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Pegaptanib in Exudative Age-Related Macular Degeneration
A Viewpoint by Steven Schwartz

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Age-related macular degeneration (AMD) is the leading cause of new blindness in the developed world.[1] The incidence of AMD is rising faster than populations are aging and populations are aging dramatically. If this condition was an infection, it would be likened to a pandemic. The medical and socioeconomic impact is enormous. As patients lose central visual function, they have increasing difficulty with activities of daily life such as reading, walking, driving and difficulty recognising faces, food and medicines.[2] Quality of life is severely diminished and healthcare utilisation soars.[1] For example, patients with neovascular AMD have a higher incidence of falls and hip fractures than age-matched controls.[3]

AMD can be divided into atrophic (dry) and neovascular (wet) forms. While atrophic AMD accounts for the vast majority of cases, neovascular AMD accounts for 90% of cases of severe visual loss.[1] Up until the approval of pegaptanib (Macugen®)[1] for the treatment of neovascular AMD, few and limited treatments were available. The advent of pegaptanib treatment provides an effective and safely used treatment option where none existed previously. In other words, pegaptanib meets an enormous unmet medical need and, when used as demonstrated in the VISION (VEGF Inhibition Study In Ocular Neovascularisation) trial, should reduce dramatically visual loss from neovascular AMD.

In the 30 years since Folkman[4] first proposed the use of a specific antagonist of an angiogenic factor as strategy to treat disease, extensive evidence has developed validating his hypothesis. Chronic, intravenous, nonselective anti-vascular endothelial growth factor (VEGF) therapy is approved for a variety of solid tumours. Many human ocular diseases are characterised by neovascularisation and vascular leakage. VEGF levels have been shown to rise synchronously with these pathological new vessels and their leakage.[5] Animal data clearly demonstrate that disease states can be recapitulated by the introduction of VEGF into normal eyes, and that these pathological states are dependent on the presence of VEGF.[5] These data formed the basis for targeting VEGF in human ocular disease.

Rarely is the science behind a treatment so simple. In this case, it turns out that VEGF has many critical physiological functions governed by a variety of VEGF isoforms. The pathological functions of VEGF seem to be governed by a single isoform, the 165 isoform. Pegaptanib is a 28-base, ribonucleic acid aptamer covalently linked to two polyethylene glycol moieties. It was designed to specifically and selectively bind to only the 165 isoform of extracellular VEGF ($VEGF_{165}$). This selectivity and specificity may contribute to the extraordinary safety profile observed in the clinical trials. In fact, the safety profile of this drug is remarkably different from that of a nonselective VEGF inhibitor. The only safety issues of note seem to surround the delivery of the drug, the intravitreous injections, rather than any systemic or ocular drug-related effects. It is clear that the risk of infection, endophthalmitis, can be minimised by following the aseptic technique protocol developed during the VISION trial.

Chronic $VEGF_{165}$ suppression with intravitreous pegaptanib injections offers the hope of decreased visual loss from neovascular AMD. In a subset of patients, most likely those in whom treatment is initiated early on, vision can improve. Perhaps more importantly, the risk of severe visual loss is substantially reduced. This therapy offers an evidence-based treatment option where none existed previously. It marks the beginning of the pharmacotherapuetic era for the treatment of AMD and may be analogous to the shift we observed in oncology from a largely surgical to largely pharmacological treatment paradigm. ▲

1 The use of trade names is for product identification purposes only and does not imply endorsement.

References

1. Schwartz SD. Age-related maculopathy and age-related macular degeneration. In: Silverstone B, Lang MA, Rosenthal BP, et al., editors. The Lighthouse handbook on vision impairment and vision rehabilitation. New York: Lighthouse, 2000
2. Dong LM, Childs AL, Mangione CM, et al., for the Submacular Surgery Trials Research Group. Health- and vision-related quality of life among patients with choroidal neovascularization secondary to age-related macular degeneration at enrollment in randomized trials of submacular surgery: SST report no. 4. Am J Ophthalmol 2004 Jul; 138 (1): 91-108
3. Coleman AL, Stone K, Ewing SK, et al. Higher risk of multiple falls among elderly women who lose visual acuity. Ophthalmology 2004 May; 111 (5): 857-62
4. Folkman J. Tumor angiogenesis: a possible control point in tumor growth. Ann Intern Med 1975 Jan; 82 (1): 96-100
5. Ng EW, Adamis AP. Targeting angiogenesis, the underlying disorder in neovascular age-related macular degeneration. Can J Ophthalmol 2005 Jun; 40 (3): 352-68