Pilot studies suggest anti-VEGF Avastin may be effective for neovascular glaucoma

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in Las Vegas

IRIS neovascularisation and neovascular glaucoma can be added to the growing list of ocular diseases that may be treated or prevented by drugs targeting vascular endothelial growth factor (VEGF).

Two retrospective pilot studies reported at the annual meeting of the American Academy of Ophthalmology suggest that bevacizumab (Avastin, Genentech) may revolutionise neovascular glaucoma treatment in the same way that anti-VEGF agents, including ranibizumab (Lucentis, Genentech) and pegaptanib (Macugen, Pfizer), have for age-related macular degeneration – and promise to for diabetic retinopathy. As with these other vascular proliferative ocular diseases, bevacizumab appears to block or even reverse formation of abnormal blood vessels that cause neovascular glaucoma, even in advanced cases that have not responded to existing treatments.

In one study of 16 eyes in 15 patients with active neovascular glaucoma, intracameral injections of 1.25mg of bevacizumab dramatically reversed iris neovascularisation in all patients within 21 days, and led to complete resolution of glaucoma symptoms in half of them. While some subjects required a second injection and two experienced recurrence of iris neovascularisation, most participants’ intraocular pressure and vision improved within one week, said Kakkarla V Chalam, MD, PhD, professor and chairman of ophthalmology at the University of Florida, Jacksonville, US.

In a second, unrelated study, none of 35 patients with ischemic central retinal vein occlusion treated with intravitreal injections of 1.25mg of bevacizumab developed neovascular glaucoma during a six-month follow-up period, and on average saw significant reduction in macular oedema. Without treatment, one-third of patients with this condition would be expected to progress to neovascular glaucoma, typically within two to four months of the occlusion, said Gregory F Kozielec MD, of the Retina Institute of Texas, Dallas, US. Bevacizumab may have prevented this progression, he concluded.

As with studies of anti-VEGF treatments for other ocular conditions, no significant ocular or systemic complications were noted in these studies. However, both presenters emphasised the preliminary nature of their findings, which were based on retrospective analysis of interventional treatment, in some cases with patients who had failed other treatment regimens. Both authors called for controlled prospective trials to establish long-term safety and efficacy, and establish dosing guidelines.

Might anti-VEGF treatment replace PRP in the treatment of iris neovascularisation?

It is well documented that retinal tissue produces VEGF in response to the hypoxia caused by disruption of its blood supply. VEGF is physiologically functional in that it promotes repair of damaged blood vessels to restore blood flow. But it is also implicated in maladaptive physiological processes, including abnormal blood vessel growth in healthy tissues, vessel growth to support cancers and other tumours, and increased permeability of blood vessels, leading to fluid leakage and haemorrhage. Excessive production of VEGF by ischemic retina in patients with an ischemic central retinal vein occlusion or advanced diabetic retinopathy is believed to be the factor that often induces iris neovascularisation in those conditions. Unchecked, iris neovascularisation often progresses to form a fibrovascular membrane in the chamber angle that impedes aqueous outflow, and then that membrane can contract, resulting in severe secondary angle closure glaucoma.

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Kakkarla V Chalam, MD, PhD

Currently, eyes with iris neovascularisation are treated by performing panretinal photocoagulation (PRP) to destroy peripheral retinal tissue and thereby to reduce the production of VEGF. Such treatment often results in regression of the iris neovascularisation, but at a cost of reduced peripheral visual field. If PRP is performed before iris neovascularisation reaches the drainage angle, neovascular glaucoma is prevented. If a fibrovascular membrane has grown over the drainage angle prior to PRP treatment, the treatment will usually cause the vessels in the membrane toatrophy, leaving a transparent membrane that partially impedes aqueous outflow, but at least preventing the secondary angle closure component of neovascular glaucoma.

In closed-angle cases, surgical interventions, such as filtration procedures and shunts to increase aqueous outflow, or ablation of the ciliary processes to reduce aqueous production, are nearly always required to control intraocular pressure in order to prevent visual deterioration, pain and nausea, and are not successful in a substantial minority of patients.

The studies presented by Chalam and by Kozielec are a natural extension of the work of Philip Rosenfeld, MD, PhD, of the Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, who pioneered the off-label use of Bevacizumab (Avastin) in the treatment of neovascular AMD and other forms of ocular neovascularisation.

If anti-VEGF treatment proves as effective and safe for the long term for neovascular glaucoma as it has for neovascular AMD, it might replace PRP, noted Paul F Palmberg, MD, PhD, professor of ophthalmology at the University of Miami, a symposium panellist at the AAO meeting. Anti-VEGF treatment may be more successful than PRP, since it sequesters VEGF produced by all of the ischemic retina, rather than just those portions of peripheral retina sacrificed to PRP treatment, and unlike PRP anti-VEGF therapy does not destroy retinal tissue and its function. Such a shift in treatment would parallel the move away from macular laser treatments in favour of anti-VEGF treatment in AMD. However, longer-term, prospective studies are needed to measure the eventual outcome of such treatment before it replaces PRP.

In Dr Chalam’s study, three-quarters of the patients had failed PRP therapy, and the procedure could not be performed in the rest because opacities made it impossible to visualise or use lasers to treat the retina. Bevacizumab was used off-label in an attempt to rescue these patients, who otherwise faced a poor prognosis.

The results were dramatic, and in many cases, almost immediate. Of the first 12 patients, four, or one-third, showed dramatic regression of iris neovascularisation in one week; nine, or three-quarters, in two weeks; and all 12 by three weeks. In 15 of the 16 patients studied, iris neovascularisation disappeared completely, though two patients saw recurrences and a few patients required a second injection after one month.

“It was exciting to get rid of the neovascularisation,” Dr Chalam said.

Intraocular pressure was successfully controlled in two-thirds of patients at less than 22 mmHg, reaching a mean of 17.5 mmHg after treatment. The degree of IOP reduction correlated to the initial degree of iris neovascularisation, Dr Chalam reported.

“Bevacizumab, an anti-VEGF agent, is an extremely effective medication for treating neovascular glaucoma, and aids in controlling IOP” he concluded.

Patients in Dr Kozielec’s study also achieved good IOP control, reaching a mean of 18.7 mmHg at six months. Baseline central retinal vein occlusion was confirmed by angiography in all 35 participants, and checked monthly over the six-month study period. All participants also received monthly angle exams by gonioscopy, and retinal thickness measured by OCT. Patients received an initial injection of bevacizumab, and a follow-up injection at one month at the discretion of the clinician based on disease progress. In all, 35 injections were delivered.

At the end of six months, gonioscopic exams showed no evidence of iris neovascularisation in any patient, and no patient progressed to neovascular glaucoma. Mean central foveal thickness as measured by OCT also dropped from 661 microns at the outset to 352 after six months, indicating a reduction in macular oedema. These results were achieved with no PRP treatment, but with referral to primary care physicians for treatment of systemic conditions, including hypertension (80 per cent of sample) and diabetes mellitus (42 per cent of sample).

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