

# Ruboxistaurin: Useful in Preventing Visual Loss in Diabetic Patients

Patients treated with the PKC-beta inhibitor had less visual acuity loss over a 3-year period versus those treated with placebo.

BY LAURA SUAREZ, MANAGING EDITOR

**A** total of 2,113 patients with diabetes and at least one microvascular complication have currently been treated with the protein kinase-C beta (PKC-beta) inhibitor ruboxistaurin (proposed brand name Arxxant; Eli Lilly and Company, Indianapolis). Totalling a treatment exposure of over 3,000 patient years, researchers have indicated that ruboxistaurin is well tolerated and provides patients with less loss of visual acuity, more frequent visual acuity improvement and less frequent visual acuity decline.

During the Association for Research in Vision and Ophthalmology 2006 Annual Meeting, Lloyd Paul Aiello, MD, PhD, presented results from the Protein Kinase-C Beta Inhibitor Diabetic Retinopathy Study 2 (PKC-DRS2) — a follow-up of the PKC-DRS study that evaluated the safety and efficacy of ruboxistaurin in a population of 252 patients. Investigators tracked patients for diabetic retinopathy progression (ie, primary endpoint), moderate visual loss and sustained moderate visual loss (ie, secondary endpoints). Compared with placebo, the treatment did not prevent the progression of diabetic retinopathy, however, over a 3-year period, a 35% risk reduction of visual loss occurred in patients treated with ruboxistaurin.

## SUSTAINED MODERATE VISUAL LOSS

The primary endpoint of the current phase 3, randomized, multicenter, double-masked, parallel placebo-controlled, clinical trial was sustained moderate visual loss (ie,  $\geq 15$  loss on the Early Treatment of Diabetic Retinopathy Study [ETDRS] scale that was maintained for either the last 6 months of the trial or the last 6 months of study participation). Patients with type 1 or 2 diabetes and moder-

Extrapolated to the 2030 population at risk, ruboxistaurin treatment may avoid sustained moderate vision loss over a 3-year period in more than 665,000 patients worldwide.

ately severe to very severe nonproliferative diabetic retinopathy were treated with ruboxistaurin (n=345) or placebo (n=340). Dr. Aiello and investigators concluded that the agent, at an oral dose of 32 mg/day, successfully lowered the incidence of sustained moderate visual loss. Compared with patients who received placebo, patients receiving ruboxistaurin had a 40% reduced incidence of sustained moderate visual loss (9.1% to 5.5%,  $P=.034$ ). A Cox proportional hazard model multivariable analysis showed that this outcome is independently associated with ruboxistaurin treatment.

“When extrapolated to the population at risk by 2030, the treatment with ruboxistaurin might avoid sustained moderate vision loss over a 3-year period in an excess of 54,000 patients in the United States and [more than] 665,000 patients worldwide,” Dr. Aiello said. Dr. Aiello is director of the Beetham Eye Institute and head of the section of eye research at the Joslin Diabetes Center in Boston and associate professor, department of ophthalmology, at Harvard Medical School.

Enrollment criteria are found in Table 1. A total of 685 patients from 70 centers — mean age 59 years and diabetes duration 16 years — were followed for 36 months. Mean HbA1c in patients was 8.1%. Both eyes were con-

sidered eligible for the study in 73% of patients; in the remaining patients, the fellow eye had either proliferative diabetic retinopathy or panretinal photocoagulation and was considered ineligible. Researchers performed eye evaluations every 3 months and fundus photographs were taken every 6 months.

### BASELINE-TO-ENDPOINT CHANGES

Individual eye analyses were performed, in which investigators found a 45% reduction in sustained visual loss among patients treated with ruboxistaurin. "When examining the mean visual acuity by visit, note that ruboxistaurin patients had little change in mean visual acuity during the course of the study, while those [assigned] placebo showed a mild but persistent decline," Dr. Aiello said. He added that the baseline-to-endpoint mean change was -2.6 letters versus -0.8 letters in the placebo and ruboxistaurin groups, respectively. "Looking at baseline-to-endpoint changes in visual acuity ... we observed that although the event rate is expectedly low, ruboxistaurin-treated patients had twice as many eyes that gained 2 or more lines vision as compared with placebo-treated patients."

Treatment with ruboxistaurin, as compared with placebo, also reduced visual acuity loss of 3 or more lines by 30% and reduced clinically significant macular edema progression within 100  $\mu$ m. Patients treated with ruboxistaurin were 29% less likely to have initial laser photocoagulation during the study, and treated patients had reduced sustained moderate visual loss compared with placebo patients in the event that focal photocoagulation was needed, Dr. Aiello said.

Ruboxistaurin-treated eyes had little change in mean visual acuity during the course of the study, while placebo-assigned eyes declined.

### TOLERATION OF TREATMENT

Safety analysis was also performed. More than 1,400 placebo patients and nearly 1,400 ruboxistaurin patients were analyzed, and results indicated that the treatment is well tolerated. Of the 51 mortalities during the study, 1.5% of patients were in the ruboxistaurin group, and 2.1% were in the placebo group. Conversely, 20.8% and 23.2% of patients in the ruboxistaurin and placebo groups, respectively, had at least one serious adverse event. Only 3% and 4% of patients, respectively, discontinued the study.

**TABLE 1. ENROLLMENT AND EXCLUSION CRITERIA FOR THE PKC-DRS2 STUDY**

#### Enrollment Criteria:

- Type 1 or 2 diabetes
- $\geq 18$  years of age
- HbA1c  $< 13\%$
- At least one eye needed to have  $\geq 45$  letters on the ETDRS scale
- Moderately severe to very severe nonproliferative diabetic retinopathy

#### Exclusion Criteria:

- Prior panretinal photocoagulation
- Glaucoma
- Prior intraocular surgery

This novel oral therapy may serve as a useful tool in the attempt to prevent visual loss in patients with diabetes.

"Selective inhibition of PKC-beta by ruboxistaurin resulted in less visual acuity loss, less frequent initial focal photocoagulation and was well tolerated," Dr. Aiello concluded. "Although ... over a period of 3 years, ruboxistaurin does not completely prevent the diabetes ocular complications, these data demonstrate that this compound, as a novel oral therapy, may serve as a useful tool in our attempt to prevent visual loss in patients with diabetes."

Eli Lilly and Company recently filed a New Drug Application to the Food and Drug Administration (FDA) for review of ruboxistaurin for the treatment of diabetic retinopathy. The company announced in April that the application was fileable and will be given a priority review by the FDA. ■

*Lloyd P. Aiello, MD, PhD, is director of the Beetham Eye Institute and head of the section of eye research at the Joslin Diabetes Center, in Boston and associate professor, department of ophthalmology, at Harvard Medical School. Dr. Aiello discloses that he is a consultant for Lilly Research Laboratories. He may be reached at LP.Aiello@joslin.harvard.edu.*

Aiello LP. Effect of the orally administered PKC-beta inhibitor, ruboxistaurin, on visual acuity in the PKC-DRS2 study. Presented at the Association for Research in Vision and Ophthalmology 2006 Annual Meeting. April 29 to May 4, 2006. Ft. Lauderdale, Fla.