

# Pegaptanib Can Reduce Proliferative Diabetic Retinopathy Progression

Data from 10 patients presented at ARVO were very promising; additional patients will be now be studied.

BY CONNI BERGMANN KOURY, EDITOR-IN-CHIEF

Intravitreal injection of pegaptanib sodium (Macugen; OSI/Eyetech Pharmaceuticals and Pfizer, New York, NY) produced a marked regression of neovascularization and diabetic macular edema (DME) in patients with advanced diabetic retinopathy.

Victor H. Gonzalez, MD, presented results of a 10-patient prospective study at the Association for Research in Vision and Ophthalmology (ARVO) 2006 Annual Meeting in Fort Lauderdale, Fla. Dr. Gonzalez, of the Valley Retina Institute in McAllen, Texas also spoke to *DIABETIC MICROVASCULAR COMPLICATIONS TODAY* in a telephone interview.

Intravitreal injections of 0.3 mg pegaptanib were given every 6 weeks. Assessment was performed with slit-lamp biomicroscopy, fundus exam, fluorescein angiography and optical coherence tomography. The endpoints of the study were reduction in the progression of proliferative diabetic retinopathy (PDR), defined as regression of neovascularization of the disc and neovascularization elsewhere; change in BCVA from baseline; and change in retinal thickness measured at the center point.

Dr. Gonzalez said that pegaptanib is being evaluated in an ongoing study of patients with DME. In that trial, investigators found that not only did the agent improve DME, but some patients with PDR experienced regression without laser treatment.

“For this reason, we undertook this study to look specifically at PDR in patients who met the Early Treatment of Diabetic Retinopathy Study [ETDRS] criteria for laser photocoagulation,” Dr. Gonzalez said. “The objective was to see if we could take a patient with PDR and active neovascularization and blockade vascular endothelial growth factor (VEGF)<sub>165</sub> — the isoform of

VEGF that has been demonstrated in trials and in experimental animal models to be significantly elevated in the presence of PDR — and alter the natural history of PDR.”

Patients in the trial were examined at 3 weeks to evaluate if there was significant regression of PDR. For ethical reasons, laser photocoagulation was to be performed in patients who had not regressed at least 50% from baseline. The investigators found that all 10 patients had significant regression of neovascularization at week 3, no matter what size the lesion was or where it was, Dr. Gonzalez said. Patients had also either stabilized or improved vision by week 3.

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## EXPANDING THE STUDY

As a result of the ARVO data, Dr. Gonzalez said his team is going to be enlarging the study. “We will randomize patients either to pegaptanib injection or pan-retinal photocoagulation [PRP]. We are in the process of recruiting patients; 10 for the active treatment and 10 for the laser arm.”

Dr. Gonzalez said that what he suspects is that the pegaptanib patients will have significant regression — as will the PRP patients. “But we will be doing some other functional studies, everything from vision to visual fields, to see which of the two treatments is better long term.

## META-ANALYSIS OF TWO RUBOXISTAURIN TRIALS SHOW CONSISTENT RESULTS

A meta-analysis of two ruboxistaurin (Proposed name Arxxant; Eli Lilly and Company, Indianapolis) trials found that patients assigned the agent had a reduced occurrence of sustained moderate visual loss and reduced progression of diabetic macular edema center of the macula, and an increased chance of visual acuity improvement in patients with moderately severe to very severe nonproliferative diabetic retinopathy (NPDR).

The meta-analysis of the two similarly designed trials, PKC-DRS and PKC-DRS2, was presented by Lloyd P. Aiello, MD, at the American Diabetes Association 66th Scientific Sessions in Washington, DC. The PKC-DRS, a multidose trial of 252 patients tested whether the oral protein kinase C (PKC) beta inhibitor slowed progression of NPDR to proliferative DR. While no effect was seen for this outcome, ruboxistaurin did reduce the occurrence of sustained moderate visual loss (loss of  $\geq 15$  Early Treatment of Diabetic Retinopathy Study [ETDRS] letters sustained for the last 6 months of study). Dr. Aiello is head of Joslin's Section on Eye Research, director of Joslin Clinic's Beetham Eye Institute and associate professor of ophthalmology at Harvard Medical School.

PKC-DRS2 tested these outcomes in 685 patients at the dose with greatest effect in the PKC-DRS.

The data included in the meta-analysis derived from both trials is for 401 patients assigned placebo and 412 patients

assigned 32 mg/day ruboxistaurin, according to Dr. Aiello. The two trials were 3-year, multicenter, randomized, placebo-controlled, double-masked, phase 3 trials. Included patients had a best-corrected ETDRS visual acuity  $\geq 45$  letters, moderately severe to very severe NPDR (ETDRS level  $\geq 47A/47B$  and  $\leq 53E$ ), and no prior panretinal photocoagulation in at least one eye. There were no restrictions on presence of DME or focal/grid photocoagulation at baseline. Mean HbA1c was 8.2% and mean blood pressure were 138/78 mm Hg at baseline.

Sustained moderate visual loss occurred in 10.2% of placebo-assigned versus 6.1% of ruboxistaurin-assigned patients, a 41% risk reduction ( $P=.011$ ), Dr Aiello reported. Mean visual acuity was better in eyes of ruboxistaurin patients after about 12 months. In 2.4% of placebo eyes there was a  $\geq 15$ -letter gain versus 4.7% of ruboxistaurin eyes ( $P=.021$ ). A  $\geq 15$ -letter loss occurred in 11.4% of placebo versus 7.4% of ruboxistaurin eyes ( $P=.012$ ).

Among eyes with clinically significant macular edema (CSME)  $>100 \mu\text{m}$  from the center of the macula at baseline, 66.9% versus 50.0% progressed to CSME  $\leq 100 \mu\text{m}$  from the center of the macula ( $P=.002$ ). ■

Aiello LP, Vignati L, Sheetz MJ, et al. Effect of ruboxistaurin on diabetic macular edema and visual loss: Meta-analysis of the PKC-DRS and PKC-DRS2. Presented at the American Diabetes Association 66th Scientific Sessions. June 9-13, 2006. Washington, DC.

There were no systemic side effects and no ocular side effects associated with pegaptanib treatment during the ARVO series of patients, Dr Gonzalez said. The only side effects were mild and related to injection of the medication. In fact, to date, there have been no significant systemic side effects in any of the pegaptanib trials.

The 10 original patients from the ARVO study will be monitored for a total of 6 months follow-up and the final data should be available near the end of the year.

The 10 original patients from the ARVO study will be monitored for a total of 6 months follow-up and the final data should be available in late fall or early winter.

### THE FUTURE LOOKS BRIGHT

"From my personal experience, pegaptanib works really well in PDR. When I saw these patients at 3 weeks after treatment, there was a *wow* factor. I expected the drug to work, but not that fast or that impressively."

Dr. Gonzalez said that, while the research is still early, he believes that the agent will help surgeons significantly decrease the amount of laser they have to administer to

these patients as well as eventually eliminate the need for macular laser treatment.

"I think most of the laser that we are going to require is going to be out in the periphery and very selective. If you eliminate the areas of capillary nonperfusion, you decrease the VEGF levels, which in turn decreases the stimulus for vascular leakage. I believe we will not have to laser the macula in the future. None of those first 10 patients that also had clinically significant macular edema required laser. Once we brought the VEGF levels down the DME improved, the neovascularization improved and visual acuity either stabilized or improved in all of the patients."

Dr. Gonzalez said that he believes the future is very bright for the management of diabetic retinopathy. "There are very few *wows* and definitely this is a *wow*. I think the future is bright for reducing the severe vision loss that these patients have had to suffer for such a long time. I think we can manage them now without having to sacrifice a lot of the retina, which is what we used to do." ■

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Gonzalez VH, Vann VR, Banda RM, Guel DA. Use of pegaptanib sodium (Macugen) for the regression of proliferative diabetic retinopathy. #2329. Presented at the Association for Research in Vision and Ophthalmology 2006 Annual Meeting. May 2, 2006. Fort Lauderdale, Fla.