

Ruboxistaurin Reduced the Risk of Visual Loss in Patients with DR

The orally administered protein kinase C inhibitor was well tolerated.

BY CONNI BERGMANN KOURY, EDITOR-IN-CHIEF

Ruboxistaurin (Arxxant, Eli Lilly and Company) reduced the risk of visual loss in patients with moderately severe to very severe nonproliferative diabetic retinopathy. The protein kinase C (PKC) inhibitor did not prevent the progression of retinopathy.

The Protein Kinase C Beta Inhibitor Diabetic Retinopathy Study was the first clinical trial evaluating the effect of a protein kinase isoform-selective inhibitor on ocular complications in patients with diabetes, according to a report in *Diabetes*. It was a multicenter, double-masked randomized, placebo controlled study of 252 patients.

Lead investigator Lloyd P. Aiello, MD, PhD, and colleagues reported that patients had an Early Treatment Diabetic Retinopathy Study (ETDRS) retinopathy severity level between 47B and 53E, inclusive, an ETDRS visual acuity of 20/125 or better, and no history of panretinal photocoagulation for diabetic retinopathy or glaucoma. Dr. Aiello is director of the Beetham Eye Institute, Joslin Diabetes Center, Boston.

The largely white cohort had a mean age of 56 ± 12 years, and most had type 2 diabetes. The mean HbA1c was $8.8 \pm 1.4\%$, and mean duration of diabetes was 16 ± 8 years. They were randomized to placebo or ruboxistaurin at 8, 16 or 32 mg/day for 36 to 46 months.

PERFORMED AT EVERY VISIT

Dr. Aiello and colleagues reported that ophthalmic exams were performed at every visit during the treatment period. They included a best-corrected visual acuity assessment using ETDRS protocol, intraocular pressure and Age-Related Eye Disease Study (AREDS) clinical lens grading every 3 months. Diabetic retinopathy and diabetic macular edema were assessed by masked grading of ETDRS seven-field stereoscopic color fundus photographs.

“Photos were obtained at screening, 3 months, 6 months, every 3 months through 24 months and every 6 months thereafter and were graded using ETDRS protocol, modified to include estimates of area of retinal thickening in each subfield of the ETDRS grid and of proximity of retinal thickening to the center of the macula,” Dr. Aiello wrote in *Diabetes*.

The progression of diabetic retinopathy was the primary outcome studied. It was defined as a \geq three-step worsening in the ETDRS retinopathy eye severity scale or receiving panretinal photocoagulation for diabetic retinopathy in one study eye. Other outcomes included moderate visual loss (MVL) defined as a decrease from baseline in ETDRS visual acuity score of ≥ 15 letters, (doubling or more of the visual angle), investigators wrote. Sustained MVL was defined as a decrease from baseline of ≥ 15 letter observed at each of two consecutive visits ≥ 6 months apart.

PERCENTAGE OF PATIENTS

There were no statistically significant differences among treatment groups in the time to progression of diabetic retinopathy or in the cumulative percentage of patients who reached this outcome.

Similarly, there were no statistically significant differences among treatment groups when the components of the composite primary outcome were considered individually, Dr. Aiello and colleagues reported.

When compared with placebo, the 32-mg dose of ruboxistaurin was associated with a delayed occurrence of MVL ($P=.038$) and of sustained MVL ($P=.226$). The investigators wrote that the beneficial effect on sustained MVL was evident only in eyes with definite diabetic macular edema (DME) at baseline (10% 32 mg/day ruboxistaurin vs 25% placebo, $P=.017$).

LILLY TO SUBMIT NDA FOR RUBOXISTAURIN IN DIABETIC RETINOPATHY TREATMENT

A statistically significant reduction of sustained moderate visual loss occurred in patients with moderately severe to severe nonproliferative diabetic retinopathy.

Eli Lilly and Company has completed a new phase 3 clinical trial in which the company's investigational drug ruboxistaurin (Arxxant) reduced the occurrence of vision loss in patients with diabetic retinopathy. Based on these results, the company will submit a new drug application (NDA) to the Food and Drug Administration by the end of 2005, for the initial indication of diabetic retinopathy.

In this phase 3 trial, 685 patients with moderately severe to severe nonproliferative diabetic retinopathy were treated with ruboxistaurin. The primary objective was to test the hypothesis that once-daily oral administration of the agent over 3 years would reduce the occurrence of sustained moderate visual loss (MVL). There was a statistically significant reduction in this outcome, the researchers reported.

"We are extremely pleased to be one step closer to providing a possible solution for patients with diabetic retinopathy," said Steven Paul, MD, Lilly's executive vice president, science and technology. "If ruboxistaurin is approved by the FDA, it would be the first oral medication for the treatment of this serious complication of diabetes."

Results of the phase 3 clinical trial will be presented at future medical meetings later this year or in early 2006. According to the company, its policy is to publish the results of all clinical trials. Specific publication plans have not yet been determined.

"Since Lilly has been the industry leader in pioneering diabetes therapies for more than 80 years, we believe in the value of innovation and the need for new treatments for this epidemic disease," said Sidney Taurel, Eli Lilly and Company chairman, president and chief executive officer.

An ongoing trial to determine if ruboxistaurin has an effect on diabetic macular edema progression in patients with less severe diabetic retinopathy is expected to be completed in 2010. ■

They wrote that in multivariate Cox proportional hazard analysis, 32 mg/day ruboxistaurin significantly reduced the risk of MVL compared with placebo (HR 0.37 [95% CI 0.17-0.80], $P=0.12$).

So, while ruboxistaurin did not prevent diabetic retinopathy progression, it did reduce the risk of visual loss and it was well tolerated among patients in the study.

ACTIVATED EARLY

Dr. Aiello and colleagues offered several explanations for the apparent lack of efficacy for retinopathy progression shown in this trial. "Study patients had moderately severe to very severe nonproliferative diabetic retinopathy at baseline. It has been well established that the PKC beta is activated very early in diabetes, well before clinically apparent retinopathy," they wrote. "Thus, in our study participants, significant biochemical and pathologic retinal changes that are no longer amenable to PKC beta inhibition may have already occurred before enrollment."

There did appear to be a beneficial effect of ruboxistaurin on the secondary outcomes of MVL and sustained MVL, the investigators wrote. These are clinically meaningful endpoints, and although the reduction did not reach statistical significance in the case of sustained MVL, the risk reductions for sustained MVL and MVL were in

the same direction and of similar magnitude, they wrote.

MVL, including sustained MVL, is often caused by DME involving the center of the macular. In this study, Dr. Aiello wrote, 79% of patients had DME in at least one study eye at baseline and 34% had DME involving the center of the macular in at least one study eye at baseline. "The rate of sustained MVL was higher in eyes with definite DME at baseline, and it was among these eyes that there was a trend for a beneficial effect of 32 mg/day ruboxistaurin," he wrote.

The trial was not designed to demonstrate the effect of ruboxistaurin on DME or visual function, however. Patients were enrolled regardless of their DME status at baseline.

Dr. Aiello said that the trial demonstrated that, unlike less selective compounds, Ruboxistaurin up to 32 mg/day was well tolerated without significant adverse effects over 30 to 52 months of treatment. The data support further evaluation of ruboxistaurin to prevent MVL in diabetes. ■

Lloyd P. Aiello, MD, PhD is director of the Beetham Eye Institute, Joslin Diabetes Center, Boston. He can be reached at LloydPaul.Aiello@joslin.harvard.edu.

Aiello LP and the PKC-DRS Study Group. The effect of ruboxistaurin on visual loss in patients with moderately severe to very severe nonproliferative diabetic retinopathy. *Diabetes*. 2005;54:2188-2197.