

Emerging Treatments for Diabetic Retinopathy

A number of studies show future treatments can control DR and minimize progression.

BY LEAH D. FARR, ASSOCIATE EDITOR

Although current attempts to address diabetic retinopathy (DR) are aimed at preserving vision and reducing progression of the disease, researchers hope emerging treatments will do much more.

Currently, pharmacological and surgical methods such as renin-angiotensin system blockage or laser photocoagulation therapy rarely restore vision. Emerging breakthroughs in intravitreal injections, implants, and investigational systemic treatments, however, may provide patients with improved visual acuity while giving retinal specialists the ability to treat and halt disease progression at an earlier stage, said Andrew P. Schachat, MD, at the 2007 Hawaiian Eye Meeting in Koloa, Hawaii.¹

There are a number of targets to consider when looking to minimize a patient's risk of developing retinopathy. Aggressive management of glucose, blood pressure, weight, and lipids, may all help to reduce the development and progression of DR and especially diabetic macular edema (DME).^{2,3}

MANAGEMENT OF SYSTEMIC FACTORS

If you were to pick only one aspect of a diabetic patient's systemic care to single out, blood glucose levels are the most important, Dr. Schachat said. This is because there is approximately a 75% reduced risk in the long-term rates of DR progression or other microvascular diseases for patients who effectively manage their diabetes.

"Unfortunately, however, we've found that even patients with good metabolic control may still develop these diseases, so increasing our treatment options is crucial for the future success in the management of DR," Dr. Schachat said.

Blood pressure control is critical, as noted in data from the United Kingdom Prospective Diabetes Study (UKPDS) that showed a 34% reduction in the progression of retinopathy and a 47% reduction in deterioration of visual acuity⁴ in patients with better blood pressure control.

Additionally, "there are a number of ongoing studies that may give more information on diabetes control and the

minimization of retinopathy progression," Dr. Schachat said. "We have various clinical trials of [angiotensin-converting enzyme] ACE inhibitors among this population,⁵ and although retinopathy is not the primary endpoint of these studies, there will be some DR outcomes measured. There is also the Diabetic Retinopathy Candesartan Trials (DIRECT) which is examining angiotensin receptor blockers [ARBs]."⁶

Furthermore, accumulating evidence supports the idea that aggressive lipid control and treating exudates may be closely linked. Multiple observational studies are also examining what effects triglyceride and LDL-cholesterol lowering have in diabetic patients with microvascular complications. Small studies and case reports already suggest that this type of management will minimize progression of DR,⁷ Dr. Schachat said.

NOT AS EFFECTIVE AS NEEDED

Still, current treatments are not as effective as they could be, Dr. Schachat said. "Because of this, we are looking at new options, such as minimal-intensity laser photocoagulation, intravitreal injections, and systemic treatments.

"We are hearing a lot more about corticosteroids like triamcinolone, dexamethasone and fluocinolone acetonide for potential applications in DME. Hyaluronidase may safely dissolve the vitreous—which might clear vitreous hemorrhaging more quickly. And of course, we are hearing a lot about the anti-VEGF drugs pegaptanib [Macugen; OSI/Eyetech and Pfizer, both in New York, NY], ranibizumab [Lucentis; Genentech, San Francisco], bevacizumab [Avastin, Genentech].

Of several investigational treatments, Dr. Schachat's presentation focused mainly on ruboxistaurin (Eli Lilly and Company, Indianapolis) and its predecessor, midostaurin. Midostaurin (protein kinase C [PKC] 412) is a nonselective kinase inhibitor with potential applications for DME and proliferative DR.⁸ PKC regulates many functions including contractility, hemodynamics, cellular proliferation, and overactivation of protein kinase—which is involved in

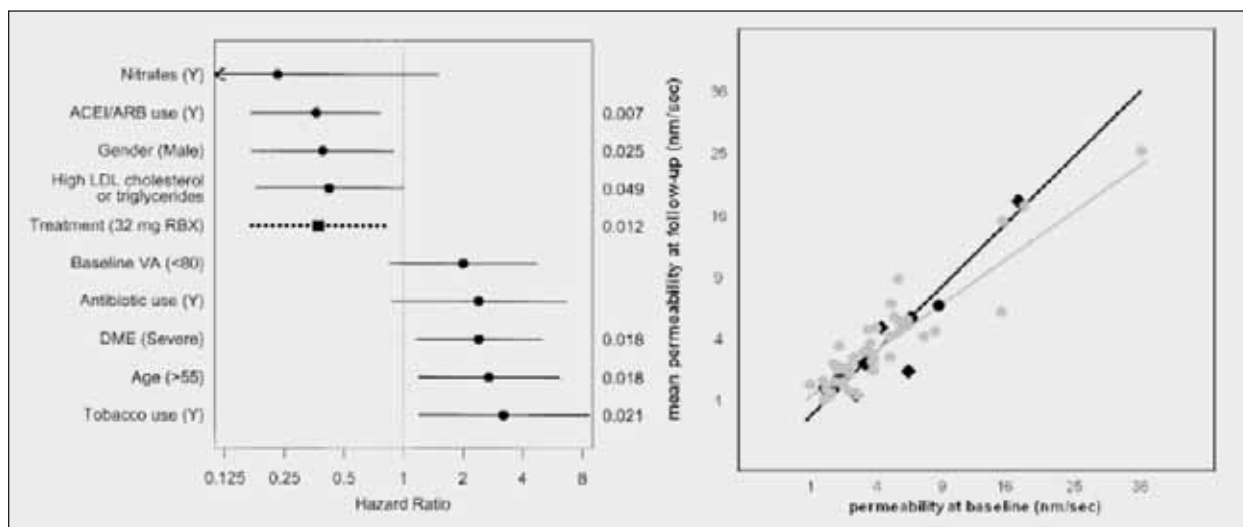


Figure 1. Ruboxistaurin reduced risk of moderate visual loss and retinal vascular leakage.

hyperglycemia-induced microvascular damage, increased retinal capillary permeability, and determines whether VEGF levels increase or decrease.

"We are finding that this predecessor drug reduces foveal thickness and improves visual acuity in DME," Dr. Schachat said. In controlled clinical trials, midostaurin showed some efficacy. "The problem with this daily oral drug was that there was nausea, vomiting, and occasional liver function abnormalities that increased in the larger dose groups."

These adverse events prevented further development, he said.

"This drug is a nonselective PKC inhibitor. If you block all the protein kinase Cs, it really is not surprising that you would have more systemic side effects," Dr. Schachat explained. Ruboxistaurin on the other hand, blocks one specific protein kinase C, and theoretically should have less adverse effects. This treatment is a once daily, oral therapy that could, if safe and effective, help patients with proliferative DR to preserve vision.⁹

"In two prospective clinical trials, the sponsors have found that ruboxistaurin is well tolerated and does reduce the risk of vision loss," Dr. Schachat said (Figure 1). There was a 45% reduction in sustained moderate vision loss in patients treated with ruboxistaurin. From baseline to endpoint, these patients also lost on average one letter, versus three letters for the placebo group. Twice as many treated patients gained ≥ 2 or more lines of vision, and visual acuity decline (≥ 3 line loss) was reduced by 30%. Additionally, clinically significant DME progression was reduced in treated patients as well as a need for laser treatments."

The US Food and Drug Administration has granted an

approvable letter for this treatment; however, another trial is required before final approval.¹⁰

It is now better understood that systemic and investigational intravitreal injections carry some risk but appear to improve vision, he said. As new methods of treatment are discovered, doctors should continue to aggressively control glycemia and blood pressure.

"Lipid control, ACE inhibitors, laser photocoagulation and vitrectomy may give additional benefits as we wait for the investigational treatments coming down the pipeline," he concluded. ■

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