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Phase I/II clinical trial results of verteporfin enhanced feeder vessel therapy in subfoveal choroidal neovascularization in age-related macular degeneration.

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ABSTRACT

Background/Aims: To investigate the safety and efficacy of extrafoveal photodynamic therapy (PDT) occlusion of feeder vessels (FVs) in patients with subfoveal choroidal neovascularization (CNV) due to age-related macular degeneration.

Methods: FVs were identified using dynamic fluorescein and indocyanine green angiography with scanning laser ophthalmoscope. The standard dose of verteporfin and laser wavelength were used. The light dose was escalated by increasing the duration of the light dose so the light regimen was 50 J/cm^2 for patients 1 and 2, 100 J/cm^2 for patients 3,4,5, 125 J/cm^2 for patients 6 and 7 and 150 J/cm^2 for patients 8 and 9. Patients were examined at weeks 1,4 and 12.

Results: The mean improvement on EDTRS chart 3 months after treatment was an increase of 2.1 lines (p=.07). Closure of the FV was achieved angiographically in 3 eyes at various light doses, in 3 eyes the FV was hypoperfused and in 3 eyes the vessels were were neither closed nor hypoperfused. At the last follow up all FVs were reperfused. There was no evidence of retinal damage.

Conclusion: Verteporfin enhanced FV therapy does not cause subfoveal retinal damage and may have potential to improve central vision in subfoveal CNV due to exudative macular degeneration. We are not recommending this as a monotherapy for CNV.

INTRODUCTION

Choroidal neovascularization (CNV) is responsible for most of the severe vision loss associated with age-related macular degeneration (AMD).[1] The concept of treatment of subfoveal neovascular membranes in AMD by specifically targeting its feeder (afferent) vessel has been considered an attractive therapeutic approach in order to avoid collateral damage to larger retinal areas adjacent to and involving the fovea.[2-7] The initial clinical success with absence of histopathologic data on treated choroidal neovascularization feeder vessels led to elaboration of a theoretical model of choriocapillaris blood flow and its relation with CNV.[8]

According to this model, CNV feeder vessels (FV) lie in the Sattler layer, and enter the choriocapillaris in close proximity to the other penetrating vessels that form the choriocapillaris/CNV communication. This has been supported by clinical observations.[9] Previous studies also demonstrated that 22-42% of patients with CNV have demonstrable feeder vessels.[2,3] A feeder vessel perfuses the choroidal neovascular membrane and can be distinguished from a draining vein by high speed ICG video angiography and timing. Published reports suggest that these vessels, when successfully photocoagulated by laser, produce reduction of the associated CNV blood flow. It has been reported that even partial occlusion of a feeder vessel may be sufficient to effectively reduce CNV blood flow and cause a favorable clinical response.[4]

Various methods of laser feeder vessel obstruction have been employed including the 630 nm red,[1] the 576 nm yellow,[2,7] the 514 nm argon green,[3] the 810

nm diode laser [7,10-12] and photodynamic therapy (PDT), normal light dose.[13] Feeder vessels are typically extrafoveal, and thus higher light doses (prolonged duration of treatment) may allow even more complete verteporfin mediated destruction of feeder vessels as collateral damage to overlying retina is less of a visual safety concern. In this FDA-approved pilot study we investigated the safety and efficacy of extrafoveal photodynamic therapy (PDT) occlusion of feeder vessels in patients with CNV due to AMD with escalation of light dose.

SUBJECTS and METHODS

Patient population

This was a phase I/II light-dose escalating study approved by the Institutional Review Board of the University of California San Diego and the United States Food and Drug Administration. The patients were seen at the Jacobs Retina Center in La Jolla, California between August 2003 and December 2005. Patients signed informed consents that comply with FDA Regulations and the International Conference on Harmonization guidelines prior to undergoing any study-related procedures.

All selected patients had fluorescein angiographic (FA) evidence of minimally classic CNV with high-speed indocyanine green (ICG) documentation of a single extrafoveal feeder vessel. Inclusion criteria in the study were $\geq$ 50 years old and the presence of CNV in the study eye. In the case of eligibility of both eyes, only one eye was to be treated. The decision was made between the patient and physician. Patients had to have best-corrected visual acuity (VA) score in the study eye between 65 and 20 letters measured with an Early Treatment Diabetic Retinopathy Study (ETDRS) chart (Lighthouse Inc., New York, NY), which is an approximate Snellen equivalent of 20/50 to 20/400. For the purpose of statistical analysis this was transformed into the logarithm of the minimum angle of resolution (logMAR) equivalent to create a linear scale of visual acuity (logMAR=log[1/Snellen equivalent]). Extrafoveal feeder vessels supplying the area of the CNV lesion had to be clearly identified, with the

greatest linear dimension of the entire lesion less than 5400 microns at the initial treatment. The patients had to be able to return for all study visits.

Excluded were the patients with hypersensitivity/allergy to fluorescein, ICG or verteporfin; with the FV located directly beneath a major retinal artery or vein; the patients unable to be photographed; or the patients with other ocular diseases associated with CNV (angioid streaks, pathologic myopia, histoplasmosis, blunt trauma, multifocal choroiditis). Additional exclusion criteria were pregnancy; prior PDT for minimally classic or occult with no classic CNV; and prior or ongoing treatment for AMD (macular scatter laser photocoagulation, subfoveal laser photocoagulation, transpupillary thermotherapy, radiation or pharmacotherapy).

Feeder Vessel Identification

At the baseline visit, all of the patients underwent a general ophthalmologic evaluation with dilated exam. Dynamic FA and ICG examinations were performed using the Heidelberg HRA I scanning laser ophthalmoscope (SLO) (Heidelberg Engineering, Heidelberg, Germany). The SLO is configured to record ICG fluorescence at a rate of 12 frames/second with a two second frame buffer. High-speed video ICG angiography was used to identify feeder vessels in the presence of CNV. The identification of feeder vessel(s) was based on their appearance preceding that of the retinal vessels during the early phases of

dynamic FA and ICG and on their relationships with choroidal circulation and the CNV during the course of the angiography (Fig. 1a, 2a, 3a). After the feeder vessel was identified on the H-S ICG the corresponding spot of area to be treated was transposed on to an early FA image to facilitate the location of laser delivery. The eligible patients were those with a single feeder vessel identified, and, therefore only one vessel was treated.

Treatment

The treatment procedure started with FDA approved dose intravenous infusion of verteporfin 6 mg/m^2 administered during 10 minutes. Five minutes after the end of infusion, photocoagulation energy was delivered by 689 nm laser light with the following range of parameters: light intensity 600 mW/cm^2, laser spot size 1000-2000 microns (used at the discretion of the investigator depending on the size of feeder vessel). The treatment effect (dose) was escalated by increasing the duration of the light dose so the light regimen was 50 J/cm^2 (83 sec. duration) for patients 1 and 2, 100 J/cm^2 (166 sec. duration) for patients 3,4,5, 125 J/cm^2 (208 sec. duration) for patients 6 and 7 and 150 J/cm^2 (291 sec. duration) for patients 8 and 9 (Table 1). The light application was interrupted at consistent time intervals to give the patient a chance to blink and rest. In order to keep the fractionation of the light delivery controlled, the light treatment was stopped every 83 sec. (every 50 J/cm^2 delivered) and commenced

30 sec. later. The treatments were all performed by one investigator (WRF). All patients were instructed to follow sun-protective precautions.[14]

Follow-up

Patients returned for follow-up at weeks 1,4 and 12 after the treatment. The complete ophthalmologic exam included ETDRS visual acuity (VA), intraocular pressure measurement, dilated fundus exam, stereoscopic fundus photography and FA/high-speed ICG video angiography (week 4 and 12 post-treatment). The primary study objective at these visits was to assess the safety of extrafoveal PDT. The secondary objective was to assess preliminary signs of efficacy of this treatment as measured by the extent of reduction of the CNV membrane on ICG, closure of FV on video angiography, reduction or absence of leakage determined by FA and change in VA from baseline. The area of leakage on fluorescein angiogram was delineated using Eye Explorer Software Version 1.3.2.0 (Heidelberg Engineering, Vista, CA). The pre- and post-treatment findings were compared using one-tailed paired t-tests.

RESULTS

The study included 9 eyes of 9 patients (5 men/4 women) with average age (mean±SD) 79.57±5.07 years. After the procedure we evaluated visual acuity and the degree of occlusion or reduction of perfusion of the feeder vessel by scanning laser video angiography, and the presence or change in late leakage from CNV on FA and visual acuity.

Table 1 shows light dose received by patients. None of the patients reported any adverse effect related to injection or post-treatment course. On ophthalmoscopic examination of the treated eyes, we observed no increase in exudation, hemorrhage or laser-related damage of the fovea or perifoveal area. No damage to retinal vasculature was seen on FA at any studied time points.

Pre-treatment VA ranged from 20/50 (0.4 logMar) to 20/400 (0.05 logMar) (median 0.829 logMar). Visual acuity after the treatment ranged from 20/32 (0.625 logMar) to 20/400 (0.1 logMar) (median 0.585 logMar)(p=.07). One patient (11.1%) lost one line, two patients (22.2%) did not lose or gain any line, two patients (22.2%) gained 1 line, two patients (22.2%) gained two lines and two patients (22.2%) gained three lines of vision on EDTRS chart 3 months after treatment. On average, patients after therapy gained 2.1 lines (11 letters). Elimination of the lowest light dose showed significant improvement (p=.04) between pre- and post-PDT VA results.

The first post-treatment video angiography showed that closure of the feeder vessel was achieved in 3 eyes (33.3%)(Fig.1b), in 3 eyes (33.3%) the feeder vessel was hypoperfused (Fig.2b) and in 3 eyes (33.3%) feeder vessels

were neither closed nor hypoperfused (Fig. 3b). At the last follow up all FVs were reperfused (Figs. 1c, 2c, 3c). The pre- and post-treatment area of fluorescein leakage on FA was 13.32 ± 10.33 mm^2 and 11.68 ± 8.62 mm^2, respectively (p=.25). When eliminating the lowest energy dose there was a difference between pre- and post-treatment leakage area (p=.07).

DISCUSSION

Photocoagulation of feeder vessels in AMD-associated CNV with different types of lasers resulted in various amounts and duration of anatomic and functional stabilization.[3,5-7,9] Feeder vessel closure initially used argon green and then yellow dye lasers in order to use a hemoglobin-absorbing wavelength to damage feeder vessels. Such photocoagulation caused full thickness retinal damage and choriocapillaris damage as well.[2,3] Subsequently, the 810 nm diode laser was studied because of its ability to penetrate tissue and potentially spare the overlying retina.[7,11] With this wavelength, vascular closure is difficult because the laser is poorly absorbed by hemoglobin[15] and coupling the laser with ICG as a desirable photosensitizing agent was suggested to make this modality more effective.

Photodynamic therapy has shown statistical benefit both in classic and occult choroidal neovascularization.[16,17] Verteporfin therapy has vaso-occlusive mechanism that affects both the CNV and normal choroid.[18,19] A single PDT application produces an area of hypofluorescence of the choriocapillaris, which at 1 week is identical in size to the area of the treatment spot used, consistent with a direct occlusive effect. However, clinical doses of PDT[20] and/or reduced light dose[21] leave the overlying RPE and the neurosensory retina undamaged. Choroidal perfusion changes in the photosensitized area are considered transient, with restoration occurring within 3 months.[20,22] As our study protocol included FA/ICG examination 1 month after the treatment, we could not evaluate

this phenomenon at 1 week when choriocapillaris hypoperfusion is most prominent. A combination of PDT and subsequent FV laser coagulation using standard photocoagulation wavelengths has been used in the treatment of CNV in AMD[7,13] and CNV secondary to choroidal rupture after blunt trauma.[23]

We investigated the safety and efficacy of using PDT to directly occlude feeder vessels in subfoveal CNVs in patients with exudative AMD. There is only one similar case reported in the literature with report of visual improvement.[13] As we do not precisely know the amount of energy necessary for feeder vessel closure we chose a dose escalating study approach. We held the systemic drug dose and timing of the treatment the same.

In our group the most common FV pattern was its insertion in CNV membrane from the nasal side (the "racket-like pattern")(Figs.1a, 2b) which is consistent with previous studies.[3] One patient had a vessel supplying CNV from the temporal side and in one (Fig. 3a) the vessel originated from the choroidal vascular bed directly beneath the CNV and was hidden by the membrane as soon as it was filled with dye (the "umbrella-like pattern"). The first examination after PDT treatment to the feeder vessels showed that patients in the first light dose group had no decrease in CNV perfusion after treatment; angiography revealed that the FVs remained perfused. In the second light dose group, we saw FV closure in 1 patient (Fig. 1b) and hypoperfusion in another and permanent closure in the last one. In the third dose, one patient had closed FV, one had hypoperfusion of FV (Fig. 3b) and the other, with an umbrella-like pattern feeder vessel, had no treatment effect. In the group with the highest light dose 1 patient

had FV closure and 1 had no treatment effect. At the last follow-up FVs in all study patients were either still perfused or re-perfused.

Failure of FV closure after its laser photocoagulation has been previously reported.[3] The phenomenon of non-occlusion and/or reperfusion after PDT treatment is well known. Schmidt-Erfurth et al. showed that vessel occlusion after PDT is not complete and that the CNV complex remains patent at the FV level in 50% of treated patients.[18] Multiple PDT applications within short intervals have been shown to reduce the vessel patency in CNV but did not influence the frequency of recurrence of new vessels. Tomographic analysis also revealed loss of the superficial choriocapillaris layer and maintenance of perfusion of larger choroidal vessels. Based on these data it is tempting to speculate that a similar mechanism occurred in our patients in early post-treatment period.

Provided that high enough laser energy is used to occlude the FV there are other factors associated with blood supply to CNV, namely FV number and width. Even though strict inclusion criteria in this study included the presence of only one vessel, it is possible that CNV membranes were supplied by more than one feeder vessel. In a histopathologic study of choroidal neovascular membranes by Green et al. 54% of examined eyes had 2 or more vascular sources.[24] It is therefore very likely that in human CNV, smaller feeder vessels are present but are not angiographically visible.

Although we were able to only partially occlude the FVs as evidenced by ICG angiography, functional outcomes in our patients showed improvement in VA. Only one patient lost 1 line of VA, however, there was an average gain of 2.1

ETDRS lines (11 letters). Sub-analysis, eliminating the lowest light dose, showed significant improvement (p=.04) between pre- and post-PDT VA results. There was also a smaller area of fluorescein leakage when we compared pre- and post-treatment fluorescein angiograms with borderline significance for the higher treatment doses.

These results indicate that targeted PDT treatment of FVs has an impact on the course of the disease. Our study shows no evidence of retinal damage even at the higher doses of light. Focal obliteration of FV using high light dose PDT appears more efficacious than FV treatment with standard light dose PDT. We are not recommending this as a monotherapy for CNV. Our study was performed prior to the availability of anti-VEGF therapy for CNV. However, such modality seems to reduce the perfusion of the CNV complex and may be considered beneficial in combination with anti-VEGF or other pharmacotherapy.

REFERENCES

1. Seddon JM. Epidemiology of age-related macular degeneration. In: Ryan SJ, editor. Retina. St. Louis: Mosby, 2001:1039-1050.
2. Shiraga F, Ojima Y, Matsuo T, et al. Feeder vessel photocoagulation of subfoveal choroidal neovascularization secondary to age-related macular degeneration. Ophthalmology 1998;105:662-669.
3. Staurenghi G, Orzalesi N, La Capria A, et al. Laser treatment of feeder vessels in subfoveal choroidal neovascular membranes. Ophthalmology 1998;105:2297-2305.
4. Flower RW. Experimental studies of indocyanine green dye-enhanced photocoagulation of choroidal neovascularization feeder vessels. Am J Ophthalmol 2000;129:501-512.
5. Costa RA, et al. Invest Ophthalmol Vis Sci 2002;43[suppl]4:2502.
6. Mantel I, Zografos L. Photocoagulation des vaisseaux rétiniens nourriciers d'une anastomose choriorétinienne dans le cadre d'une dégénérescence maculaire liée a l'âge. J Fr Ophthalmol 2003;26(5):493-497.
7. Coscas F, Stanescu D, Coscas G, Soubrane G. Traitement des vasseaux nourriciers de la néovascularisation choroidienne rétrofovéale dans la dégénérescence maculaire liée a l'âge. J Fr Ophthalmol 2003;26(6):602-608.

8. Flower RW, von Kerczek C, Zhu L, et al. Theoretical investigation of the role of choriocapillaris blood flow in treatment of subfoveal choroidal neovascularization associated with age-related macular degeneration. Am J Ophthalmol 2001;132:85-93.
9. Staurenghi G, Flower RW. Clinical observations supporting a theoretical model of choriocapillaris blood flow in treatment of choroidal neovascularization associated with age-related macular degeneration. Am J Ophthalmol 2002;133:801-808.
10. Wolfe JD, Csaky KG. Indocyanine green enhanced retinal vessel laser closure in rats: histologic and immunohistochemical observations. Exp Eye Res 2004;79:631-638.
11. Reichel E, Puliafito CA, Duker JS, Guyer DR. Indocyanine green dye-enhanced diode laser photocoagulation of poorly defined subfoveal choroidal neovascularization. Ophthalmic Surg 1994;25:195-201.
12. Costa RA, Calucci D, Cardillo JA, Farah ME. Selective occlusion of subfoveal choroidal neovascularization in angioid streaks by using a new technique of ingrowth site treatment. Ophthalmology 2003;110:1192-1203.
13. Sickenberg M, Ballini JP, van den Bergh H. Photothérapie dynamique a la Visudyne® et occlusion du vaisseua afférent: rationnel d'une association synergique et options cliniques illustrées. J Fr Ophthalmol 2004;27(1):93-102.
14. Treatment of Age-related Macular Degeneration With Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal

neovascularization in age-related macular degeneration with verteporfin - TAP report 1. Arch Ophthalmol 1999;117:1329-1345.

15. Baumal CR, Puliafito CA. Laser interactions with the retina and retinal pigment epithelium. In: Marmor MF, Wolfensberger TJ, editors. The Retinal Pigment Epithelium: Function and Disease. New York: Oxford University Press, 2001 587-603.
16. Bressler NM. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials - TAP report 2. Arch Ophthalmol 2001;119:198-207.
17. Verteporfin in Photodynamic Therapy Study Group. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularization - VIP report 2. Am J Ophthalmol 2001;131:541-560.
18. Schmidt-Erfurth U, Michels S, Barbazetto I, Laqua H. Photodynamic effects on choroidal neovascularization and physiological choroid. Invest Ophthalmol Vis Sci 2002;43(3):830-841.
19. Tzekov R, Lin T, Zhang K, et al. Ocular changes after photodynamic therapy. Invest Ophthalmol Vis Sci 2006;47:377-385.

20. Schotzer-Schrehardt U, Viestenz A, Naumann GOH, et al. Dose-related structural effects of photodynamic therapy on choroidal and retinal structures of human eyes. Graefe's Arch Clin Exp Ophthalmol 2002;240:748-757.
21. Michels S, Hansmann F, Geitzenauer W, Schmidt-Erfurth U. Influence of treatment parameters on selectivity of verteporfin therapy. Invest Ophthalmol Vis Sci 2006;47:371-376.
22. Schmidt-Erfurth U, Miller J, Sickemberg M, et al. Photodynamic therapy of subfoveal choroidal neovascularization: clinical and angiographic examples. Graefe's Arch Clin Exp Ophthalmol 1998;236:365-374.
23. Mennel S, Hausmann N, Meyer CH, Peter S. Photodynamic therapy and indocyanine green guided feeder vessel photocoagulation of choroidal neovascularization secondary to choroid rupture after blunt trauma. Graefe's Arch Clin Exp Ophthalmol 2005;243(1):68-71.
24. Green WR, Enger C. Age-related macular degeneration histopathologic studies. The 1992 Lorenz E. Zimmerman Lecture. Ophthalmology 1993;100:1519-1535.

FIGURE LEGENDS

Fig. 1a - Fluorescein angiography/ICG image of the posterior pole of the right eye in a patient before verteporfin photodynamic treatment of the feeder vessel complex. Arrow points to the treated spot.

Fig. 1b - Fluorescein angiography/ICG image of the posterior pole of the same patient 1 month after verteporfin photodynamic treatment with 50 J/cm^2 light dose. Arrow shows closure of the feeder vessel complex.

Fig. 1c - Fluorescein angiography/ICG image of the posterior pole of the same patient 3 months after verteporfin photodynamic treatment with 50 J/cm^2 light dose. Arrow shows reperfusion of the feeder vessel complex.

Fig. 2a - Fluorescein angiography/ICG image of the posterior pole of the left eye before verteporfin photodynamic treatment of the feeder vessel complex. Arrow points to the treated spot.

Fig. 2b - Fluorescein angiography/ICG image of the posterior pole of the same patient 1 month after verteporfin photodynamic treatment with 100 J/cm^2 light dose. Arrow shows hypoperfusion of the feeder vessel.

Fig. 2c - Fluorescein angiography/ICG image of the posterior pole of the same patient 3 months after verteporfin photodynamic treatment with 100 J/cm^2 light dose. Arrow shows reperperfusion of the feeder vessel.

Fig. 3a - Fluorescein angiography/ICG image of the posterior pole of the left eye before verteporfin photodynamic treatment of the feeder vessel complex. Arrow points to the treated spot, arrowheads delineate borders of the choroidal neovascular membrane.

Fig. 3b - Fluorescein angiography/ICG image of the posterior pole of the same patient 1 month after verteporfin photodynamic treatment with 125 J/cm^2 light dose. Arrow shows no change in perfusion of the feeder vessel, arrowheads delineate borders of the choroidal neovascular membrane.

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Fig. 3c - Fluorescein angiography/ICG image of the posterior pole of the same patient 3 months after verteporfin photodynamic treatment with 125 J/cm^2 light dose. Arrow shows no change in perfusion of the feeder vessel, arrowheads delineate borders of the choroidal neovascular membrane.

Table.1. Patients demographic characteristics with (pre-) and post-treatment visual acuity and light dose regimen in verteporfin enhanced feeder vessel therapy group.

Patient	**Sex**	**Treated eye**	**Dose (J/cm^2)**	**Pre-Tx area of leakage (mm^2)**	**Post-Tx area of leakage (mm^2)**	**Pre-Tx ETDRS**	**Post-Tx 1 week ETDRS**	**Post-Tx 4 weeks ETDRS**	**Post-Tx 3 months ETDRS**
1.	M	OD	50	36.46	29.10†	20/100	20/100	20/100	20/50†
2.	M	OS	50	12.13	15.59†	20/160	20/125	20/160	20/200 †
3.	F	OD	100	3.75	3.58†	20/50	20/63	20/50	20/32*
4.	F	OS	100	0.73	0.51†	20/80	20/80	20/125	20/63*
5.	F	OD	100	8.11	7.06†	20/400	20/100	20/100	20/100*
6.	M	OS	125	9.75	5.52†	20/200	20/160	20/160	20/160*
7.	F	OS	125	16.18	14.11†	20/400	6'/200	20/200	20/125*
8.	M	OD	150	15.7	15.2	20/400	20/400	20/400	20/400*
9.	M	OD	150	17.1.	14.5	20/100	20/80	20/80	20/100*

OD - right eye, OS - left eye, M - male, F - female, Tx - treatment, ETDRS - Early Treatment Diabetic Retinopathy Study visual acuity chart, † - p-value pre-treatment versus 3 months post-treatment for the entire group ($p>0.05$), * - p-value pre-treatment versus 3 months post-treatment excluding the lowest energy dose ($p<0.05$),