ABSTRACT

In December 2004, the US Food and Drug Administration (FDA) approved pegaptanib sodium. Pegaptanib is a 28-base ribonucleic acid aptamer designed to bind to and block the activity of the 165-amino acid isoform of extracellular vascular endothelial growth factor. This article describes the pivotal clinical trials that led to the FDA approval of pegaptanib sodium for all subtypes of neovascular age-related macular degeneration, and reports 24-month data for ongoing trials. The author is the external academic investigator for the trials and lead author of the study's first published report.


Although photocoagulation and photodynamic therapy (PDT) have proven effective in neovascular age-related macular degeneration (AMD), results depend on lesion size, lesion composition, and location. The VEGF Inhibition Study in Ocular Neovascularization (VISION) reported on 2 concurrent, randomized, double-blind, controlled clinical trials designed to evaluate pegaptanib in the treatment of neovascular AMD. It is the first study to prove an antiangiogenic agent to be effective in the treatment of neovascular AMD.

Inclusion criteria for the VISION study were deliberately broad to attempt to mirror the realities of clinical practice. The 1186 patients who were enrolled represented all angiographic lesion subtypes of neovascular AMD—predominantly classic, minimally classic, and occult with no classic. Best corrected visual acuity ranged from 20/40 to 20/320 in the study eye. Lesions up to and including 12 optic-disk areas were studied. At least 50% of the total lesion size was required to have active choroidal neovascularization (CNV) in predominantly classic lesions. Minimally classic lesions were defined as those lesions with less than 50% classic CNV. Occult lesions were those lesions with no classic CNV.

Study subjects without predominantly classic CNV at baseline had to demonstrate evidence of disease progression. Specifically, eyes that were identified as “minimally classic” or “occult with no classic” subtypes were required to have subretinal hemorrhage or lipid, or 3-line or more loss of visual acuity in the previous 12 weeks. This requirement was consistent with other trials and was necessary to avoid enrolling end-stage or nonprogressive lesions.

Patients were randomized to receive intravitreous injection of pegaptanib (0.3 mg, 1 mg, or 3 mg) or sham injection in the study eye every 6 weeks. For ethical reasons, ophthalmologists could choose to use verteporfin plus PDT in patients with predominantly classic lesions. Patient compliance was high; at 1 year, an average of 8.5 injections had been administered per patient out of a possible total of 9 injections.
The primary efficacy endpoint of the VISION study was the proportion of patients who lost fewer than 3 lines of visual acuity between baseline and week 54. Secondary endpoints included measures of mean visual acuity, in addition to gains in visual acuity of 0 or more lines or 3 or more lines.

At week 54, all 3 doses of pegaptanib demonstrated efficacy in the primary endpoint of preserving visual acuity (losing <3 lines) in the intent-to-treat population: 70% (0.3 mg), 71% (1 mg), and 65% (3 mg) versus 55% for usual care subjects (P = .0001, .0003, and .0310, respectively). Benefits were not shown to be dose-dependent. The efficacy of pegaptanib (measured by the mean loss of visual acuity from baseline to each study visit) was reported after the first treatment at week 6, as shown in Figure 1, and increased over time up to week 54. Outcomes for the secondary endpoint showed that 31%, 37%, and 33% of patients receiving pegaptanib (3.0 mg, 1.0 mg, and 0.3 mg, respectively) had no change in visual acuity or a gain of 1 or more viewable letters compared to 23% in the control group (P = .02, P <.001, and P = .003, respectively). Of note, a treatment effect was observed as early as 6 weeks, continuing to week 54. At all 3 doses, pegaptanib reduced the incidence of severe vision loss (≥6 lines) compared to placebo (Figure 2). Some study subjects gained 3 or more lines of vision: 6%, 8%, and 4% (0.3 mg, 1.0 mg, and 3.0 mg, respectively) compared to 2% of subjects who received usual care (P = <.05; Figure 3).

No factors except pegaptanib were identified as significantly influencing the response to pegaptanib 0.3 mg versus usual care using multiple logistic regression analysis. There was no association reported between lesion size or angiographic subtype, baseline visual acuity, gender, race, or eye color and treatment benefit. Treatment benefit was well distributed across a broad patient population.

Two fluorescence angiographic examinations were performed during the course of the study, at weeks 30 and 54. Angiography revealed diminished vascular leakage, smaller size of CNV, and slowed lesion growth in patients treated with pegaptanib compared to the control group.
SAFETY PROFILE

Pegaptanib was found to be generally safe and well tolerated. No apparent systemic or ocular drug-related safety issues were noted in any of the 3 treatment groups. Reported adverse events appeared to be related to the injection procedure as opposed to the study drug. The most common adverse events were eye pain, vitreous floaters, and punctate keratitis.

Although rare, 3 types of serious adverse events were reported. Endophthalmitis occurred in 12 patients, 1 of whom experienced severe vision loss. Nonetheless, 75% of the patients who developed endophthalmitis chose to remain in the study and received subsequent injections. Five patients experienced traumatic cataract as a result of the injection, and 3 patients were reported to have rhegmatogenous retinal detachment. There was no evidence of a sustained elevation in intraocular pressure or an acceleration of cataract formation among patients in the treatment groups compared to those patients in the sham-injection group.

TWO-YEAR DATA

Preliminary results reported at 2 years in the 1053 patients who continued in the VISION study evaluated time to first 15-letter loss, which was significantly sooner in patients who discontinued pegaptanib during the second year compared to those patients who continued therapy after 1 year (Figures 4A and 4B). In the second year, 35 events of at least a 15-letter loss were noted in patients who discontinued therapy until such loss compared to 21 events in patients receiving 2 years of continuous therapy ($P = <.05$).

The safety profile of pegaptanib at 2 years was not significantly different from year one. No systemic safety concerns were identified, and no new ocular safety concerns emerged. After a protocol amendment implemented during year two of the study to reinforce aseptic technique, there was a decrease in the incidence of endophthalmitis compared to the first year of study, with only 2 cases in 6066 injections (0.03%) after the protocol change compared to 16 cases in 8679 injections (0.18%) before it. The mortality rate was consistent for a population with macular degeneration. There was a very low patient discontinuation rate (1%) because of adverse events, which speaks to the tolerability of repeated intravitreal injections and of the medication. Full details and data for these outcomes are in preparation for publication elsewhere in the near future.

CONCLUSIONS

Pegaptanib is the first antivascular endothelial growth factor therapy shown to reduce the risk of vision loss in large randomized visual trials. Two concurrent, randomized controlled trials have shown pegaptanib to be effective in all subtypes of neovascular AMD, with no apparent dose-response relationship. In the combined analysis of the primary endpoint, the number of patients who lost less than 3 lines of visual acuity at 54 weeks, efficacy was demonstrated for all 3 doses and was not dose dependent. In the group receiving 0.3 mg pegaptanib, 70% of patients lost less than 3 lines of visual acuity compared to 55% of subjects receiving sham injections. Severe vision loss (≥6 lines) was 10% in subjects treated with pegaptanib versus 22% in the control group. Angiographic images indicated a reduction in the growth of the total size of the lesion of CNV and in the severity of leakage with pegaptanib. The drug was generally safe and well tolerated through 2 years of study.

Figure 3. Maintain and/or Gain Visual Acuity
Treatment effect was early, beginning at 6 weeks, and sustained treatment benefit was suggested through 2 years of treatment with pegaptanib compared to usual care. The benefit appears to be greater after 2 years of treatment compared to 1 year. These data suggest that a second year of therapy may be warranted to maximize treatment benefit.

**DISCUSSION**

Dr D’Amico: A clear-cut approach to monitoring therapy outcomes with pegaptanib therapy has yet to be established. Although visual acuity monitoring has been proposed, are we measuring a specific acuity level or a change in visual acuity? Do we determine the value of treatment based on the patient’s or physician’s expectations for improvement?

When monitoring with optical coherence tomography (OCT), are we looking for retinal thickness, cysts, and subretinal fluid? If we base our decisions on whether fluid comes and goes in the retina, do we know for certain whether such episodes of retinal fluid formation and drying are harmful?

If we monitor with ophthalmoscopy, are we proposing that fibrosis and atrophy are always adequately identifiable to allow you to determine when a lesion will no longer benefit from treatment? Are we looking for retinal pigment epithelium detachment and hemorrhage?

Fluorescein angiogram and indocyanine green are also unreliable, as fluorescein patterns may look acceptable when vision is poor, and vice versa. There is no apparent correlation between fluorescein angiography and visual acuity change in pharmacotherapy.

On the first day after injection, the patient is contacted by phone and the absence of symptoms of a substantial nature is verified. A few days later, I make a follow-up phone call and schedule the patient for the next 6-week injection. I will check visual acuity before injection. If the visual acuity is satisfactory, perhaps within 4 lines of the last reading, I will perform only ophthalmoscopy at the time of injection to ensure that the retina is intact. I do not plan to use OCTs nor fluorescein angiography routinely at subsequent injections for evaluative purposes. However, this position is controversial. If the ophthalmoscopy indicates there is a problem, such as massive subretinal hemorrhage, retinal detachment, or a fibrotic lesion with significantly reduced visual acuity, I
would do an additional study to ensure that there would be no benefit to continued treatment.

Dr Rosenfeld: I think OCT is a very valuable learning instrument for physicians who are just beginning to use intravitreal pharmacotherapies, and OCT imaging could be used for purposes of modifying therapy. In addition, OCT provides useful information that can contribute to future use and modifications of research treatments for neovascular AMD. In terms of patient management, I will closely observe central retinal thickness and the amount of fluid under and in the retina. If the lesion swells or grows, I may refer the patient to a clinical trial of a different treatment regimen. Not every patient will fit into the paradigm of treatment every 6 weeks.

Dr Gragoudas: I would agree that OCTs can provide valuable data for future studies, but at the present time I see no reason to use fluorescein angiography or OCT 6 weeks after the first injection, except for investigational purposes. If 6 months into treatment visual acuity has deteriorated significantly and advanced fibrosis is seen, we are most likely dealing with the end stage of the disease and I am willing to discontinue treatment.

Dr Ho: Based on the best existing evidence, I counsel my patients on day 1 that pegaptanib therapy involves injections every 6 weeks for 1 or possibly 2 years. However, I agree with Dr Rosenfeld that ongoing monitoring contributes to our evolving knowledge, thus I will be obtaining angiograms and OCT—not systematically, but in cases that appear to be responding atypically. Reimbursement, resource utilization, and the pharmacoeconomic value of this monitoring are separate issues. However, my goal is 2-fold: give patients the therapy program that is best supported by medical evidence, and learn as much as possible in this first year of open-label treatment with this therapy.

Dr Regillo: The studies for pegaptanib therapy were not designed to answer when treatment should be stopped. We should monitor with fluorescein angiogram and OCT, not every 6 weeks, but perhaps every 3 to 6 months, and then compare results with pretreatment images to see if the patient is responding to therapy. I think, in general, a large percentage of patients will respond to some degree. I agree with Dr Ho that we are going to put patients through the treatment program for at least 1 year.

Dr D'Amico: For the community physician who is on the front line, are we even close to being able to formulate guidelines for what to do at a 6-, 12-, or 18-week pegaptanib injection visit?

Dr Schachat: No, there is no evidence to support a change in the therapeutic regimen from that given in the product protocol. If you deviate from the published protocol, you will get a result that may be better, the same, or worse. I would argue for following the published protocol to practice in an evidence-based manner. However, there is some evidence that 2 years of treatment seems to be better than 1 year of treatment.

Dr Rosenfeld: We talked about fluid resolving, patients doing better—that’s a home run. Another scenario is increased retinal thickness and decreasing vision. Four years ago, when PDT was our only option, we completed a full course of therapy. However, now there are other treatment options, and also clinical trial options. Monitoring allows you to better assess the patient’s status, thus we can consider alternate treatment strategies. A third scenario is that there is no change and the vision is stabilized; then we continue with the regimen.

Dr D'Amico: Assume that you injected a patient with pegaptanib 6 weeks ago, and the patient now presents for a second injection. What do you and your staff do routinely? Has the patient been seen between injections?

Dr Ho: This is a very important and relevant question, and not all of us agree as to how we should approach this issue. For pegaptanib therapy, I will educate the patient about signs and symptoms of endophthalmitis and, at the injection visit, place the patient on a topical antibiotic. The next week, my staff will call the patient to confirm that he is not experiencing any symptoms, and then I will see the patient back in 6 weeks. However, my post-triamcinolone injection procedure will be very different. I will see those patients within the first week of treatment, educate them, and give them topical antibiotics. I have much less comfort with triamcinolone than with pegaptanib.

Dr Regillo: That is also my process when treating with pegaptanib, but some physicians in our group plan to examine the patient within 1 week of the injection. However, the evidence shows that this return visit does not improve the rate of diagnosis of endophthalmitis. Therefore, I think a phone call is a reasonable approach.

Dr Rosenfeld: In my practice, before discharge, patients are given an instruction sheet on proper post-procedural care that includes signs and symptoms of an ophthalmological problem. The day after injection,
we call the patient. If there are no problems, we see our patients back at 6 weeks.

*Dr D'Amico:* I think bringing all seniors with AMD back for a 1-week post-op evaluation 6 times a year will result in more broken legs in the parking lot than in cases of endophthalmitis detected early. Education and communication such as a scheduled phone call are key, but a postinjection visit is unnecessary. In the clinical trial, patients were called 3 days after the injection.¹

*Dr Schachat:* The endophthalmitis specialists in our large practice told us they believed that a return visit was of no benefit. However, given the medical-legal risks involved with lack of follow-up, I am not willing to rely solely on a phone call; patients are sometimes difficult to reach. Therefore, we have developed consent forms that instruct patients to call our office if they experience any changes or have concerns. When patients do call, we ask them to come in for examination.

**REFERENCES**