

# Experimental treatment for diabetic macular oedema shows promise

## Nadja Geipert

A DAILY dose of the protein kinase C (PKC) inhibitor ruboxistaurin (Lilly) significantly slowed vision loss in patients with diabetic macular oedema, according to the results of a phase III, multi-centre, randomised, clinical trial. However, the medication failed to slow progression of diabetic retinopathy in patients at the non-proliferative stage, which was the primary endpoint of the study.

The study involved 170 men and 82 women ranging in age from 20 to 84 years diagnosed with diabetes I or II and moderately severe to very severe non-proliferative retinopathy. The patients were randomised into four treatment groups: one placebo group and three groups of patients who received 8, 16 or 32 mg per day of the drug orally for at least three years.

The investigators performed detailed eye examinations including visual acuity tests every three months. Retinopathy progression was defined, using ETDRS criteria, as a three-step or greater worsening of the condition if the patients had two eyes affected, or a two-step worsening if one eye was affected. Patients who required the application of scatter photocoagulation were also considered to have progression. Moderate vision loss was defined as a doubling of the visual angle.

## Slower vision loss but retinopathy unabated

The researchers found no statistically significant difference in retinopathy progression between the treatment groups and placebo group. However, there was a significant slowing of moderate vision loss in the group that

received 32 mg/ per day compared to the placebo group. This difference was greatest in patients who had macular oedema. Only 11% in the 32 mg group experienced a doubling of the visual angle compared to 20% in the placebo group.

The experimental drug was well tolerated, with no side effects reported.

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“In a nutshell, ruboxistaurin had no effect on the progression of diabetic retinopathy, but there was an intriguing trend that the patients who were on ruboxistaurin at the highest dosage had decreased visual loss. This difference was most significant for those patients who had macular oedema at baseline,” said Lawrence Chong MD, associate professor of clinical ophthalmology at the University of Southern California, Keck School of Medicine and chief of retina service at the Doheny Eye Institute, and one of the study’s investigators.

“I think there is definitely promise with this treatment approach. Laser only stabilises the condition, but people with macular oedema still go on to lose their vision. The only other treatment for macular oedema is having steroids injected in the eye, which is not a trivial procedure. In

addition, the effectiveness of steroids is still unproven,” said Emily Chew, MD, from the division of epidemiology and clinical research at the (US) National Eye Institute in Bethesda, Maryland. She was not an investigator on the study.

Laser treatment has become a highly effective standard of care for treating diabetic retinopathy

and preventing vision loss, however; this is not true for macular oedema, according to Dr Chew.

The experimental agent ruboxistaurin selectively inhibits the enzyme PKC -isoform, which belongs to a family of thirteen enzymes called PKC. Elevated blood glucose levels activate PKC. A particular clinical interest in PKC -isoform developed after several animal studies demonstrated that it causes blood vessels to become leaky and is involved in the formation of new ones—both hallmarks of diabetic vascular complications.

Combined, these clinical observations justified making the enzyme a primary target for the treatment of the three main diabetic microvascular complications: retinopathy, neuropathy and nephropathy.

## Agent has low toxicity

Ruboxistaurin’s apparent lack of toxicity is important, according to Dr Chong and is attributed to its selectivity in targeting only a single isoform of the thirteen PCK enzyme sub-types. Ruboxistaurin’s apparent efficacy of preventing vision loss in macular oedema patients gives hope that it may be effective in treating diabetics with this particular eye condition, according to Dr Chong.

A study that specifically evaluates the drug’s effectiveness in treating macular oedema has already been completed and has been submitted for publication, according to Dr Chong, who was an investigator on that study as well but could not comment on its results. Other NEI studies with the drug are ongoing.

The drug’s maker Eli Lilly has not given up on ruboxistaurin for the treatment of retinopathy. Last August, the company stated in a press release that the results of another ruboxistaurin retinopathy phase III trial yielded results that justified submitting the drug for FDA-approval for the treatment of diabetic retinopathy.

In the same statement, Lilly also announced that two Phase III trials that investigated the drug’s potential for the treatment of neuropathy did not show a significant effect. In addition, during the annual meeting of the American Diabetes Association, another study showed that ruboxistaurin seemed to slow down nephropathy. If approved, ruboxistaurin would be the first oral medication for the treatment of diabetic retinopathy.

“This might take us into a new way of treating diabetes,” said Dr Chong.

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