Pegaptanib was effective and safe without a dose-response relation in neovascular, age-related, macular degeneration

Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsod M, Guyer DR. **Pegaptanib for neovascular age-related macular degeneration.** N Engl J Med. 2004;351:2805-16.

Clinical impact ratings: Geriatrics ★★★★★★☆

QUESTION

In patients with neovascular, age-related, macular degeneration, what are the effectiveness and safety of pegaptanib?

METHODS

Design: 2 concurrent, randomized, placebo-controlled trials (Vascular Endothelial Growth Factor Inhibition Study in Ocular Neovascularization Clinical Trial).
Allocation: {Concealed}†.*
Blinding: Blinded {clinicians, patients, data collectors, outcome assessors, data analysts, and data safety and monitoring committee}†.*
Follow-up period: 54 weeks.
Setting: 117 sites in the United States, Canada, Europe, Israel, Australia, and South America.
Patients: 1208 patients ≥ 50 years of age (58% women, mean age 76 y) who had subfoveal sites of choroidal neovascularization secondary to age-related, macular degeneration and a range of best corrected visual acuity of 20/40 to 20/320 in the study eye, and 20/800 or better in the other eye. All angiographic subtypes of lesions were eligible if lesions were a total size ≤ 12 optic-disk areas. 586 patients were included in 1 trial at 58 sites in the United States and Canada, and 622 patients were included in the other trial at 59 sites in Europe, Israel, Australia, and South America.
Intervention: Intravitreous injections into 1 eye per patient of pegaptanib, 0.3 mg (n = 297), 1.0 mg (n = 305), or 3.0 mg (n = 302); or sham injections (n = 304) every 6 weeks for 48 weeks (9 treatments).
Outcomes: Rate of visual-acuity loss < 15 letters and adverse events.
Patient follow-up: 98% (intention-to-treat analysis).

MAIN RESULTS

Combining data from the 2 trials, all doses of pegaptanib had greater rates of a visual-acuity loss < 15 letters than sham injection (Table), with no differences among the 3 pegaptanib groups. Groups did not differ for adverse events, including vascular hypertensive disorders, hemorrhagic adverse events, thromboembolic events, and gastrointestinal perforations.

CONCLUSION

In patients with neovascular, age-related, macular degeneration, pegaptanib was effective and safe without a dose-response relation.

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*See Glossary.
†Information provided by author.

Pegaptanib vs sham injection in neovascular, age-related, macular degeneration at 54 weeks‡

Outcome	Pegaptanib dose	Pegaptanib	Sham injection	RBI (95% CI)	NNT (CI)
Proportion of patients with visual-acuity loss < 15 letters	0.3 mg	70%	55%	26% (12 to 44)	7 (5 to 15)
	1.0 mg	71%	55%	28% (13 to 46)	7 (5 to 13)
	3.0 mg	65%	55%	18% (3 to 35)	11 (7 to 53)

‡Abbreviations defined in Glossary; RBI, NNT, and CI calculated from data in article.

COMMENTARY

Until recently, nihilism has characterized the therapeutic approach of most physicians to macular degeneration. Despite the fact that it is the most common cause of binocular visual impairment in older persons in industrialized countries, few therapeutic interventions exist (1). The study by Gragoudas and colleagues reports the combined data from 2 rigorous trials that studied the inhibition of activity of vascular endothelial growth factor (VEGF). Both studies were organized by the VEGF Inhibition Study In Ocular Neovascularization (VISION) steering committee in identical manner to "fulfill the worldwide regulatory requirements."

In this study, the outcomes assessed were change and direction of the rate of visual loss and adverse events. Patients were not denied access to photodynamic therapy if that was appropriate. Experimental interventions, such as macular translocation surgery, transpupillary thermotherapy, or other pharmacologic techniques, to inhibit angiogenesis were not permitted according to study protocol. Serious adverse events of endophthalmitis, retinal detachment, and traumatic cataract occurred in 22 patients during the course of 7545 injections, and 2 had severe loss of visual acuity. Some cases of infective endophthalmitis may have been avoided by closer adherence to the treatment protocol.

The bottom line is that pegaptanib slowed, and in some cases reversed, the decline in visual acuity with few complications. A wide range of patients with "wet" macular degeneration are eligible, but treatment is only available from retinal specialists. Longer-term follow-up, details of patients' experiences, and economic analyses are needed before clinicians can confidently refer their patients. This study may not yet be a cause for optimism, but it may be the end of undue pessimism.

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Reference

1. **Evans JR, Fletcher AE, Wormald RP, et al.** Prevalence of visual impairment in people aged 75 years and older in Britain: results from the MRC trial of assessment and management of older people in the community. Br J Ophthalmol. 2002;86:795-800.