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Pegaptanib
In Exudative Age-Related Macular Degeneration

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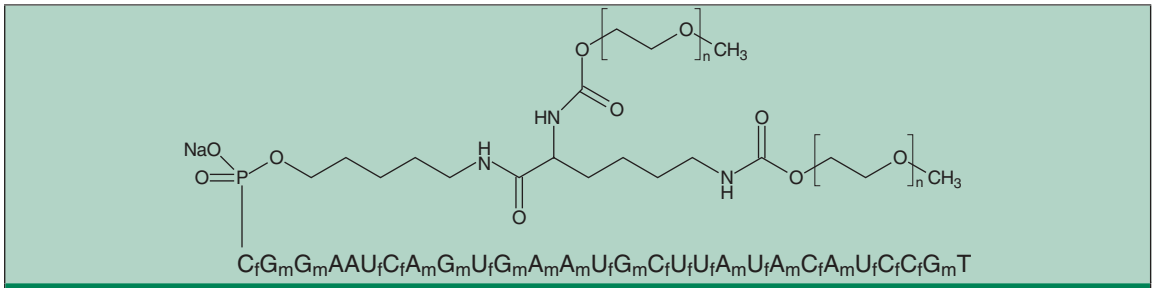
Contents

Abstract

- Pegaptanib, an aptamer, is an antagonist of vascular endothelial growth factor that has shown efficacy in the treatment of patients with exudative age-related macular degeneration (AMD).
- In two randomised, double-masked trials in patients with exudative AMD (n = 1208), the proportion of responders (those losing <15 letters of visual acuity) at 54 weeks was significantly higher in intravitreous pegaptanib 0.3mg recipients than in those receiving sham injections (70% vs 55%; $p < 0.001$). These trials were conducted concurrently and analysed as a single study; the treatments were given every 6 weeks for 48 weeks. The improvement in visual acuity with pegaptanib was maintained in a 1-year extension of these trials.
- Similar favourable results with pegaptanib 0.3mg were seen in terms of the secondary efficacy endpoints (e.g. proportion of patients experiencing severe loss of visual acuity or legal blindness in the study eye). These vision-improving effects of pegaptanib were associated with beneficial angiographic effects.
- Intravitreous pegaptanib 0.3–3mg was well tolerated with most ocular adverse events being mild-to-moderate and transient. Serious injection-related adverse events occurred in ≤1.3% of patients treated with pegaptanib. There were no systemic adverse events that could be definitely attributed to pegaptanib.

Features and properties of pegaptanib (Macugen®)	
Indication	
Exudative (neovascular or 'wet') age-related macular degeneration	
Mechanism of action	
Antiangiogenic agent	Selectively antagonises vascular endothelial growth factor
Dosage and administration	
Dose	0.3mg
Route of administration	Intravitreous injection
Frequency	Once every 6 weeks
Pharmacokinetic profile (single 3mg intravitreous monocular dose [i.e. 10 times the recommended dose])	
Maximum plasma concentration	0.08 μg/mL
Area under the plasma concentration-time curve	25 μg • h/mL
Apparent terminal half-life	10 days
Tolerability (intravitreous pegaptanib 0.3–3mg once every 6 weeks for 48 weeks)	
Serious injection-related adverse events	Endophthalmitis, retinal detachment and traumatic lens injury



Pegaptanib sodium. A = adenosine; A_m = 2′-O-methyladenosine; C_f = 2′-deoxy-2′-fluorocytidine; G_m = 2′-O-methylguanosine; T = thymidine; U_f = 2′-deoxy-2′-fluorouracil; n ≈ 450.

Age-related macular degeneration (AMD) is a major public health issue in the developed world, as it is the leading cause of irreversible vision loss in individuals aged 50 years and over.[1,2] In the US, approximately 8 million people aged ≥55 years have a stage of AMD in one or both eyes and are considered to be at high risk for progressing to advanced AMD.[3] One million of these would develop advanced AMD within 5 years whether or not they use preventive dietary supplementation for the condition.[3,4]

AMD has been classified into two types: nonexudative or 'dry' (geographic atrophy only) and exudative or 'wet' (characterised by choroidal neovascularisation [CNV]).[5,6] Nonexudative AMD is more prevalent (comprising up to 85% of AMD cases)[6] and eventually progresses to the exudative type in approximately 10–20% of patients.[5] Nevertheless, approximately 1.02% of the US population aged ≥40 years has exudative AMD in at least one eye.[7] These figures assume even more significance considering that the exudative subtype accounts for the majority of cases of severe vision loss due to AMD.[5]

Laser photocoagulation and photodynamic therapy (PDT) have been employed in the treatment of CNV in exudative AMD.[5,6] However, treatment efficacy is low and only a small proportion of patients show predominantly classic fluorescein angiographic subtype of lesions suitable for these treatments.[5] Persistent or recurrent CNV within 2 years was seen in approximately 50% of patients in whom thermal laser photocoagulation was used.[8] PDT with verteporfin prevented vision loss, but did not restore vision, and treatment was repeated several times in the majority of patients.[9]

These treatment limitations have led researchers to explore newer, more effective treatments for exudative AMD. With the recognition of the important role of vascular endothelial growth factor (VEGF) in the pathogenesis of AMD, antiangiogenesis therapy using VEGF antagonists has been investigated in several experimental and clinical studies (reviewed elsewhere[1,2,5]). One such VEGF antagonist is the aptamer pegaptanib (pegaptanib sodium; Macugen®)[1], which has been evaluated in the treatment of patients with exudative AMD. Although there is preliminary evidence of efficacy (with favourable tolerability) of intravitreous pegaptanib 0.3mg in reducing visual acuity loss and decreasing central retinal thickness in patients with diabetic macular oedema,[10] this review focusses on the use of pegaptanib in exudative AMD only.

1. Pharmacodynamic Properties

Pegaptanib is a pegylated, 28-base aptamer and a selective antagonist of VEGF.[11,12] VEGF stimulates endothelial cell proliferation (angiogenesis) and facilitates vascular permeability and inflammation by selectively binding to and activating its receptors expressed almost exclusively on the surface of vascular endothelial cells.[13] Overproduction

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

of VEGF is a major factor underlying pathological angiogenesis in exudative AMD and the actions of VEGF are thought to contribute to the progression of the disease.[14]

- Pegaptanib binds to extracellular $VEGF_{165}$, the major pathological 165-amino-acid isoform, and inhibits its binding to VEGF receptors.[11] In human umbilical vein endothelial cell cultures, pegaptanib inhibited binding of $VEGF_{165}$ with a 50% inhibitory concentration of 0.72–1.4 nmol/L; complete inhibition occurred at 10 nmol/L.[11] $VEGF_{165}$-mediated phosphorylation of tyrosine kinase receptors and calcium mobilisation was also inhibited in a dose-dependent manner. In addition, pegaptanib 10 nmol/L completely inhibited endothelial cell proliferation induced by $VEGF_{165}$ in this model.[11]
- Pegaptanib was effective in various experimental models of neovascularisation.[12] The drug almost completely inhibited VEGF-induced leakage of indicator dye from guinea pig cutaneous vasculature (Miles assay) and decreased VEGF-dependent angiogenesis by up to 65% in rat cornea.[12] In a mouse model of hyperoxia-induced retinopathy of prematurity, there was a significant reduction (80%; $p = 0.01$) in retinal neovasculature in animals treated with intraperitoneal pegaptanib (3 or 10 mg/kg/day for 5 days) compared with that in saline-treated animals. Pegaptanib also inhibited the growth of human A673 rhabdomyosarcoma xenografts implanted in nude mice by up to 76%.[12]
- This pegaptanib activity translated into beneficial effects on the human eye[12,15] (see also section 3). Three months after single intravitreous injections of pegaptanib 0.25–3mg per eye, stable or improved vision was observed in 80% (12 of 15) of patients with subfoveal CNV secondary to AMD and a visual acuity of <20/200 in the study eye.[12] Vision was improved to a clinically significant extent (gain of ≥3 lines) in four patients (27%).[12]

2. Pharmacokinetic Properties

Human pharmacokinetics, limited to those in plasma, were characterised at 10 times the recommended dose because of the very low systemic absorption of intravitreous pegaptanib. Ethical concerns with vitreous sampling have not allowed the study of pegaptanib pharmacokinetics in the human eye.

- Following intravitreous administration of a pegaptanib 3mg monocular dose (i.e. 10 times the recommended dose) in humans, a mean maximum plasma concentration of approximately 0.08 μg/mL was seen within 1–4 days; the corresponding mean area under the plasma concentration-time curve was approximately 25 μg • h/mL.[16] Multiple dose administration (four doses of pegaptanib 3mg once every 6 weeks) did not result in accumulation of pegaptanib in the plasma of patients with exudative AMD (data available as an abstract).[17]
- Experimental studies have shown that absorption rate is likely to be the rate-limiting step in the disposition of the drug.[12,16,18] After intravitreous administration of radiolabeled pegaptanib in rabbits, the main distribution of radioactivity was to the vitreous fluid, retina and aqueous fluid; outside the eye, the highest radioactivity concentrations were found in the kidney.[16]
- Pegaptanib is metabolised by endo- and exonucleases, and excreted in the urine as parent drug and metabolites.[16] 2′-Fluorouridine, a component nucleotide of pegaptanib, has been found in plasma and urine after administration of intravenous or intravitreous pegaptanib in rabbits.[16] In humans, pegaptanib has an apparent terminal half-life of 10 days after a 3mg monocular dose.[16,17]
- There is no clinically significant effect of age, sex or renal impairment on the plasma concentrations of intravitreous pegaptanib.[16] However, repeated administration in patients with renal impairment may lead to highly variable plasma pegaptanib concentrations, especially in those with severe renal impairment.[16]

3. Therapeutic Efficacy

The therapeutic efficacy of pegaptanib in the treatment of exudative AMD has been evaluated in two identically designed randomised, double-masked, dose-ranging, multicentre trials conducted concurrently (VISION [VEGF Inhibition Study In Ocular Neovascularisation]).[19] Patients aged ≥50

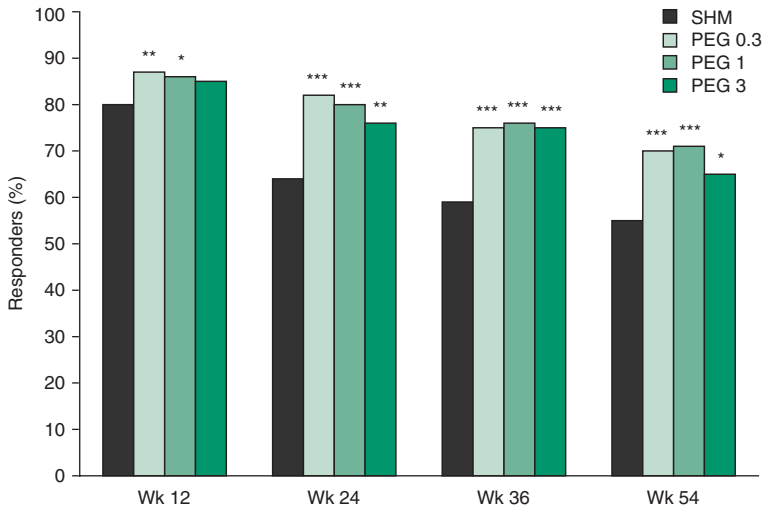


Fig. 1. Efficacy of pegaptanib (PEG) in patients with exudative age-related macular degeneration. The proportion of patients who lost <15 letters of visual acuity from baseline (responders) at 12, 24, 36 and 54 (primary efficacy variable) weeks after treatment with intravitreous PEG 0.3mg (n = 294), 1mg (n = 300) or 3mg (n = 296) or sham injections (SHM) [n = 296] once every 6 weeks for 48 weeks. Results of two randomised, double-blind trials that were conducted concurrently and analysed as a single trial (VISION [VEGF Inhibition Study In Ocular Neovascularisation]).[19] **VEGF** = vascular endothelial growth factor; * $p \leq 0.04$, ** $p \leq 0.01$, *** $p < 0.001$ vs SHM.

years were included in the trials if they had subfoveal CNV secondary to AMD and best corrected visual acuity ranging from 20/40 to 20/320 in the study eye and of ≥20/800 in the other eye.

Patients were randomised to receive either sham injection or intravitreous injection of pegaptanib 0.3–3mg into the study eye once every 6 weeks for 48 weeks with a follow-up period to 54 weeks.[19] Appropriate techniques were used to maintain masking. Patients in the control group received sham injections consisting of a needleless syringe pressed against the anesthetised eye wall. At the discretion of the ophthalmologist, verteporfin PDT was allowed only in patients with predominantly classic lesions.[19]

The trials enrolled patients with all angiographic subtypes.[19] Across the treatment arms, 24–27% of patients had predominantly classic lesions (defined as lesions comprising ≥50% classic CNV), 34–38% had minimally classic lesions (<50% classic CNV) and 38–40% had occult lesions (no classic CNV). The lesion size in enrolled patients had to be ≤12 disc areas (including blood, scar/atrophy and CNV); across treatment arms, mean lesion size of randomised patients was 3.7–4.2 optic-disc areas.[19]

Key ocular exclusion criteria included atrophy in >25% of lesion area or subfoveal scarring in the study eye and previous subfoveal thermal laser therapy.[19]

A total of 1208 patients (586 in one trial and 622 in the other) were randomised, 1186 of whom received at least one study treatment with pegaptanib 0.3mg (n = 294), 1mg (n = 300) or 3mg (n = 296), or the sham injection (n = 296), and were included in the efficacy analyses.[19] The mean number of treatments received by patients across all treatment arms was 8.5 of a possible total of 9 treatments. There were no significant differences among the four arms in the proportion of patients who underwent PDT before enrolment, at baseline or during the study.[19]

The primary efficacy variable was the proportion of patients who lost <15 letters of visual acuity (responders) after 54 weeks in an intent-to-treat analysis of the two trials combined together.[19] The secondary efficacy endpoints included maintenance or gain of visual acuity ≥0, ≥5, ≥10 or ≥15 letters, severe loss of visual acuity (loss of ≥30 letters) and legal blindness (visual acuity ≤20/200) at week 54.[19]

To evaluate the efficacy of longer-term therapy, pegaptanib recipients were re-randomised in equal ratios, after the 54-week phase of the study, to either discontinue or continue the treatment for a further 48 weeks (data available as an abstract).[20] Similarly, sham injection recipients were re-randomised in a ratio of 1 : 1 : 1 : 1 : 1 to either discontinue or continue sham injections, or to switch to one of the doses of intravitreous pegaptanib (0.3, 1 or 3mg). At week 102, 89% of patients who were re-randomised at 54 weeks were evaluable (941/1053); the mean number of treatments was 15.7 of a possible total of 17 overall.[20]

The discussion in this section focuses on only the approved dose of intravitreous pegaptanib (0.3mg).

- Intravitreous pegaptanib 0.3mg was significantly more effective than sham injections in reducing the loss of visual acuity in patients with exudative AMD.[19] At 54 weeks, the proportion of responders in pegaptanib 0.3mg recipients was significantly higher than that in patients receiving sham injections (70% vs 55%; $p < 0.001$) [figure 1]. Data analysed separately for each trial also showed statistically significant results in favour of pegaptanib 0.3mg compared with sham injections ($p \leq 0.03$).[19]

- Pegaptanib 0.3mg recipients who continued their treatment for a second year (n = 133) showed a significantly higher response rate (59% vs 45%; $p < 0.05$) and smaller loss of visual acuity (average 9.4 vs 17 letters; $p \leq 0.05$) at 102 weeks than those who received sham injections through that period (n = 107).[20] Also, there was a 67% decrease in the rate of occurrence of 15-letter loss of visual acuity in patients receiving pegaptanib for 2 years compared with those who received 1 year of pegaptanib therapy ($p \leq 0.05$).[20]

- A significant ($p < 0.002$) treatment benefit with pegaptanib 0.3mg was seen as early as week 6 of the study (first visit after treatment initiation).[19] In terms of the change from baseline in visual acuity with pegaptanib 0.3mg versus sham injections, treatment benefit increased as the study progressed. Baseline visual acuity, angiographic subtype or size of the lesion, or the use of PDT at baseline or during the study did not affect the treatment outcome.[19]

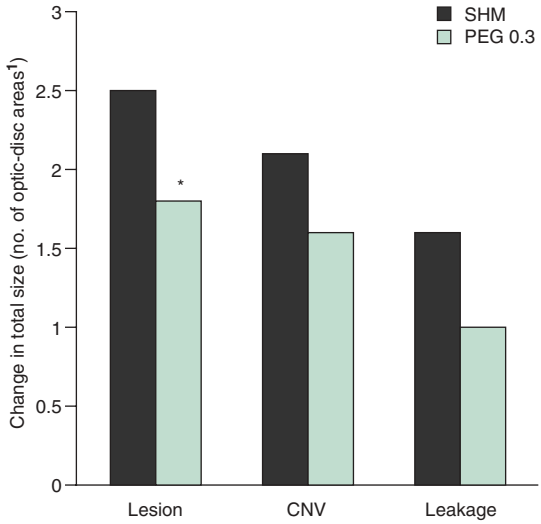


Fig. 2. Ocular angiographic effects of pegaptanib (PEG) in patients with exudative age-related macular degeneration. The changes in the size of lesion, choroidal neovascularisation (CNV) and leakage at 54 weeks after treatment with intravitreous PEG 0.3mg (n = 294) or sham injections (SHM) [n = 296] once every 6 weeks for 48 weeks. Results of two randomised, double-blind trials that were conducted concurrently and analysed as a single trial (VISION [VEGF Inhibition Study In Ocular Neovascularisation]).[19] Data from the pegaptanib 1 and 3mg treatment arms are not presented. **1** One optic-disc area = 2.54mm^2. **VEGF** = vascular endothelial growth factor; * $p < 0.01$ vs SHM.

- Similar beneficial effects were seen in patients receiving higher dosages of pegaptanib (figure 1).[19] However, there were no significant differences among the three doses of pegaptanib and no apparent dose-response relationship in terms of the primary endpoint.[19]

- Significantly smaller proportions of patients in the pegaptanib 0.3mg group than in sham injection group experienced severe loss of visual acuity (10% vs 22%; $p < 0.001$) or legal blindness (38% vs 56%; $p < 0.001$) in the study eye.[19] Also, significantly higher proportions of pegaptanib 0.3mg than sham injection recipients demonstrated maintenance or gain of ≥0, ≥5, ≥10 or ≥15 letters of visual acuity (all $p \leq 0.04$).[19]

- The rates of growth of the total size of a lesion, CNV and leakage tended to be slow in patients receiving pegaptanib 0.3mg compared with those in sham injection recipients, with the relative increase in lesion size reaching statistical significance at 54

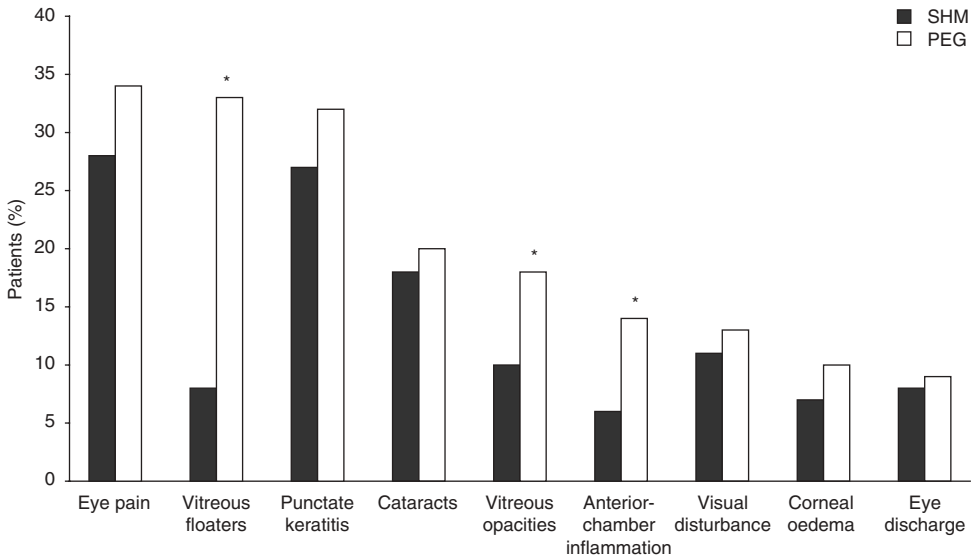


Fig. 3. Ocular adverse events with pegaptanib (PEG) in patients with exudative age-related macular degeneration (AMD). The incidence of common ocular adverse events that were more frequent in intravitreous PEG 0.3–3mg recipients (n = 890) than in sham injection (SHM) recipients (n = 298) during 54 weeks. Patients were randomised to receive PEG or SHM once every 6 weeks for 48 weeks in two double-blind trials that were conducted concurrently and analysed as a single trial (VISION [VEGF Inhibition Study In Ocular Neovascularisation]).[19] **VEGF** = vascular endothelial growth factor. * $p \leq 0.001$ vs SHM.

weeks (figure 2).[19] A significant difference between pegaptanib 0.3mg and sham injection groups was also seen in the increase in leakage at 30 weeks (0.7 vs 1.3 optic-disc areas; $p < 0.01$), but not at 54 weeks.[19]

4. Tolerability

The tolerability data for intravitreous pegaptanib (pooled for 0.3–3mg doses) are based on the two large phase III trials discussed in section 3 and, unless indicated otherwise, pertain to the first year of the trial.

- Pegaptanib was generally well tolerated throughout the 2-year study period, with most ocular adverse events being mild-to-moderate, transient and unrelated to the study drug.[19,21] Figure 3 summarises the common ocular adverse events that were more frequent in patients receiving pegaptanib 0.3–3mg than in sham injection recipients in the first year.[19] The adverse event profile was generally similar in patients who received pegaptanib for up to 2 years (data available as an abstract).[21]
- Serious injection-related adverse events occurred in ≤1.3% of the 890 patients treated with pegaptanib 0.3–3mg, and in <0.2% of the 7545 injections (endophthalmitis, 0.16% of injections; retinal detachment, 0.08%; and traumatic lens injury, 0.07%); severe loss of visual acuity was seen in one patient (0.1%) each in association with endophthalmitis or traumatic lens injury.[19] Among the 374 patients assigned to pegaptanib for >1 year, the rate of retinal detachment was 0.15% of injections (4 of 2663 injections) during the second year of treatment; there were no cases of endophthalmitis or traumatic cataract during this period.[21]
- Compared with patients receiving sham injections, pegaptanib recipients did not show any evidence of sustained elevation in intraocular pressure or acceleration of cataract formation even after 2 years.[19,21] There were no adverse effects on the retinal or the choroidal vascular beds.[19]
- There were no systemic adverse events that could be definitively attributed to pegaptanib.[19] Moreover, there was no significant difference between pegaptanib 0.3–3mg and sham injection groups in

the rates of vascular hypertensive disorders (10% each), haemorrhagic events (2% vs 3%) or thromboembolic events (6% each). No hypersensitivity reactions to, or antibody formation against, pegaptanib were observed. Similar death rates were observed in all groups (2%) and considered normal for this population.[19]

- Adverse events led to the discontinuation of treatment in 1% of patients in each of the pegaptanib or sham injection groups.[19]

5. Dosage and Administration

The recommended dosage of pegaptanib in the treatment of exudative AMD is 0.3mg administered once every 6 weeks by intravitreous injection into the affected eye.[16]

6. Pegaptanib: Current Status

Intravitreous pegaptanib, approved in the US for the treatment of exudative AMD, is the first, and currently the only, aptamer to have entered the marketplace. In well controlled trials in patients with any subtype of exudative AMD, pegaptanib 0.3mg significantly reduced visual acuity loss compared with sham injections, and was generally well tolerated.

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