ABSTRACT

Although potential treatments for neovascular age-related macular degeneration represent a fertile area of research, approved treatment options are limited. Some approved therapies are effective in certain disease subtypes but not in others. Lesion size and location also play a role in therapeutic outcome. This article reviews existing treatment modalities and indications for their use. Results of clinical trials, in addition to subgroup analyses related to lesion size and composition, are highlighted. These findings will help physicians tailor treatment to the specific clinical presentation of the disease.


LASER PHOTOCOAGULATION THERAPY

More than 20 years ago, the Macular Photocoagulation Study Group initiated a series of clinical trials in patients with choroidal neovascular lesions in one or both eyes.1-3 The trials evaluated the use of laser photocoagulation to ablate CNV in eyes with extrafoveal (≥200 µm from the foveal center), juxtafoveal (1–199 µm from the foveal center), and subfoveal lesions. The investigators reported a statistically significant reduction in the risk of severe visual loss with laser treatment up through 5 years of follow-up.2 However, laser treatment was not entirely successful in permanently eradicating neovascularization, and recurrence/persistence rates of 54% for extrafoveal CNV and 78% for juxtafoveal CNV were noted.1

In addition to the high recurrence rate, there are other significant limitations to the use of laser photocoagulation therapy. Only a small number of eyes (approximately 13% in one study) have nonsubfoveal CNV (Figure 1).4 Laser treatment of subfoveal lesions results in an immediate, severe reduction in central vision.5 Because laser photocoagulation indiscriminately damages the overlying neurosensory retina, any treatment extending into the foveal center will cause irreversible loss of visual acuity. Any visual benefit that may result on the basis of limiting a patient’s central scotoma is not typically realized on average for patients treated in this way until 1 or 2 years later in the course of the exudative AMD. Eligibility criteria used by the MPS Group in trials have been adopted as guidelines for determining which kinds of CNV lesions are most suitable for treatment.2,6 The generally accepted guide-
lines still in practice today include treating symptomatic, well-demarcated extrafoveal and juxtafoveal lesions. However, subfoveal laser treatment was never widely adopted because of the severe, acute vision loss from the treatment and is not used to any significant degree at this time with the availability of alternative treatments.

To maximize the success rates of laser photocoagulation in the treatment of CNV, the laser spots must be relatively intense and confluent. The entire CNV complex, including any surrounding elevated blocked fluorescence and contiguous thin blood, must be included in the area treated. In addition, the treatment must extend at least 100 µm beyond the peripheral boundaries of the CNV complex. This approach may not be possible for juxtafoveal lesions within 100 µm of the foveal center, thus rather than risk laser treatment of the foveal center, many clinicians now prefer alternative treatments such as photodynamic therapy (PDT) or pegaptanib for these neovascular lesions.

**Photodynamic Therapy**

In April 2000, the US Food and Drug Administration (FDA) approved the use of PDT with verteporfin for the treatment of predominantly classic CNV secondary to AMD based on findings from 2 multicenter randomized clinical studies—the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) investigations. PDT consists of a 2-step process, beginning with the intravenous infusion of the photosensitizing drug verteporfin. The current treatment regimen was developed from the protocol used in the clinical trials of verteporfin therapy. A verteporfin dose of 6 mg/m² body surface area is infused over 10 minutes. During this time, the drug selectively accumulates in the CNV. The drug retained in the CNV is then activated using a nonthermal (nondestructive) laser 15 minutes after the start of the infusion. The laser light wavelength is 689 nm, corresponding to the peak absorption of verteporfin and is applied in a continuous fashion for 83 seconds at an intensity of 600 mW/cm² to give a light dose of 50 J/cm² (Figure 2). The size of the laser spot should be approximately 1000 µm greater than the greatest linear dimension of the CNV complex.

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**Figure 1. Laser Eligibility in Neovascular Age-Related Macular Degeneration**

| 3% PED | 13% “Classic” nonsubfoveal CNV |
| 84% Other CNV |

CNV = choroidal neovascularization; PED = pigment epithelial detachment. Figure is courtesy of Jason Slakter, MD. Data from Freund et al.

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**Figure 2. Verteporfin Treatment Regimen**

Verteporfin infusion over 10 min
6 mg/m² BSA in 30 mL D,W

Light application 15 min after start of infusion

Follow-up every 3 months until stable
Treat if there is fluorescein leakage from CNV

Verteporfin infusion

Light applied for 83 seconds
Wavelength: 689 nm
Light intensity: 600 mW/cm²
Light dose: 50 J/cm²

BSA = body surface area; CNV = choroidal neovascularization. Figure courtesy of Novartis Pharmaceuticals, East Hanover, New Jersey. Data from Arch Ophthalmol. 1999;117:1329-1345.
Patients are followed-up at 3-month intervals. At these visits, if the fluorescein angiogram shows leakage from the CNV, patients should be retreated. The decision to retreat a patient should not be based on the vision acuity per se. Although the CNV complex may still grow over time, ultimately there should be less and less angiographic leakage from the CNV after repeated treatments until leakage stops altogether.

The pivotal phase III (TAP) trials definitively demonstrated that verteporfin PDT effectively improved vision outcomes. The primary efficacy outcome in the studies was the percentage of patients with moderate vision loss, defined as a loss of at least 3 lines (15 letters) of visual acuity. In the total study population ($n = 609$), verteporfin-treated eyes were more likely to avoid moderate vision loss at 12 months compared to those eyes receiving placebo; 61% of verteporfin-treated eyes had lost less than 3 lines of visual acuity compared to 46% of control group eyes ($P < .001$). This benefit was maintained at 24 months when 53% of verteporfin-treated patients had lost less than 3 lines compared to 38% of the patients given placebo.

In a subgroup analysis at 12 months, the best results were achieved in eyes with predominantly classic lesions, defined as those lesions in which the area of classic CNV made up at least 50% of the area of the entire lesion at baseline; 38% of treated patients lost 3 lines or more of vision, versus 61% of placebo-treated patients. Findings for 24 months were consistent with those findings reported at 12 months.

An extension trial showed a good durability of effect through 5 years and provided additional information regarding optimal length of treatment. The study showed that on average, patients required approximately 5 treatments over the course of 2 years and only rarely needed additional treatments in the years that followed. Figure 3 illustrates the positive outcomes that may be achieved with PDT. In this patient, whose small subfoveal classic CNV lesion makes him an ideal candidate for PDT, the visual acuity and the lesion size were stable after 1 year of treatment.

The TAP reports indicated a role for verteporfin in predominantly classic CNV, prompting further analysis designed to answer the question as to why verteporfin did not appear to benefit minimally classic CNV. Analysis of the TAP data showed that eyes with minimally classic CNV showed no benefit at 12 months or 24 months. However, additional subgroup analysis did reveal a slight benefit at 24 months in small minimally classic lesions ($\leq 4$ disc areas).

The potential efficacy of verteporfin PDT for relatively small minimally classic subfoveal CNV was further supported by the phase II Verteporfin in Minimally Classic (VIM) trial. The study arms compared verteporfin with a reduced light protocol (300 mW/cm² and 25 J/cm²) to verteporfin with a standard light protocol (600 mW/cm² and 50 J/cm²) and also included 2 placebo arms that underwent the 2 light protocols but did not receive verteporfin. Both verteporfin study arms showed a statistically significant benefit from treatment compared to placebo: -2.8 letters standard light ($P = .024$) and -1.6 letters with reduced light ($P = .008$) versus -9.4 letters with placebo. The study showed a trend toward diminished letter loss with the reduced light compared to the standard light protocol.

**Figure 3. Illustration of Optimal Clinical Results in Treating Subfoveal Classic CNV with Verteporfin PDT**

*This patient had 20/80 vision at baseline before verteporfin PDT. (A and B) The small, subfoveal classic CNV (shown on the fluorescein angiogram) makes this patient an ideal candidate for PDT. One year later after 3 treatments (C and D) the visual acuity was stable at 20/80. The fluorescein angiogram shows no significant CNV growth and only minimal dye leakage. OCT imaging demonstrates normalization of the foveal contour. OCT imaging is not part of recommended follow-up to therapy, but it may be useful for confirming questionable fluorescein leakage.*

CNV = choroidal neovascularization; OCT = optical coherence tomography; PDT = photodynamic therapy.
standard light protocol in minimally classic lesions, but this finding did not reach statistical significance.12

What conclusions can we reach regarding the use of PDT for minimally classic lesions? Based on the TAP analyses8,9 and the small-scale VIM trial,12 standard verteporfin PDT appears to be beneficial for small (≤4 disc area) lesions. Based on placebo assessment, we know that conversion to predominantly classic lesions and larger predominantly classic lesions results in worse prognosis. It is possible that the effect of PDT may be to reduce the rate of conversion from minimally classic or occult with no classic to predominantly classic lesions.13 Therefore, it is certainly reasonable to consider treating small minimally classic lesions with verteporfin PDT.13

In the TAP trials, there was a trend for visual benefit in eyes with occult with no classic subfoveal CNV. This treatment benefit was confirmed at the 24 month follow-up point in the Verteporfin in Photodynamic Therapy clinical trial.14 Treated eyes were statistically less likely to have moderate and severe vision loss, and the treatment benefit was greatest in eyes with relatively small CNV (≤4 disc areas) at baseline.

What do we know about the safety of verteporfin PDT? Visual disturbance, which included abnormal vision, decreased vision, and visual field defect, was the most frequently reported ocular adverse event in the verteporfin group after 2 years (22.1%)9 and 5 years (30%).15 A severe decrease in vision (≥4 lines) occurring within 7 days after treatment with verteporfin has been reported by 1% to 5% of patients.16,17 Partial recovery of vision occurred in some patients. Patients with a severe decrease in vision should not be retreated until vision completely recovers to pretreatment levels. Then, the potential risks and benefits of subsequent treatment should be carefully considered by the treating physician.16

The incidence of injection-site events in the verteporfin group during the 2-year double-masked portion of the study was 15.9%9 versus 19%15 at 5 years. Photosensitivity reactions occurred in 3.5% of patients by 2 years.7 At 5 years, this rate was even lower (3%).15 Infusion-related back pain was reported by 3% of patients over 5 years.15

Photodynamic therapy has a proven benefit in predominantly classic and small occult-only CNV. Treatment of these lesion types results in a statistically significant reduction in vision loss. Recent clinical trials do not yet support altering the current treatment regimen. Lesion size appears to be the most important baseline factor affecting outcome of therapy. Treatment of smaller minimally classic lesions may be considered. Combining PDT with other treatment modalities may offer some potential for improved anatomic and visual outcomes.

NEW AND INVESTIGATIONAL TREATMENTS

In December 2004, the FDA approved the anti-vascular endothelial growth factor (VEGF) agent pegaptanib sodium for the treatment of all subtypes of neovascular AMD. Pegaptanib sodium is described in detail in a separate article in this monograph by Dr Evangelos S. Gragoudas.

The angiostatic cortisone, anecortave acetate, and the antiangiogenic agent ranibizumab are currently under investigation for treatment of neovascular AMD. Additional information on anecortave acetate is provided in the sidebar “Other Inhibitors of Neovascularization,” which accompanies the article by Dr Philip J. Rosenfeld. The article contains information on the investigational antiangiogenic drug ranibizumab. Efficacy and safety data have recently been released through a press release, but details have yet to be presented and the phase III trial results are not yet published.18

One pilot study has reported on the use of verteporfin PDT in combination with intravitreal triamcinolone acetonide for CNV.19 In this small non-comparative case series, some improvement in visual acuity was reported. In addition, less retreatments with PDT were needed to halt angiographic leakage from the CNV lesions. However, increased intraocular pressure was a problematic side effect requiring topical medicines in a significant number of patients. Randomized clinical trials are underway to evaluate the potential added efficacy of this type of combination treatment.

CONCLUSIONS

Laser photocoagulation is rarely used in the treatment of neovascular AMD, primarily because presentations of nonsubfoveal CNV are extremely rare in AMD. Verteporfin PDT is FDA indicated for use in subfoveal predominantly classic AMD, but some analyses have suggested a possible role for this treatment for selected small lesions of the minimally clas-
sic or occult subtype. Verteporfin PDT is approved for this indication by a regulatory agency in Europe and elsewhere in the world, and it is considered viable therapy by the American Academy of Ophthalmology’s Preferred Practice Pattern. Pegaptanib sodium is discussed in a separate article by Dr Gragoudas in this monograph and is approved by the FDA for all AMD CNV lesion subtypes, although only 1-year data have been published to date.

Despite its investigational status, the combination of PDT with triamcinolone is increasingly being used in clinical practice with anecdotal reports of some success, but there is no firm proof yet of improved efficacy over PDT alone. Short-term outcomes appear favorable, but longer-term data from prospective randomized trials are needed. The recent approval of pegaptanib provides a useful addition to what has been a limited clinical armamentarium. Anecortave acetate has not yet been approved by the FDA as of May 31, 2005, and ranibizumab results have suggested, although not yet published in the peer-reviewed literature, that 1-year outcomes can result in 95% of treated cases having less than 3-line loss compared to 62% of untreated cases.18

REFERENCES


15. Data on file, Novartis Pharmaceuticals.


