



Evangelos Gragoudas

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PATIENTS with neovascular age-related macular degeneration treated with pegaptanib (Macugen, Pfizer/Eyetech) showed clinically significant improvements regardless of angiographic subtype, lesion size, or initial level of visual acuity, according to two large multicentre randomised clinical trials.

The two concurrent clinical trials, known collectively as the VEGF Inhibition Study in Ocular Neovascularisation (VISION), enrolled patients in 117 sites in the United States, Canada, Europe, Israel, Australia and South America. The protocol randomised patients to receive intravitreal injections of pegaptanib ranging from 0.3 mg to 3.0 mg or a placebo. Patients received injections in one eye every six weeks over a period of 48 weeks.

"The VISION study results are very encouraging for the many patients with an urgent medical need who have been waiting for a new, safe and effective neovascular AMD therapy," said lead study author Evangelos Gragoudas MD, Director of the Retina Service at the Massachusetts Eye and Ear Infirmary and professor of ophthalmology at Harvard Medical School.

The researchers observed a reduced risk of visual-acuity loss

VEGF inhibitor shows benefit across AMD sub-types in large trials

as early as six weeks into the trial with all doses of pegaptanib. The benefit increased through the 54-week studies. Patients on active treatment had less chance of moderate or severe vision loss. The treatment reduced the risk of progression to legal blindness and promoted stability of vision. In a few cases, patients showed

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improvements in vision.

Among patients receiving the 0.3 mg injection, 70% lost fewer than 15 letters of visual acuity, compared with 55% among those receiving the sham injection.

Those patients also saw a reduction in the risk of severe loss of visual acuity (loss of 30 letters or more), 10% for those on active treatment, compared with a 22% risk for those on placebo. Moreover, 33% of those on the 0.3 mg regime maintained or gained visual acuity, compared with 23% of those on placebo. All

of the differences were highly statistically significant. There did not appear to be a response favouring the higher dose of pegaptanib.

Patients enrolled in the trial were all 50 years of age or older and had subfoveal choroidal neovascularisation caused by AMD. Enrollment criteria required a range of best-corrected visual acuity of 20/40 to 20/320 in the study eye and of 20/800 or better in the other eye.

Reductions in lesion size and leakage

Masked angiographic evaluations indicated reductions in the growth of the total size of lesions or of choroidal neovascularisation and in the severity of leakage. The researchers note a caveat, that these quantitative findings may have been confounded by changes in vascular permeability resulting from the treatment. Reduction in vascular permeability is the putative mechanism of action of the anti-VEGF aptamer.

Patients received up to nine injections over the course of the studies. The per-injection rate of endophthalmitis of 0.16% was consistent with that seen in other studies involving intravitreal injection of different drugs. The rates of retinal detachment and of traumatic lens injury, 0.08% and 0.07% were also not beyond what would be expected.

However, because multiple injections were required, the risk of endophthalmitis during the first year was 1.3%. The risk of endophthalmitis for cataract surgery, in contrast, runs from 0.06% to 0.4%. Accordingly, the researchers caution treating ophthalmologists to adhere carefully to an appropriate aseptic

technique for each injection. They also recommend monitoring patients closely after each injection and educating patients regarding endophthalmitis symptoms.

The researchers also note that current results only cover one year, and that longer term studies will be required to evaluate the effect of treatment on the course of the disease. They are hopeful that the validation of aptamer-based therapy suggested in these studies could also offer opportunities to treat other vascular eye diseases including diabetic retinopathy and retinal-vein occlusion.

"Macugen is the first anti-angiogenic treatment approved in ophthalmology and represents the beginning of a new era. The anti-angiogenic approach specifically addresses, for the first time, an underlying cause of blindness in age-related macular degeneration. Anti-angiogenesis has evolved from theory to therapy," said Judah Folkman MD, the pioneering scientist who first proposed antiangiogenic treatment strategies decades ago.

Results may improve with longer treatment

Steven D. Schwartz MD, Chief, Retina Division, Associate Professor of Ophthalmology Jules Stein Eye Institute presented two year data at last year's meeting of the American Academy of Ophthalmology. He reported that vision preservation continued during the second year for patients who continued treatment. In fact, it was better than in those treated for one year. Those treated for two years had a 45% treatment benefit over standard care, a statistically significant difference.

In an editorial accompanying the New England Journal of Medicine publication of the results, Frederick L. Ferris MD, director of the US National Eye Institute comments that the magnitude of the effect reported for Macugen in these studies, where only 10% of patients saw improvement in vision, is similar to that seen with photodynamic therapy.

But he concludes that having a second treatment approach offers the opportunity to test combinations of treatments, which may improve outcomes.

"Although this treatment is not all that we would wish for, and although the mechanism of the treatment benefit remains unclear, the study by Gragoudas and colleagues marks the start of a new era in the treatment of age-related macular degeneration and other causes of ocular neovascularisation.... The hope is that it is the first step in the development of multiple effective treatments for neovascularisation, especially for treatments that can be used to prevent the occurrence of neovascularisation and its devastating complications," he notes.

Macugen also represents the first use of an aptamer in human medicine. Aptamers represent a new class of medicines and are composed of a single strand of nucleic acid that binds to and inhibits a particular target with high affinity, specificity and tolerability. Macugen was approved by the US Food and Drug Administration in December 2004.

The VISION study results and Dr Ferris's commentary appear in the New England Journal of Medicine (Dec 30 2004, Volume 351, No 27).

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