Diana V Do

Evidence builds for anti-VEGF treatment for diabetic retinopathy, macular oedema

Drugs effective short-term as primary and adjuvant therapy; long-term tests in progress

Howard Larkin
in Las Vegas

DRUGS blocking vascular endothelial growth factor (VEGF) may soon play a central role in preventing or even restoring vision loss due to diabetic eye disease, several recent studies suggest.

While laser treatment can slow long-term loss of visual field and acuity, it is frequently at the cost of some immediate vision loss, noted Victor H Gonzalez MD, University of Texas, US.

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> **Victor H Gonzalez MD**

"Patients complain that when they get lasered they lose their peripheral vision or their night vision, and that is obviously what we are trying to avoid. That is why we continue to look for better treatments, including pharmacological interventions," said Dr Gonzalez, who presented a Phase 2 clinical trial of pegaptanib (Macugen, Pfizer) for treating diabetic retinopathy and macular oedema at the annual meeting of the American Academy of Ophthalmology.

In the Phase 2 study, 172 patients at 39 centres received intravitreal injections of 0.3mg pegaptanib every six weeks for 12 to 30 weeks. Treated patients showed better visual acuity, greater reductions in retinal thickness, and reduced need for photo-coagulation to control retinopathy and oedema than sham treated eyes one year after the last injection. At week 36, 34 per cent of treated eyes gained 10 or more letters in visual acuity compared with 10 per cent of untreated eyes, and 18 per cent of treated eyes gained 15 or more letters compared with seven per cent of untreated eyes.

Mean central retinal thickness declined 68 microns among treated eyes compared with four microns for sham eyes, and 49 per cent of treated eyes showed decreases of 75 microns or more compared with 19 per cent of sham eyes.

At week 82, one year after the last possible injection, the pegaptanib-treated eyes showed an average reduction in central retinal thickness of 122 microns compared with 49 microns for sham eyes. Eyes treated with pegaptanib also required photocoagulation less frequently than sham eyes during the 52 weeks of follow-up after the last injection. All injections appeared well tolerated, though one case of endophthalmitis was reported in 652 injections.

All 10 patients treated by Dr Gonzales showed regression of neovascularisation at six weeks. Eight of 13 eyes treated with pegaptanib showed regressed neovascularisation and/or reduced leakage compared with no improvement in seven sham or fellow eyes one year after injections.

He noted that all the microaneurysms and haemorrhages in eyes he treated improved at week six. Pegaptanib-treated eyes also retained visual acuity and showed more neovascular regression than eyes treated with pan retinal photocoagulation (PRP). At the end of the study period, pegaptanib treated eyes still had better visual acuity, reduced retinal thickness and none required photocoagulation.

How lasting are treatment effects?

However, Dr Gonzalez noted that about 50 per cent of the eyes in the larger study group showed renewed neovascularisation one year after the last injection, indicating a possible need for ongoing injections. The study protocol has been extended to examine longer-term treatment effects. Asked if pegaptanib's limited range of anti-VEGF activity might limit use compared with wider-spectrum alternatives, Dr Gonzalez replied that the clinical results are good, the drug well tolerated, and investigations should continue. He believes it could reduce the need for PRP to treat diabetic retinopathy, and reduce the risk of collateral damage associated with laser surgery. Pegaptanib is now in Phase 3 trials for treating diabetic macular oedema.

Ranibizumab (Lucentis, Genentech) is also demonstrating effectiveness in controlling diabetic macular oedema. A study of 20 patients receiving intravitreal injections of 0.5mg ranibizumab at baseline and at months one, two, four, and six showed a significant reduction in excess foveal thickness at seven months. At the same time, the mean visual acuity improved from 28.1 to 40.4 letters, or 20/80 to 20/40.

The intraocular injections were well tolerated and were not associated with any local or systemic adverse events, according to a poster presented by Diana V Do MD, assistant professor of ophthalmology at the Johns Hopkins Wilmer Eye Institute, Baltimore, US. The report is based on a Phase 1 trial of ranibizumab for diabetic macular oedema. A multicenter phase 2 trial, the READ 2 Study, is currently under way to compare ranibizumab vs. focal laser photocoagulation vs. a combination of ranibizumab and focal laser for diabetic macular oedema. The drug is approved for treating age-related macular oedema in the US and Switzerland, and has been recommended for approval by an EU scientific review panel.

As it has with age-related macular oedema, bevacizumab has already emerged as an anti-VEGF alternative for treating diabetic retinopathy and macular oedema. "Avastin is much more available and affordable than Macugen or Lucentis," noted Lihteh Wu MD, of Instituto De Cirugia Ocular, Costa Rica. Dr Wu is a member of the Pan-American Collaborative Retina Study Group (PACORES), which examines retina issues in countries throughout Central and South America.

Bevacizumab, which is FDA approved for treating colon and lung cancer, is widely used to treat a range of ocular conditions, especially in less-affluent countries. But concerns remain, particularly since patients using the drugs in chemotherapy are at increased risk for cardiovascular and stroke events. However, these risks are presumed to be reduced at the much lower doses used for intravitreal injections, and early studies appear to confirm that, according to Dr Wu.

At the AAO meeting Dr Wu reported that no systemic side effects were reported in 1,903 injections delivered to 1,475 patients in eight countries during a four-month follow-up. Endophthalmitis was reported in four cases. Bevacizumab in 1.25mg and 2.5mg injections appears to be safe in the short term, the group concluded. The finding is consistent with several other early safety studies. Bevacizumab is in clinical trials for treatment of diabetic macular oedema and retinopathy at centres in Iran and Mexico.

J Fernando Arevalo MD, of Clinica Oftalalmologica Centro, Caracas, Venezuela, presented another study conducted by PACORES that demonstrated bevacizumab's effectiveness for treating diabetic macular oedema. In a retrospective review of 78 eyes in 64 consecutive patients at centres in five countries with a mean follow-up of 6.9 months, patients treated with intravitreal injections of 1.25 or 2.5mg bevacizumab showed an improvement in best corrected visual acuity from logMAR -0.87 to -0.6, a result that was statistically significant with nearly half an improvement of two lines or more. Mean central macular thickness as measured by OCT also decreased significantly, from an average of 391 microns to 267 microns.

Dr Arevalo noted that many patients required additional injections to maintain gains, generally after about 12 weeks. Also, some patients did not respond to bevacizumab injections. Therefore, he believes that while anti-VEGF compounds show great promise, they may be best used in conjunction with photocoagulation to extend the gains. Combining anti-VEGF with other pharmaceutical approaches, such as steroids, might also be useful.

Useful for proliferative diabetic retinopathy

Bevacizumab may be a useful adjunct to vitreal surgery for proliferative diabetic retinopathy, according to a report by Robert L Avery MD, of California Retina Associates, Santa Barbara, US. In a retrospective review of 45 consecutive patients treated with intravitreal bevacizumab, angiography showed a dramatic reduction or complete resolution of neovascularisation in all cases. Bleeding during cutting and removal of fibrovascular tissues during vitrectomy was greatly reduced.

"When the vessels don't bleed that makes for an easier case," commented Dr Avery.

He said clinical experience suggested that surgery within seven days of the bevacizumab injection produced the best results. He also stressed the need for additional research to determine if the process has any impact on epithelial cells and other tissues over the long term.

Combining anti-VEGF with other therapies may hold the most promise, Dr Arevalo emphasised. Photocoagulation, vitreal surgery, steroids, RNA treatments that shut down VEGF production and implantable devices that could minimise the need for frequent intravitreal injections are all likely to play a role. "We may discover there are synergies because the different treatments attack the disease at different stages in the process. Together they may be more effective than alone."

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