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Pegaptanib for Neovascular Age-related Macular Degeneration

Summary

- **Neovascular (wet) age-related macular degeneration (AMD) results from the growth of abnormal blood vessels under the retina (choroidal neovascularization). Sudden and permanent vision loss occurs as these vessels grow, leak, bleed, and scar.**
- **A human protein, vascular endothelial growth factor (VEGF), is implicated in the development of wet AMD. Pegaptanib attaches to VEGF and blocks its action.**
- **In two concurrent, high quality studies using identical research methods, pegaptanib demonstrated a therapeutic advantage over placebo for the prevention of vision loss due to neovascular AMD.**
- **Pegaptanib is injected into the eye every six weeks. This carries the risk of endophthalmitis (intraocular infection), lens damage (if accidentally penetrated), and retinal detachment. Systemic side-effects have not been associated with pegaptanib.**

The Technology

The abnormal growth of blood vessels under the retina is responsible for vision loss in AMD and other diseases of the eye. This process is driven by VEGF and other factors.[1] VEGF has potent permeability and inflammatory effects on vascular endothelial cells.[2] It has been found in the choroidal neovascular membranes in wet AMD, and is overexpressed in the choroidal blood vessels of eyes with AMD.[3,4] Anti-VEGF therapy in neovascular AMD is based on the rationale that arresting the signals responsible for neovascularization will allow the disease to be stabilized.

Pegaptanib attaches to VEGF and prevents it from binding to vascular endothelial cells, blocking vascular growth and leakage.[5]

Pegaptanib is marketed as Macugen™ by EyeTech and Pfizer Pharmaceuticals in the US, and by Pfizer outside the US.

Regulatory Status

In Canada, a notice of compliance was granted on May 2, 2005 for the treatment of wet macular degeneration.[6] Commercialization of the product began in September 2005.

Patient Group

AMD is a degenerative disease of the central part of the retina (the macula) that is used for detailed visual tasks. AMD can be atrophic (dry) or neovascular (wet). In neovascular AMD, retinal damage occurs as new blood vessels grow under the macula leak, bleed, and scar, leading to permanent vision loss.

The early changes of macular degeneration are typically those of the atrophic form, which occurs in 90% of people with AMD. Neovascular macular degeneration develops in <20% of people with atrophic AMD, but it is responsible for 90% of severe vision loss.

In Canada, AMD accounts for >50% of new diagnoses for clients registering with the Canadian National Institute for the Blind.[7] The prevalence of neovascular AMD in Canada in 2001 was estimated to be >100,000.[8] In the US, the number of cases of AMD is expected to

increase from 2.7 million in 1970 to 7.5 million by 2020.[9] This is a concern, because of the impact of visual disability on the activities of daily living and quality of life. Adults with visual impairment caused by AMD are nine times more likely to require help with household chores and eight times more likely to need help with shopping. They also report emotional distress similar to that of patients with life-threatening illnesses such as melanoma and AIDS.[10]

Current Practice

Neovascular AMD is classified on the basis of the type of leakage pattern observed on intravenous fluorescein angiography (diagnostic retinal photographic imaging), and the location of abnormal blood vessel growth (extrafoveal, juxtafoveal, subfoveal). Angiographic patterns of leakage for choroidal neovascularization lead to prognostic and treatment implications. The two patterns of leakage are classic and occult. Positive treatment effects from thermal (destructive) laser have been demonstrated for extrafoveal and juxtafoveal lesions that are classic in appearance.[11,12] Until recently, the only proven treatment for central (subfoveal) neovascular AMD was photodynamic therapy (PDT) using verteporfin (Visudyne™, QLT Inc., Vancouver BC). This treatment reduces vision loss in predominantly classic choroidal neovascularization by selectively destroying the abnormal choroidal new vessels (while sparing the neurosensory retina) using a light-sensitive dye that is activated by a low energy laser.[13] Occult and minimally classic subfoveal lesions have demonstrated a treatment response to verteporfin, primarily when the lesions are small and vision is poor.[14,15] Treatments are administered every three months with retreatment typically recommended if there is ongoing leakage on fluorescein angiography.

The Evidence

Two concurrent, prospective, randomized, double-blind, multicentre, controlled clinical trials were performed to evaluate pegaptanib as a treatment for neovascular AMD. Only the pooled data have been published for the first year of treatment.[16]

The baseline features of the treatment and control groups were similar. Information regarding the number of individuals screened versus enrolled was not provided. Overall, 1,208 individuals were randomized, 1,190 were treated, and 1,186 had standardized baseline visual acuities performed. Study inclusion criteria included: 50 years of age or older, subfoveal choroidal neovascularization, best corrected visual acuity between 20/40 and 20/320, any angiographic type of neovascular AMD, and lesion sizes up to 12 disc areas.

Individuals with predominantly classic choroidal neovascularization were permitted to receive verteporfin PDT during the study at the investigators' discretion. Centralized randomization was performed with the appropriate masking of investigators as to treatment status (physicians who gave injections did not evaluate clinical outcomes). Visual acuity outcomes were evaluated by masked technicians. An intent-to-treat analysis was performed, with the

Table 1: Intravitreal pegaptanib 0.3 mg (lowest effective dose) compared with sham intraocular injection

Dose of Pegaptanib	Number of Participants	Stable Vision* (loss of <15 letters)	Severe Vision Loss* (loss of ≥30 letters)	Legal Blindness* (vision ≤20/200)
0.3 mg	294	206	28	111
sham	296	164	65	165

* $p<0.001$ for all comparisons between pegaptanib and placebo; outcomes assessed at week 54

last results carried forward for missing data. The primary outcome was the proportion of individuals losing <15 letters of vision at week 54 (stable vision). Secondary vision end-points included the proportion of subjects losing ≥30 letters (severe vision loss), or progressing to legal blindness (≤20/200 vision).

Subjects received a 90 µL intravitreal injection of one of the three pegaptanib doses (0.3 mg, 1.0 mg, or 3.0 mg) every six weeks for 48 weeks (nine injections in total) or a sham intravitreal injection (subconjunctival anesthetic administered, and the blunt hub of a needle pressed on the globe without ocular penetration).

Each of the three doses of pegaptanib was effective for the primary end-point when compared with the sham injection. Because all three doses were effective, the analysis focused on the 0.3 mg dose (lowest effective dose).

Benefit was derived from pegaptanib treatment at the 0.3 mg dose for all choroidal neovascular leakage patterns and lesion sizes of >4 or <4 disc areas. For 0.3 mg of pegaptanib, an 18% absolute reduction in legal blindness, compared to sham treatment, translates into a number needed to treat of 5.6 (the number of patients who need to be treated to prevent one case of legal blindness). One abstract also suggests a benefit for pegaptanib over sham treatment at year 2.[17]

Adverse Effects

During the first year of the study, 7,545 injections were performed in 890 adults. No systemic adverse events or hypersensitivity reactions were attributed to pegaptanib, and death rates were equal among groups. Antibodies to pegaptanib were not found.

Those receiving injections were significantly more likely to experience vitreous floaters, vitreous opacities, and anterior-chamber inflammation. Eye pain, punctuate keratitis, cataracts, eye discharge, and corneal edema were also more frequent in the treated eye. The most serious adverse events related to the injection procedure included endophthalmitis (n=12, 0.16% per injection, 1.3% per patient), traumatic lens injury (n=5, 0.07% per injection, 0.6% per patient), and retinal detachment (n=6, 0.08% per injection, 0.7% per patient). Of the 23 individuals who experienced adverse events, one individual with endophthalmitis and one individual with lens injury lost >30 letters of vision.[19]

Administration and Costs

Pegaptanib is administered on a six-weekly basis. Treatment is not titrated to the disease status of the eye, but is administered continuously for at least one year. Clinical or angiographic evaluations of the post-injection macular status are not used to guide retreatment decisions. In the US, the drug is sold at US$995 per injection.[18]

Concurrent Developments

Intravitreal triamcinolone acetonide (ITA) injections are being studied as an adjunct to PDT therapy.[19] Randomized controlled trials have not yet been completed. Studies of ITA as a stand-alone therapy for neovascular AMD suggest that this therapy may be ineffective.[20] Anecortave acetate, a synthetic cortisol derivative, shows promise for use in the treatment of neovascular AMD.[21] Other anti-VEGF therapies, including ranibizumab (Lucentis™, Genentech), are being evaluated for neovascular AMD.[22]

Rate of Technology Diffusion

Given the high cost of pegaptanib in the US, it is unlikely that this drug will be widely used in Canada unless provincial governments provide funding. Because angiography is not required to guide treatment (after the initial diagnosis of neovascular AMD) and a PDT laser is not needed, some physicians and patients might find treatment with pegaptanib preferable to PDT.

Implementation Issues

Pegaptanib will likely be used for all angiographic lesion types of AMD, particularly for large minimally classic and occult lesions where verteporfin may be less effective.

In clinical practice, patients may hesitate to undertake a treatment involving intraocular injections every six weeks for one or two years. This may be particularly true for patients who travel long distances to access specialized eye care.

Ophthalmologists specializing in retinal care are concerned about the lack of clinical end-points for titrating therapy, and the potential clinical burden that pegaptanib injections may create. If pegaptanib is found to be effective for retinal venous occlusive disease and diabetic retinopathy (studies are underway), retina specialists may be encumbered by the extra procedural work. This issue may be alleviated if easily administered, prolonged-release drug delivery devices are developed.[23]

As with PDT for neovascular AMD, pegaptanib has a modest effect on vision, and rarely results in visual improvement. Multiple concomitant therapies will likely be needed to achieve better visual results for patients with neovascular AMD.

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CCOHTA appreciates comments from its reviewers.

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