

Possible role for anti-angiogenic agent in VHL disease

Cheryl Guttman
in Fort Lauderdale



Michael Cusick

THE VEGF inhibitor pegaptanib sodium (Macugen™, Eyetech) may be useful in the treatment of patients with severe ocular symptoms of von Hippel-Lindau (VHL) disease, according to preliminary results of a study undertaken by investigators at the National Eye Institute

of the US National Institutes of Health.

In an open-label, prospective, non-randomised pilot study, two of five VHL patients treated with intravitreal injections of the anti-angiogenic agent had an amelioration of retinal haemangiomas and an improvement or stabilisation of their visual acuity, Michael Cusick MD told the annual meeting of the Association for Research in Vision and Ophthalmology.

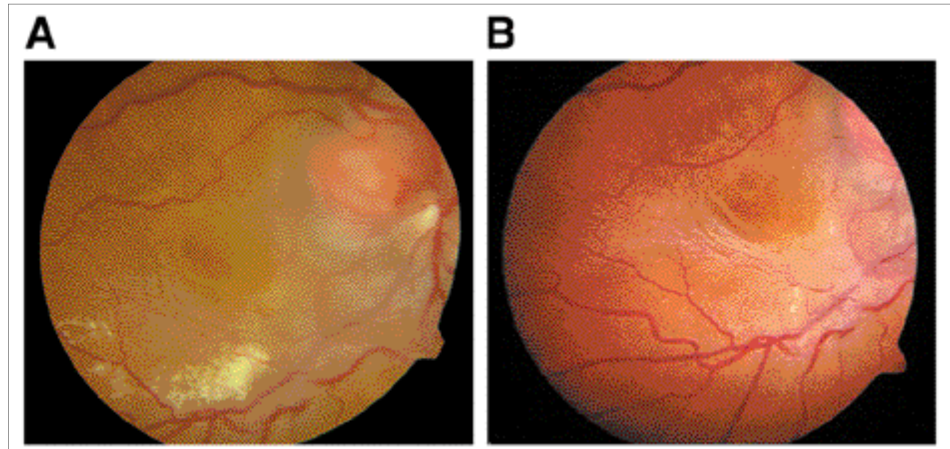
While three patients were unable to complete a planned course of six injections due to adverse events probably unrelated to their treatment injections, two patients who completed their treatment regimen achieved reduction in retinal hard exudate in their treated eye.

Furthermore, in one of the patients who completed their therapy ETDRS best-corrected acuity improved from 30 to 45 letters (20/250 to 20/100) and mean central (1.0 mm diameter) retinal thickness decreased from 204 microns to 175 microns after the six injections.

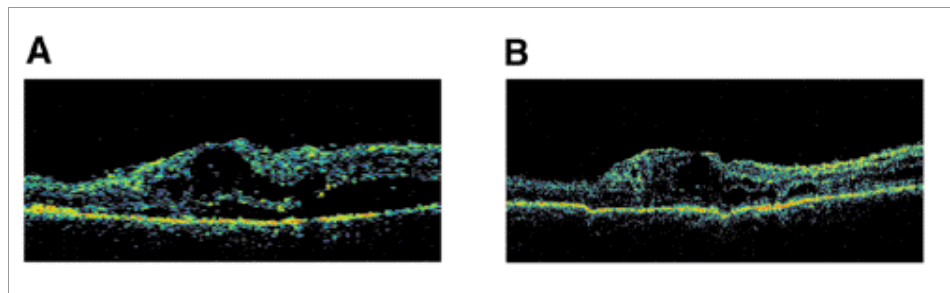
In the second patient, visual acuity remained stable at 20/60 while mean central retinal thickness fell from 613 microns at baseline to 426 microns 6 weeks after the first injection.

"These initial results suggest pegaptanib sodium injections may help decrease macular thickening and the retinal hard exudate that affect visual acuity in these eyes, perhaps through its ability to suppress vasopermeability. Therefore, it may have a role in intervention, especially if used in combination with another, possibly focal treatment modality. We will continue to follow these patients to further assess the effectiveness of the therapy," said Dr. Cusick.

The five patients in the study included four women and one man and ranged in age from 23 to 48 years old. All had retinal



Subject 1. A. Fundus photograph at baseline; B. Fundus photograph showing resolution of hard exudate after four injections of pegaptanib sodium.



Subject 1. A. OCT at baseline; B. OCT showing resolving cystoid oedema after four injections of pegaptanib sodium.

Courtesy/ Michael Cusick MD

followed for 8 and 12 months, respectively.

The three patients who were unable to complete treatment developed adverse events after receiving three injections, none of which was considered likely to be related to the study drug. Those events included increased macular leakage secondary to tumour growth in one eye with a worsening of BCVA by more than 15 letters, retinal detachment in an area of previous traction and increased posterior capsule opacification

There is some precedent for studying anti-VEGF therapy in eyes with severe ocular disease of VHL. Studies in eyes with choroidal neovascularisation due to age-related macular degeneration show pegaptanib sodium decreases macular thickening, and systemic anti-VEGF therapy using the VEGF inhibitor SU5416 has shown benefit in two published case reports of patients with ocular haemangiomas of VHL disease.

In one of those reports a patient with a large juxtapapillary lesion and demonstrated sustained improvements in BCVA, contrast sensitivity and visual field while receiving intermittent SU5416 therapy over 18 months. The second report described a patient with a large peripheral tumour treated for seven months who achieved reduction in cystoid macular oedema and improved visual acuity. Consistent with the NEI experience, neither of those patients showed any change in the size of the primary haemangiomas.

"There may be several reasons why the size of the retinal haemangiomas is not affected by the inhibition of VEGF by pegaptanib sodium. It is possible that the

retinal haemangiomas in this study are relatively mature, and less dependent upon VEGF for growth. Also, it is possible that the three minor isoforms of VEGF, which are not bound by pegaptanib sodium, play an important role in maintaining the tumour. Another issue that needs to be considered is whether prior vitrectomy affects the pharmacokinetics of intravitreally administered pegaptanib sodium. Available pharmacokinetics data are from studies performed in normal animal eyes, and vitrectomy may be associated with changes that affect drug dissolution and elimination," Dr. Cusick said.

Michael Cusick
mxc@nei.nih.gov

"Pegaptanib sodium injections may help decrease macular thickening and the retinal hard exudate that affect visual acuity in these eyes"

haemangiomas and decreased visual acuity secondary to macular oedema. Three eyes had juxtapapillary haemangiomas, while one had a peripheral lesion and the remaining eye had both juxtapapillary and peripheral tumours.

Only one patient with a juxtapapillary lesion had received no prior treatment. The rest had either undergone vitrectomy or multiple vitrectomies combined with laser photocoagulation either alone or with cryotherapy. Baseline best-corrected acuity ranged from 69 letters (20/40) to 18 letters (worse than 20/400). Mean macular thickness ranged from 165 to 645 microns at baseline, but was greater than 500 microns in three of the five eyes.

The treatment regimen consisted of intravitreal injections of pegaptanib sodium 3.0 mg/100 microlitres every six weeks over 30 weeks for up to six injections with follow-up to 12 months. Only two subjects received the full treatment course, and they have been

around a pseudophakic IOL.

Other adverse events included a 200 micron increase in macular thickness in one eye and a transient, post-injection decrease in IOP in one eye. Tumour size was unchanged, and there was minimal to no change in leakage on fluorescein angiography after administration of the drug.

The rationale for studying pegaptanib sodium as a treatment for ocular haemangiomas associated with VHL disease is based on the observation of increased VEGF expression in those tumours.

"VHL is an autosomal dominant disorder characterised by mutation and inactivation of both alleles of the gene for VHL protein. VHL protein is an important regulator of the degradation of hypoxia inducible factors, and in its absence, the hypoxia inducible factors become unregulated, and able to induce various angiogenic factors, including VEGF, in the presence of normal oxygen levels," Dr. Cusick explained.

VHL FAQ

Von Hippel-Lindau (VHL) is a genetic condition involving the abnormal growth of blood vessels in parts of the body that are particularly rich in blood vessels. It is caused by a flaw in one gene, the VHL gene, on the short arm of chromosome 3, which regulates cell growth. VHL occurs in every ethnic group, everywhere in the world. Researchers estimate that a new mutation, where no VHL has been in the family previously, occurs about once in 4,400,000 live births. Over all, one person in 32,000 in the world has VHL. Some 20% are new mutations and 80% are children of parents who themselves had VHL. Symptoms often become clinically significant in the teens or early adult years. However, 10% of patients have eye or adrenal problems before age 10, while a growing number of people may have no clinical problems until their 80's.