ORIGINAL ARTICLE

Pegaptanib for Neovascular Age-Related Macular Degeneration

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ABSTRACT

BACKGROUND

Pegaptanib, an anti–vascular endothelial growth factor therapy, was evaluated in the treatment of neovascular age-related macular degeneration.

METHODS

We conducted two concurrent, prospective, randomized, double-blind, multicenter, dose-ranging, controlled clinical trials using broad entry criteria. Intravitreous injection into one eye per patient of pegaptanib (at a dose of 0.3 mg, 1.0 mg, or 3.0 mg) or sham injections were administered every 6 weeks over a period of 48 weeks. The primary end point was the proportion of patients who had lost fewer than 15 letters of visual acuity at 54 weeks.

RESULTS

In the combined analysis of the primary end point (for a total of 1186 patients), efficacy was demonstrated, without a dose–response relationship, for all three doses of pegaptanib ($P<0.001$ for the comparison of 0.3 mg with sham injection; $P<0.001$ for the comparison of 1.0 mg with sham injection; and $P=0.03$ for the comparison of 3.0 mg with sham injection). In the group given pegaptanib at 0.3 mg, 70 percent of patients lost fewer than 15 letters of visual acuity, as compared with 55 percent among the controls ($P<0.001$). The risk of severe loss of visual acuity (loss of 30 letters or more) was reduced from 22 percent in the sham-injection group to 10 percent in the group receiving 0.3 mg of pegaptanib ($P<0.001$). More patients receiving pegaptanib (0.3 mg), as compared with sham injection, maintained their visual acuity or gained acuity (33 percent vs. 23 percent; $P=0.003$). As early as six weeks after beginning therapy with the study drug, and at all subsequent points, the mean visual acuity among patients receiving 0.3 mg of pegaptanib was better than in those receiving sham injections ($P<0.002$). Among the adverse events that occurred, endophthalmitis (in 1.3 percent of patients), traumatic injury to the lens (in 0.7 percent), and retinal detachment (in 0.6 percent) were the most serious and required vigilance. These events were associated with a severe loss of visual acuity in 0.1 percent of patients.

CONCLUSIONS

Pegaptanib appears to be an effective therapy for neovascular age-related macular degeneration. Its long-term safety is not known.

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THE USE OF A SPECIFIC ANTAGONIST OF an angiogenic factor as a strategy to treat disease was proposed in the *Journal* more than 30 years ago.[1] Since that time, extensive evidence has suggested a causal role of vascular endothelial growth factor (VEGF) in several diseases of the human eye in which neovascularization and increased vascular permeability occur.[1-12] In humans, ocular VEGF levels have been shown to rise synchronously with and in proportion to the growth and leakage of new vessels.[2-4] Animal models of corneal,[5] iridic,[6] retinal,[7] and choroidal[8] neovascularization have shown that neovascularization is dependent on the presence of VEGF. In a complementary fashion, the introduction of VEGF into normal animal eyes resulted in a recapitulation of the pathologic neovascularization that occurs in these tissues during disease.[9-12] Taken together, these data provided a strong rationale for the targeting of VEGF in human disorders that manifest as ocular neovascularization and increased vascular permeability.

Age-related macular degeneration is the leading cause of irreversible, severe loss of vision in people 55 years of age and older in the developed world, and it remains an area of unmet medical need.[13] The neovascular form of the disease represents approximately 10 percent of the overall disease prevalence, but it is responsible for 90 percent of the severe vision loss.[14] It is expected to develop in almost 1 million people over the age of 55 years in the United States within the next five years, making it a major public health issue in an increasing population of older persons.[15]

Neovascular age-related macular degeneration is characterized by choroidal neovascularization that invades the subretinal space, often leading to exudation and hemorrhage. If the condition is left untreated, damage to photoreceptors and loss of central vision usually result, and after several months to years, the vessels are largely replaced by a fibrovascular scar.[16-18] Patients in whom a central scotoma develops have difficulty performing critical tasks that are typically associated with central vision, such as reading, driving, walking, and recognizing faces, and the difficulty has a major effect on their quality of life.[19]

With greater understanding of the pathogenesis of neovascular age-related macular degeneration, drug therapies targeted at the causal molecular mechanisms have been advanced. Pegaptanib (Macugen), a 28-base ribonucleic acid aptamer (from the Latin *aptus*, to fit; and the Greek *meros*, part or region) covalently linked to two branched 20-kD polyethylene glycol moieties, was developed to bind and block the activity of extracellular VEGF, specifically the 165-amino-acid isoform ($VEGF_{165}$). Aptamers characteristically bind with high specificity and affinity to target molecules, including proteins. The binding relies on the specific three-dimensional conformation of the properly folded aptamer. To prolong activity at the site of action, the sugar backbone of pegaptanib was modified to prevent degradation by endogenous endonucleases and exonucleases, and the polyethylene glycol moieties were added to increase the half-life of the drug in the vitreous.[20]

We hypothesized that the targeting of $VEGF_{165}$ would affect the underlying conditions common to all forms of choroidal neovascularization, including the three angiographic subtypes of neovascular age-related macular degeneration. We conducted two concurrent clinical trials to test the short-term safety and effectiveness of pegaptanib in patients with a broad spectrum of visual acuities, lesion sizes, and angiographic subtypes of lesions at baseline.

METHODS

STUDY DESIGN

We conducted two concurrent, prospective, randomized, double-blind, multicenter, dose-ranging, controlled clinical trials at 117 sites in the United States, Canada, Europe, Israel, Australia, and South America in our study. Patients were eligible for inclusion if they were 50 years of age or older and 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 of 20/800 or better in the other eye.

The angiographic subtype of a patient's lesion was defined in relation to the visualization of choroidal new vessels (classic) in the fluorescein angiogram. The total area of a predominantly classic lesion includes more than 50 percent classic choroidal neovascularization, the total area of a minimally classic lesion includes less than 50 percent classic choroidal neovascularization, and the total area of an occult lesion includes no classic choroidal neovascularization. The total size of a lesion, choroidal neovascularization, or leakage was measured on a frame on the fluorescein angiogram with the optic-disk area as the unit of measure; it is equal to 2.54 mm^2. The size of a lesion, choroidal

neovascularization, or leakage is expressed as multiples of this standard optic-disk area.

Patients with all angiographic subtypes of lesions were enrolled, and lesions with a total size up to and including 12 optic-disk areas (including blood, scar or atrophy, and neovascularization) were permitted. Details of the method are provided in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

TREATMENT AND OUTCOMES

Patients were randomly assigned to receive either sham injection or intravitreous injection of pegaptanib (Macugen, Eyetech Pharmaceuticals) into one eye every 6 weeks over a period of 48 weeks, for a total of nine treatments. To maintain masking of the patients, the patients receiving sham injections and those receiving the study medication were treated identically, with the exception of scleral penetration. All patients (including those receiving sham injection) underwent an ocular antisepsis procedure and received injected subconjunctival anesthetic. The patients receiving sham injections had an identical syringe — but without a needle — pressed against the eye wall to mimic the active doses that were injected through the pars plana into the vitreous cavity. The injection technique precluded the patient from seeing the syringe. To maintain masking of the investigators, the study ophthalmologist responsible for patient care and for the assessments did not administer the injection. In all cases, a separate, certified visual-acuity examiner masked to the treatment assignment and to previous measurements of visual acuity assessed distance visual acuity.

Owing to ethical considerations, the use of photodynamic therapy with verteporfin was permitted only in the treatment of patients with predominantly classic lesions, as defined in the product label approved by the Food and Drug Administration, and at the discretion of the ophthalmologist, who was masked as to the treatment assignment. The prespecified primary end point for efficacy was the proportion of patients who lost fewer than 15 letters of visual acuity (defined as three lines on the study eye chart) between baseline and week 54.

The trials were designed by the steering committee of the VEGF [Vascular Endothelial Growth Factor] Inhibition Study in Ocular Neovascularization Clinical Trial Group. The data were held and analyzed by the data management and statistics group. The manuscript was prepared by the writing committee. Dr. Gragoudas chaired the writing committee, served as the outside academic investigator vouching for the veracity and completeness of the data analyses, had access to the full data set, and was responsible for the decision to submit the manuscript for publication.

RESULTS

One trial included 586 patients at 58 sites in the United States and Canada and was conducted from August 2001 through July 2002; the other trial included 622 patients at 59 other sites worldwide and was conducted from October 2001 through August 2002. Of the 1208 patients randomly assigned to treatment in the two studies (297 patients assigned to receive 0.3 mg of pegaptanib; 305 patients, 1.0 mg of pegaptanib; 302 patients, 3.0 mg of pegaptanib; and 304 patients, sham injections), 1190 received at least one study treatment (295 patients received 0.3 mg of pegaptanib; 301 patients, 1.0 mg of pegaptanib; 296 patients, 3.0 mg of pegaptanib; and 298 patients, sham injections). The demographic and ocular characteristics of the patients at baseline were similar among the treatment groups (Table 1).

Four patients were not included in the efficacy analyses, because a sufficiently standardized assessment of visual acuity was not completed at baseline. Therefore, a total of 1186 patients received at least one study treatment, had visual acuity assessments at baseline, and were included in efficacy analyses (294 patients who received 0.3 mg of pegaptanib; 300 patients, 1.0 mg of pegaptanib; 296 patients, 3.0 mg of pegaptanib; and 296 patients, sham injections). A total of 7545 intravitreous injections of pegaptanib and 2557 sham injections were administered. Approximately 90 percent of the patients in each treatment group completed the study. In all the treatment groups, an average of 8.5 injections were administered per patient out of a possible total of 9 injections.

The general health status of the patients entering the trial, calculated for all patients receiving pegaptanib as compared with those receiving sham injection, was as follows: hypertension (55 percent in the pegaptanib groups vs. 48 percent in the sham-injection group), hypercholesterolemia (21 percent vs. 18 percent), diabetes mellitus (10 percent vs. 7 percent), cardiac disorders (35 percent vs. 34 percent), cerebrovascular disease (3 percent vs. 1 percent), peripheral arterial disease (3 percent vs.

Table 1. Demographic and Ocular Characteristics of Patients at Baseline.*

Characteristic	0.3 mg Pegaptanib (N=295)	1.0 mg Pegaptanib (N=301)	3.0 mg Pegaptanib (N=296)	Sham Injection (N=298)
Sex — no. (%)				
Male	133 (45)	136 (45)	105 (35)	120 (40)
Female	162 (55)	165 (55)	191 (65)	178 (60)
Race — no. (%)†				
White	283 (96)	291 (97)	286 (97)	284 (95)
Other	12 (4)	10 (3)	10 (3)	14 (5)
Age — no. (%)				
50–64 yr	19 (6)	21 (7)	18 (6)	21 (7)
65–74 yr	86 (29)	105 (35)	90 (30)	94 (32)
75–84 yr	155 (53)	147 (49)	153 (52)	160 (54)
≥85 yr	35 (12)	28 (9)	35 (12)	23 (8)
Angiographic subtype of lesion — no. (%)‡				
Predominantly classic	72 (24)	78 (26)	80 (27)	76 (26)
Minimally classic	111 (38)	108 (35)	105 (35)	102 (34)
Occult with no classic	112 (38)	115 (38)	111 (38)	120 (40)
Size of lesion§	3.7±2.4	4.0±2.4	3.7±2.5	4.2±2.8
History of ocular surgery or laser treatment — no. (%)	123 (42)	117 (39)	124 (42)	124 (42)
Visual acuity				
Study eye				
Mean	52.8±12.6	50.7±12.8	51.1±12.9	52.7±13.0
Median (range)	55 (11–75)	52 (19–77)	53 (14–76)	53 (11–77)
Other eye				
Mean	56.2±27.2	54.8±27.6	56±26.4	55.9±27.0
Median (range)	68 (3–85)	67 (3–85)	65 (4–85)	67 (2–85)

* Plus–minus values are means ±SD.
† Race was determined by the treating investigators.
‡ In relation to the visualization of choroidal new vessels (classic) in the fluorescein angiogram, a predominantly classic lesion includes 50 percent or more classic choroidal neovascularization, a minimally classic lesion includes less than 50 percent classic choroidal neovascularization, and an occult lesion includes no classic choroidal neovascularization.
§ The size of lesions was measured as the number of optic-disk areas (including blood scar or atrophy and neovascularization), each of which is 2.54 mm^2.

3 percent), and electrocardiographic abnormalities (53 percent vs. 48 percent).

In the combined analysis, all three doses of pegaptanib differed significantly from the sham injection in terms of the prespecified primary efficacy end point (Table 2). A loss of fewer than 15 letters of visual acuity was observed at week 54 in 206 (70 percent) of 294 patients assigned to receive 0.3 mg of pegaptanib (P<0.001), 213 (71 percent) of 300 patients assigned to 1.0 mg of pegaptanib (P<0.001), and 193 (65 percent) of 296 patients assigned to 3.0 mg of pegaptanib (P=0.03), as compared with 164 (55 percent) of 296 patients assigned to receive sham injection. Similar results were obtained when the analyses were restricted to the subgroup of patients who were evaluated both at baseline and at week 54 (accounting for 92 percent of those receiving 0.3 mg of pegaptanib, 92 percent of those receiving 1.0 mg of the drug, 89 percent of those receiving 3.0 mg of the drug, and 93 percent of those receiving sham injections); the similar findings indicate that missing data probably did not influence the results. In this population at week 54, a loss of fewer than 15 letters was observed in 192 (71 percent) of

Table 2. Rate of Visual-Acuity Loss, Measured as the Loss of Fewer Than 15 Letters, in 1186 Patients.*

Time	0.3 mg Pegaptanib (N=294)		1.0 mg Pegaptanib (N=300)		3.0 mg Pegaptanib (N=296)		Sham Injection (N=296)
	No. (%)	P Value vs. Sham Injection	No. (%)	P Value vs. Sham Injection	No. (%)	P Value vs. Sham Injection	No. (%)
Week 12	256 (87)	0.01	259 (86)	0.04	251 (85)	0.13	237 (80)
Week 24	242 (82)	<0.001	239 (80)	<0.001	224 (76)	0.003	190 (64)
Week 36	220 (75)	<0.001	229 (76)	<0.001	222 (75)	<0.001	175 (59)
Week 54	206 (70)	<0.001	213 (71)	<0.001	193 (65)	0.03	164 (55)

* The differences between the doses of pegaptanib were not significant.

271 patients assigned to receive 0.3 mg of pegaptanib (P<0.001), 198 (72 percent) of 275 patients assigned to 1.0 mg of the study drug (P<0.001), and 166 (63 percent) of 264 patients assigned to 3.0 mg of pegaptanib (P=0.14), as compared with 154 (56 percent) of 275 patients assigned to sham injection. There was no evidence in any of the analyses that pegaptanib at 1.0 mg or 3.0 mg was more effective than at 0.3 mg. The results of the two trials were similar, with both reaching statistical significance for the primary efficacy end point (0.3 mg of pegaptanib, P=0.03 and P=0.01).

The outcomes for the secondary end points were consistent with those for the primary end point. A greater proportion of the patients treated with pegaptanib maintained or gained visual acuity (that is, they had no change in the number of letters or a gain of one or more letters). For the combined analysis, 33 percent of patients receiving 0.3 mg of pegaptanib (P=0.003), 37 percent of those receiving 1.0 mg (P<0.001), and 31 percent of those receiving 3.0 mg (P=0.02) maintained vision or gained vision as compared with 23 percent of those receiving sham injection. At week 54, larger proportions of patients receiving pegaptanib, as compared with those receiving sham injection, also gained 5, 10, or 15 letters of visual acuity (approximately equivalent to one, two, and three lines on the study eye chart, respectively) (Table 3).

Patients in the sham-injection group were twice as likely to have a severe loss of vision (i.e., a loss of 30 letters or more or six lines on the study eye chart) as patients receiving pegaptanib at 0.3 mg (22 percent vs. 10 percent, P<0.001) or 1.0 mg (22 percent vs. 8 percent, P<0.001). Among patients receiving a dose of 3.0 mg, 14 percent had severe vision loss (P=0.01 for the comparison with the sham-injection group) (Table 3).

A smaller percentage of patients receiving pegaptanib had a Snellen equivalent visual acuity of 20/200 or worse, or legal blindness, in the study eye at week 54 than of those in the sham-injection group (pegaptanib at 0.3 mg, 38 percent; 1.0 mg, 43 percent; 3.0 mg, 44 percent; sham injection, 56 percent; P<0.001 for the comparison between all treatment groups and the sham-injection group) (Table 3).

The effectiveness of pegaptanib was evident as early as the first study visit after the treatment was started (week 6), and it increased over time up to week 54, as measured by the mean loss of visual acuity from baseline to each study visit as compared with that in the sham-injection group (P<0.002 at every point for a dose of pegaptanib at 0.3 mg or 1.0 mg, and P<0.05 at every point for a dose of 3.0 mg) (Fig. 1A).

There was no evidence that any angiographic subtype of the lesion, the size of the lesion, or the level of visual acuity at baseline precluded a treatment benefit. For those receiving pegaptanib at 0.3 mg, a treatment benefit was observed among all patients with all angiographic subtypes of lesions (P<0.03 for each subtype) (Fig. 1B), baseline levels of visual acuity (<54 or ≥54 letters, P<0.01 for each group) (Fig. 1C), and lesion sizes at baseline (<4 or ≥4 optic-disk areas, P<0.02 for each group) (Fig. 1D). Numerically superior outcomes were observed among patients with different subtypes of lesions treated with pegaptanib at 1.0 mg and 3.0 mg as well (Fig. 1B). The results of multiple logistic-regression analyses revealed that no factor other than assignment to treatment with pegaptanib was

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