New therapies offer hope for treatment of diabetic retinopathy

Dermot McGrath in Sao Paulo

THE DEVELOPMENT of new pharmacologic compounds such as somatostatin analogues, protein kinase C inhibitors and VEGF inhibitors offers hope for the future treatment of diabetic retinopathy, according to Francesco Bandello, MD.

“We are still waiting on the results of current trials involving many of these compounds, but there is definite ground for optimism that the next few years will see the arrival of new therapeutic approaches in the care of diabetic eye disease,” said Dr Bandello, speaking at a special European Retina, Macula and Vitreous Society (EURETINA) session held during the World Ophthalmology Congress.

“One potential fruitful avenue of exploration may be ruboxistaurin (Arxxant™, EliLilly), which works by inhibiting PKC beta, an enzyme implicated in the underlying process of microvascular damage. Dr Bandello said that initial clinical trial data suggests that ruboxistaurin is safe and is well tolerated in humans and may have beneficial effects in preventing visual loss from diabetic retinopathy.

“The frequency of unsatisfactory outcomes and side effects following laser photocoagulation has sparked interest in other types of treatment, in particular those based on the biochemical processes underlying the pathogenesis of diabetic retinopathy,” he said.

Promising anti-VEGF agents

Compounds that work by inhibiting vascular endothelial growth factor (VEGF), currently causing a lot of excitement in the treatment of macular degeneration, may also help with diabetic eye disease. Dr Bandello reported that phase II trials of pegaptanib sodium injection (Macugen®, Eyetech Pharmaceuticals, Inc) have demonstrated positive visual and anatomical outcomes. Researchers noted that a statistically significant number of patients treated with Macugen showed a reversal of capillary nonpermeability, retinal ischemia and neovascularisation—all important signs of diabetic retinopathy.

Researchers conducted a retrospective analysis of 69 patients within the Macugen 0.3mg and usual care arms of a wider diabetic macular oedema study who had recognised and gradable diabetic retinopathy at both baseline and week 36. Patients treated with Macugen 0.3mg therapy showed an improvement in the ETDRS diabetic retinopathy severity scale, a standard for monitoring the progression of retinopathy. At week 36, 11 of the 39 Macugen patients (28.2%) showed improvement of greater than or equal to one step versus four of 30 in the sham group (13.3%). In addition, a higher proportion of Macugen patients (five of 39, 12.8%) showed an improvement of greater than two steps at week 36 compared to sham group (one of 30, 3.3%).

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In another analysis of all patients treated with Macugen, (0.3mg, 1mg, 3mg doses), 13 were noted to have retinal neovascularisation upon their baseline examination. Of these 13 patients, regression in retinal neovascularisation was noted at week 36 in eight (62%), while no regression of neovascularisation was recognised in sham patients who had neovascularisation at baseline. Recurrence of neovascularisation followed discontinuation of Macugen in three of the eight subjects (38%) at week 52.

The anti-VEGF compound, ranibizumab (Lucentis®, Genentech/Novartis), also holds promise as an effective pharmacologic treatment for diabetic-related ocular disorders, said Dr Bandello, with the results of initial clinical trials expected later this year.

PKC inhibitors also show promise

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Dr Bandello cited the results of the Protein Kinase C Diabetic Retinopathy Study (PKC-DRS), which was completed in 2003. This phase II/III randomised, multidose, multicentre trial enrolled 617 patients in order to assess the effect of ruboxistaurin in slowing the progression of nonproliferative diabetic retinopathy (NPDR) or vision loss, including cases of moderate to severe NPDR without prior treatment for proliferative retinopathy.

The primary end point was either progression of diabetic retinopathy or photocoagulation. Although the study failed to show any significant effect on these primary end points, there was a 32% risk reduction (P = .029) of moderate visual loss in patients treated with 32.0mg ruboxistaurin compared with placebo.

There was also a trend for moderate visual loss sustained over six months to be reduced in patients taking the highest dose of ruboxistaurin. Patients with higher levels of retinopathy at entry (DR level = 53) had more benefit from the highest dosage, compared with patients with less severe retinopathy at baseline (DR level = 47). Patients with higher levels of diabetic macular oedema at baseline also had a higher benefit from the high-dose ruboxistaurin treatment with regard to sustained moderate visual loss.

Dr Bandello noted that another PKC inhibitor, PKC412 (Novartis), has also shown some potential as a treatment to arrest vision loss in diabetic patients, although he said that concerns about the side effects associated with this compound may ultimately limit its effectiveness as a systemic therapy.

Another potentially effective therapy in the pipeline is O cetrotide acetate (Sandostatin/LAR®, N owartis), a somatostatin analogue. Research with somatostatin analogues suggests that the compound is a potent modulator of growth factor activity and retinal endothelial cell proliferation in diabetic retinopathy.

Dr Bandello said that a huge amount of research is currently being conducted in the field of diabetic retinopathy.

“We can look forward to more effective therapeutic approaches as the biochemical processes underlying the disease become increasingly understood.”

Emphasising the rapid pace of discovery in this domain, Dr Bandello pointed to the recent publication of a paper implicating erythropoietin, a protein hormone whose main function is to stimulate formation of red blood cells, as a possible contributor to diabetic retinopathy.

The study by researchers at Kyoto University and published in the New England Journal of Medicine in 2005 found excessively high levels of erythropoietin in the eye fluid of patients with diabetic retinopathy. The 73 patients in the study, all of whom had diabetes, were in the last stages of retinopathy. Levels of erythropoietin were more than 12 times higher in their eyes than in the eyes of 71 people without diabetes whose levels were also measured.

“Because there is a considerable overlap among different pathways in the pathogenesis of the eye, combination therapies may ultimately prove to be more effective than monotherapy,” concluded Dr Bandello.

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