothelial growth factor, choroidal neovascularization, macular edema

Introduction

Age-related macular degeneration (AMD) is the leading cause of irreversible, severe visual loss in people aged 55 and older in the developed world (Congdon et al 2004) and it is estimated that more than 500 000 people worldwide lose their sight annually from the disease (Eyetechnical Pharmaceuticals, Inc. 2005). The neovascular (wet) form of the disease accounts for only 10% of the total incidence of the disease, but is responsible for 90% of the severe visual loss associated with the disease (Ferris et al 1984). Within the next 5 years, it is expected to affect almost 1 million people in the USA, posing a severe health issue (Bressler et al 2003) and having a major impact on the quality of life for the elderly, due to difficulties in performing routine tasks (Dong et al 2004). Wet AMD is characterized by choroidal neovascularization (CNV) that penetrates Bruch's membrane and invades the subretinal space, often leading to exudation and hemorrhage (Green 1999; Pauleikhoff 2005). If left untreated, damage results to the photoreceptors leading to loss of central vision and eventually the vessels are largely replaced by a fibrovascular scar (Green 1999). The visual prognosis is variable, based on lesion location, composition, and size (Pauleikhoff 2005).

Other factors are involved, but it is clear that vascular endothelial growth factor (VEGF) is a key molecule in the development of CNV. VEGF is regulated by hypoxia and it promotes angiogenesis and vasopermeability, which are characteristic of the disorder (D'Amore 1994; Green 1999; Pauleikhoff 2005). VEGF and its mRNA are upregulated in CNV associated with AMD (Kvanta et al 1996; Lopez et al 1996; Wells et

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al 1996) and in experimental models of CNV (Ishibashi et al 1997; Yi et al 1997). VEGF is critical for experimental CNV to develop (Vinores et al 2006) and exposure of choroidal vessels to VEGF results in CNV formation (Schwesinger et al 2001). Collectively, these data provide a strong rationale for targeting VEGF in the treatment of wet AMD. To utilize this strategy, pegaptanib (Macugen®), a 28-base ribonucleic acid aptamer, was developed to specifically bind to and block the activity of the 165 amino acid isoform of VEGF (VEGF₁₆₅), the major inducer of abnormal blood vessel growth and leakage in wet AMD. Pegaptanib has a mean apparent half-life in the vitreous of 10 ± 4 days (Patel et al 2006), but to prolong activity at the site of action, the sugar backbone was modified to prevent degradation and the aptamer was covalently linked to two branched 20-kD polyethylene glycol moieties, which increases its half-life in the vitreous (Ruckman et al 1998; Drolet et al 2000). VEGF₁₆₅ consists of a receptor-binding domain, which is found on all VEGF isoforms, and a heparin-binding domain, which is unique to VEGF₁₆₅ (Ferrara et al 2003). Pegaptanib binds to the heparin-binding domain, accounting for its specificity for VEGF₁₆₅, with an extremely high affinity ($K_d = 50$ pM) (Lee et al 2005) and inhibits the interaction of VEGF₁₆₅ with its type-1 and type-2 receptors. With cultured human umbilical vein endothelial cells, pegaptanib inhibited the binding, signal transduction, calcium mobilization, and cell proliferation mediated by VEGF₁₆₅ to an extent comparable with anti-VEGF monoclonal antibodies (Bell et al 1999).

Preclinical trials (Table 1)

Based on its vast potential for the treatment of AMD, diabetic retinopathy, and tumors, preclinical evaluation of pegaptanib was quickly undertaken to determine its safety and efficacy.

Table 1 Preclinical trials

Species	Effect	Reference
rhesus monkey	no toxic effects, no change in intraocular pressure, no immune response to aptamer	Drolet et al 2000
rhesus monkey	subcutaneous and intravenous administration effective at maintaining adequate plasma levels	Tucker et al 1999
guinea pig, rat, mouse, rabbit	almost total inhibition of VEGF-mediated vascular permeability, reduced VEGF-induced corneal angiogenesis, reduced NV in mice with OIR	Eyetechn Study Group 2002
rats	Suppressed leukostasis and vascular leakage in diabetics	Ishida et al 2003

Abbreviations: NV, choroidal neovascularization; OIR, oxygen-induced retinopathy; VEGF, vascular endothelial growth factor.

Following intravitreal administration of pegaptanib into rhesus monkeys, there were no toxic effects, no change in intraocular pressure, and no immune response to the aptamer. There was a half-life of the aptamer in the vitreous of approximately 90–100 hours, depending on the dose administered, and the compound remained fully active in the eye for at least 28 days following biweekly injections (Drolet et al 2000). Subcutaneous and intravenous administration were also effective at maintaining adequate plasma levels (Tucker et al 1999), providing a basis for subcutaneous delivery of the aptamer. In the Miles assay, pegaptanib almost completely blocked VEGF-mediated vascular leakage and inhibited corneal angiogenesis by 65% in a rat model and retinal neovascularization in a murine model of retinopathy of prematurity (Eyetechn Study Group 2002). In diabetic rats, pegaptanib significantly suppressed leukostasis and vascular leakage in both the early and late stages of the disease (Ishida et al 2003). Trans-scleral delivery of pegaptanib was also achieved in rabbits by encapsulating the aptamer in poly(lactic-co-glycolic) acid (PLGA) microspheres (Carrasquillo et al 2003). The drug was released over a period of 20 days and retained activity, providing a promising approach for the treatment of retinal and choroidal disorders with a dosing frequency of a minimum of every 6 weeks. The sustained release of pegaptanib was extended to several weeks using PLGA-based microspheres in rabbits (Cook et al 2006).

Clinical trials (Table 2)

The initial clinical trials were previously reviewed (Vinores 2003), but there have been several recent developments. Phase I trials with PEG-conjugated pegaptanib sodium began in 1998 following US Food and Drug Administration (FDA) approval, making it the first aptamer to reach clinical testing. This study, conducted by Eyetechn Pharmaceuticals, utilized dosages ranging from 0.25 to 30 mg/eye in 15 patients with wet AMD and demonstrated stabilization or improvement of vision in 80% of patients at 3 months and 26.7% showed an improvement of 3 lines or more without any toxicity (Eyetechn Study Group 2002; Guyer et al 2003). Eyetechn followed with a Phase II study involving multiple intravitreal injections with or without photodynamic therapy (PDT), which was conducted with 21 patients with subfoveal CNV secondary to AMD. In 87.5% of patients receiving only pegaptanib, vision stabilized or improved with 25% showing a 3 lines or greater improvement, whereas PDT alone was effective in only 50.5% with only 2.2% showing an improvement of 3 lines or more. The level of improvement reached 60% if pegaptanib

Table 2 Clinical trials

Trial	Dosage range	Duration	Patients	Results	References
Phase I	0.25–30 mg/eye	3 months	15	80% had stabilized or improved vision with 26.7% showing improvement, no toxicity	Guyer et al 2002; Eyetech Study Group 2002
Phase II	multiple intravitreal injections with or without PDT	3 months	21	vision stabilized or improved in 87.5%, 25% showed 3 lines or greater improvement, when combined with PDT, improvement of 3 lines or greater reached 60%	Guyer et al 2003; Eyetech Study Group 2002
Phase III	0.3, 1.0, or 3.0 mg/eye	54 week	1186	efficacy demonstrated for all 3 doses without a dose-dependency relationship, 15%–24% improvement (depending on the evaluation) in number of patients that lost fewer than 15 letters of visual acuity, 2.2–9.7x greater risk of severe visual loss (≥ 30 letters), 10% improvement in patients that maintained or gained visual acuity, adverse effects accounting for severe loss of visual acuity in 0.1%	Gragoudas et al 2004; VISION Clinical Trial Group 2005

Abbreviations: PDT, photodynamic therapy.

and PDT were administered together (Guyer et al 2003). Due to the potential for pegaptanib to provide a better alternative than laser photocoagulation for the treatment of exudative (wet) AMD, the FDA granted “fast-track” designation for Phase III clinical trials and these trials were underway by 2002 and involved 1186 patients at 117 centers (Gragoudas et al 2004). Pegaptanib has also recently been approved for the treatment of wet AMD in Canada (trials launched in 2005) and it has been filed for approval in the European Union, Australia, Switzerland, and Brazil (Eyetech Pharmaceuticals, Inc. 2005). In the US trials, doses of 0.3, 1.0, or 3.0 mg were administered and efficacy was demonstrated for all three doses without a dose-response relationship. Seventy percent of the patients who received 0.3 mg pegaptanib lost fewer than 15 letters of visual acuity compared with 55% in sham-injected controls (Gragoudas et al 2004) and the improvement was maintained in a 1-year extension of the trials (Siddiqui and Keating 2005). Separate evaluations yielded similar results, with 78% of pegaptanib-treated patients showing loss of fewer than 15 letters of visual acuity compared with 54% in patients receiving usual care (VISION Clinical Trial Group 2005). The risk of severe loss of visual acuity (≥ 30 letters) was reduced from 22% in the sham-injected group to 10% in patients receiving 0.3 mg pegaptanib (Gragoudas et al 2004). A separate evaluation found that patients receiving usual care were approximately 10 times more likely to suffer severe vision loss (29%) than those treated with pegaptanib (3%) (VISION Clinical Trial Group 2005). Significantly more patients maintained or gained visual acuity if they received pegaptanib (33% compared with 23% for sham-treated controls). Commencing 6 weeks after treatment, visual acuity was consistently better in pegaptanib-treated

patients (Gragoudas et al 2004). In a recent study involving 40 patients treated with 1 mg intravitreal pegaptanib every 6 weeks for a duration of 24 weeks, the thickness of the central retina decreased from $340 \pm 24 \mu\text{m}$ to $280 \pm 20 \mu\text{m}$ ($p=0.02$) and vascular leakage, assessed by fluorescein angiograms, decreased from 100% to 54% while stable visual acuity was maintained (Emerson et al 2006). Surprisingly, when a single eye was treated with pegaptanib, a significant macular thickness reduction was noted in the uninjected eye. This remote biological effect, possibly occurring through systemic absorption, raises concerns about pegaptanib’s possible interference with physiological angiogenesis, such as coronary collateral vessel formation and wound healing (Martin et al 2006).

In a previous evaluation of pegaptanib (Vinores 2003), no treatment-related adverse effects were noted. Even at doses 3- to 10-fold higher than the recommended 0.3 mg/eye dose, pegaptanib had an excellent safety profile (Patel et al 2006), but some adverse effects have recently been reported with the progression of the Phase III trials. Endophthalmitis occurred in 1.3% of patients, traumatic injury to the lens in 0.7%, and retinal detachment in 0.6%, accounting for the most serious adverse effects. Collectively, the adverse events accounted for severe loss of visual acuity in 0.1% of patients (Gragoudas et al 2004). There was no evidence of a sustained increase in intraocular pressure following pegaptanib injection in either a short-term (Hariprasad et al 2006) or a long-term setting (Gragoudas et al 2004); however, three patients experienced severe eye pain that did not effect visual acuity within 2 hours of the injection (Liggett et al 2006). Intraocular pressure was not elevated, only mild conjunctival inflammation around the injection site was noted, and the fundus examination was

unchanged; therefore, the etiology of the pain was unclear. Also reported were two cases of severe systemic allergic responses in association with vitreous administration of pegaptanib (Steffensmeier et al 2006). Other adverse effects reported following injection of pegaptanib include vitreous floaters, vitreous opacities, anterior chamber inflammation, reduced visual acuity, corneal edema, blurred vision, and dizziness (Doggrell 2005; Thomson CenterWatch 2005).

Combination therapies

Pegaptanib treatment, alone, produces modest effects in the treatment of AMD, but it may have added benefit when used in combination with other therapies. Intravitreal pegaptanib injections for AMD results in stabilization of vision and a significant reduction in subretinal fluid thickness, but there were no significant anatomical changes in foveal or maximal retinal thickness, pigment epithelial detachment, total lesion thickness, cystoid macular edema, or CNV membrane thickness (Ufret et al 2006), so combining pegaptanib with an alternative therapy may help to improve the outcome. In two animal models of ocular NV, pegaptanib in combination with PDT was more effective at inhibiting and promoting regression of NV than either was alone (Ju et al 2006). Pegaptanib has also been used successfully in combination with PDT for the treatment of AMD (Guyer et al 2003; Vann et al 2006). Anti-VEGF therapies, such as pegaptanib, tend to be less effective at trying to promote regression of more established vessels than at treating AMD in its early stages. In addition, PDT upregulates VEGF, potentially leading to further complications. In both studies, the combination of PDT and pegaptanib treatment improved visual acuity in 60% of the patients, which exceeded the outcome of either mode of therapy alone, and there were no additional safety concerns with the combination therapy.

Pegaptanib has also been used successfully with bevacizumab (Avastin[®]), which is a broader spectrum anti-VEGF treatment, reacting with multiple isoforms rather than specifically with VEGF₁₆₅. Preliminary results suggest that bevacizumab has the potential to improve the vision in patients who had previously been treated with pegaptanib and that pegaptanib can be used to maintain these gains while potentially minimizing the toxicity of a pan isoform VEGF inhibitor, such as bevacizumab (Tolentino et al 2006). Preliminary results in a separate study suggest that pegaptanib may also be useful when administered subsequent to bevacizumab (Hughes and Sang 2006). Patients with occult CNV associated with AMD respond better to pegaptanib than do patients with classic CNV, raising speculation that another

isoform of VEGF may be responsible for the development of classic CNV (Iyenger et al 2006) and possibly accounting for the added benefit of bevacizumab in conjunction with pegaptanib.

Outlook

VEGF has been identified as a key molecule in the development of ocular NV and vascular permeability, making it a good therapeutic target for the treatment of AMD. Pegaptanib, an anti-VEGF therapy, is the first agent to be used in clinical trials for AMD and the first aptamer used in clinical trials. The encouraging preliminary results with animal and clinical trials prompted the FDA to grant fast-track status for the treatment of AMD. The Phase III clinical trials showed modest effects, primarily at stabilization of vision and reduction of subretinal fluid. Pegaptanib or other anti-VEGF therapies were most effective against AMD in the early stages and were not particularly effective against the more established vessels. When comparing different treatments for their efficacy in treating AMD using the Lineweaver-Burke (LB) linear plot and correcting for differences in the initial visual acuity score (VAS), pegaptanib, PDT, and anecortave acetate produced a similar slope and ranibizumab (Lucentis[®]), another anti-VEGF therapy, appeared to be the most efficacious treatment, since it is the only treatment proven to reverse the slope of visual acuity on a LB plot. If all treatments are started at an initial VAS of 60 letters, the expected final VAS for ranibizumab would be 69.0 letters, for PDT 22.1 letters, for pegaptanib 18.4 letters, and for anecortave acetate 21.3 letters (Shah et al 2006). Pegaptanib, however, shows greater efficacy when combined with another mode of therapy, such as PDT or bevacizumab, and these and other combination therapies may be the most promising therapeutic approaches for treating AMD.

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