Ruboxistaurin Reduced Vision Loss in Moderate-to-Severe Nonproliferative DR

The once-daily, oral investigational therapy reduced sustained moderate vision loss over 3-year period.

REVIEWED BY LLOYD P. AIELLO, MD, PHD

Ruboxistaurin mesylate (proposed brand name Arxxant; Eli Lilly and Company; Indianapolis) reduced the risk of sustained moderate vision loss by 40% when compared to placebo in patients with moderate-to-severe nonproliferative diabetic retinopathy (DR).

The 3-year phase 3 clinical trial study findings were published online in *Ophthalmology*. Vision loss, measured in the study as sustained moderate vision loss, occurred in only 5.5% of patients treated with ruboxistaurin versus 9.1% of patients treated with placebo, equaling a 40% relative risk reduction (*P*=.034) over 3 years. Vision loss was defined as a three-line loss on a standard eye chart that was sustained for at least 6 months.

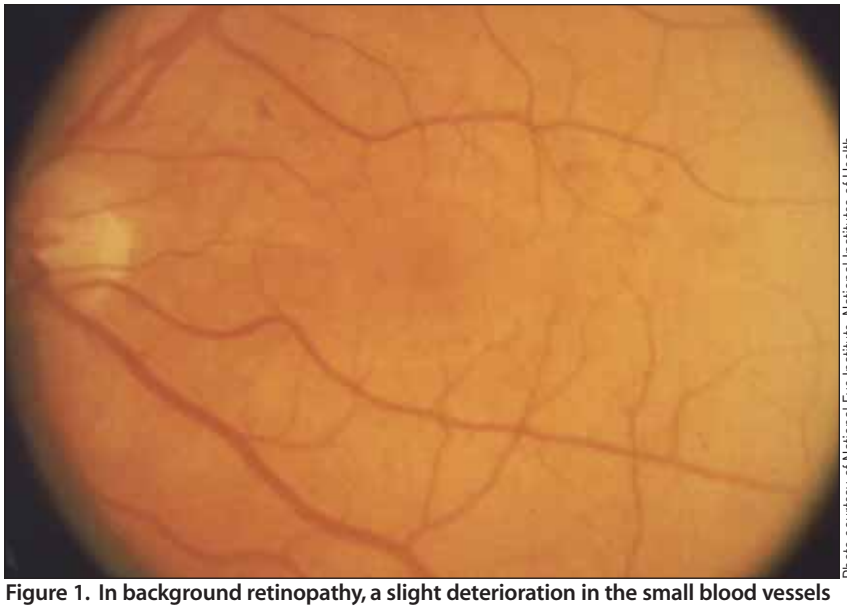

Photo courtesy of National Eye Institute, National Institutes of Health

Figure 1. In background retinopathy, a slight deterioration in the small blood vessels of the retina, portions of the vessels may swell and leak fluid into the surrounding retinal tissue.

PKC-DRS2 STUDY

This multicenter, 36-month, placebo-controlled, double-masked, phase 3 clinical trial, labeled protein kinase C-diabetic retinopathy study 2 (PKC-DRS2), involved 685 patients randomized at 70 clinical sites to either placebo (n=340) or 32 mg/day of ruboxistaurin (n=340). PKC-DRS2 examined whether ruboxistaurin could reduce the risk of long-term or sustained moderate vision loss caused by nonproliferative DR. Patients had moderate-to-severe nonproliferative diabetic retinopathy at the start of the study (Figure 1). Mean visual acuity was better in the ruboxistaurin- treated patients after 12 months. Baseline-to-endpoint visual improvement of ≥15 letters was more frequent

(4.9% vs 2.4%) and ≥15-letter worsening was less frequent (6.7% vs 9.9%) in ruboxistaurin-treated patients compared with placebo (*P*=.005). The beneficial effect of ruboxistaurin was not accompanied by a reduction in the progression of study patients from nonproliferative to proliferative DR.

Patient discontinuations due to adverse events were not statistically different between treatment groups (n=9, 2.6% placebo; n=16, 4.6% ruboxistaurin), according to a news release. There were 36 patient deaths (n=22, 6.5% placebo; n=14, 4.1% ruboxistaurin), none of which was considered by the investigator or sponsor to be related to study drug. There was no consistent pattern of adverse events to suggest a causal relationship between ruboxistaurin and any spontaneously reported adverse event.

PKC beta is a naturally occurring enzyme that has been linked to the development of DR.

Ruboxistaurin is an investigational therapy for the treatment of moderate-to-severe nonproliferative DR. It works by limiting the overactivation of protein kinase C beta, a naturally occurring enzyme that has been linked to the development of DR. It is the first of a new class of compounds being investigated for the treatment of moderate-to-severe nonproliferative DR.

Lilly submitted a new drug application to the US Food and Drug Administration (FDA) for approval of ruboxistaurin for the treatment of moderate-to-severe nonproliferative DR in February 2006. Lilly received an approvable letter from the FDA in August 2006. The FDA has indicated it will require efficacy data from an additional phase 3 study before it will consider approving the molecule. Lilly has decided to appeal the FDA's decision and has recently begun discussions with the agency. ■

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Aiello LP et al for the PKC-DRS2 Group. Effect of ruboxistaurin on visual loss in patients with diabetic retinopathy: ruboxistaurin treatment of diabetic visual loss. *Ophthalmology*. Available online before print, at: www.ophsource.org/periodicals/ophtha/article/PIIS0161642006010335. Accessed on: Dec. 1, 2006.

PKC INHIBITION IN DIABETIC MICROVASCULAR COMPLICATIONS

BY AARON I. VINIK, MD, PHD, ASSOCIATE MEDICAL EDITOR

While the full understanding of what causes nerve damage in diabetes is incomplete, many models have been developed to try to explain the process.

What has emerged to be true is that the small blood vessels are functionally deranged, such that they do not perfuse the nerves as well as they should, causing damage to the endothelial lining. There is an imbalance between the forces that cause constriction and the forces that cause dilatation of the vessels, so that the delivery of fuel and nutrients to the nerve is compromised.

We know that with oxidative stress comes the activation of the beta-2 form of protein kinase C (PKC). We have also found that a major stimulus is diacylglycerol. So now we recognize that damage cannot only be done from hyperglycemia, but it can also be from disturbed lipid metabolism and through the fatty acid diacylglycerol pathway that is activating PKC.

PKC overactivity has been shown in animal models to increase the leakiness of blood vessels and compromise their function in relationship to providing nutrients to nerves.

What makes the PKC model attractive is that in the nerve if there is overactivity of PKC, it may be possible to inhibit it distally in the pathway. Hyperglycemia and fat breakdown are proximal in the pathway, going through either direct activation of PKC or through the oxidative/nitrosative stress pathway and they have to funnel through PKC. If PKC is blocked, irrespective of what happens proximally, you can effectively abrogate this predisposition to impairment of blood flow to nerves.

If there is impairment of blood flow to the eye, this causes leaky blood vessels and hemorrhages in the exudates. This is a clear parallel between the microvascular insufficiency in the eye and in the nerve, but it is mediated very differently.

In the eye, the moment there is PKC activation, it stimulates the production of vascular endothelial growth factor (VEGF). VEGF itself stimulates the proliferation of new blood vessels in the eye. But if PKC could be blocked, VEGF would not be produced and there would be improvement in the eye. ■

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