PDT: Therapies On the Cutting Edge

Clinical trials are under way to develop innovative and effective treatment modalities for wet age-related macular degeneration.

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Associate Editor

SINCE THE U.S. FOOD AND DRUG Administration approved photodynamic therapy with verteporfin for the treatment of predominantly classic subfoveal choroidal neovascularization and other ocular pathologies secondary to age-related macular degeneration, researchers have been studying expanded uses of the technology alone and in concert with other vascular drug treatments. A new era in the treatment of CNV due to AMD has quickly emerged.

In clinical trials, researchers are experimenting with various laser-light intensities and delayed light-application techniques to establish new treatment modalities for minimally classic and occult with no classic CNV—two forms of AMD that have no FDA-approved therapies in the United States. Other studies are concluding for the first time that verteporfin (Visudyne, Novartis AG) is safe and effective for long-term use, and retrospective subgroup analyses are demonstrating that lesion size plays a critical role in positive visual-acuity outcomes regardless of lesion composition.

Following is an update on the cutting-edge research in verteporfin therapy that ophthalmologists hope will create new therapies to serve a wider range of patients.

Predominantly Classic CNV

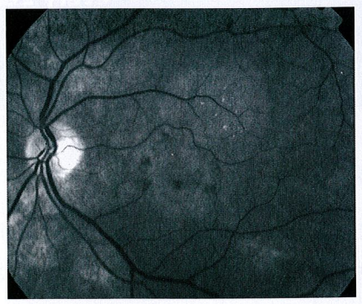
Researchers from the third-year, open-label extension of the Treatment of AMD with Photodynamic Therapy (TAP) investigation have found that vision remained relatively stable for five years in most verteporfin-treated patients with predominantly classic CNV, and that fewer retreatments were needed to maintain vision, according to Peter K. Kaiser, MD, a vitreoretinal surgeon at Cole Eye Institute in Cleveland.

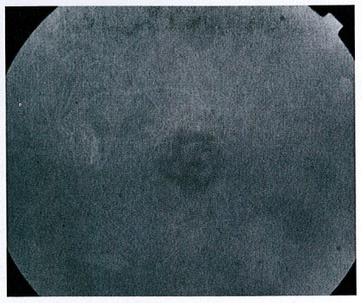
"The extension study showed that vision stabilized in most patients with predominantly classic CNV lesions who received verteporfin and that the treatment remained safe throughout the 60 months. So we now know that verteporfin therapy is safe and effective in patients for at least five years," says Dr. Kaiser.

The clinical trial included 124 of the original 159 verteporfin-treated patients (78 percent) who had completed two years of the TAP study and who were considered good candidates to benefit further from the therapy. Since not all patients in the TAP investigation participated in the extension, researchers express caution when interpreting these results.

In other research, investigators launched the Verteporfin Early Retreatment (VER) trial, an ongoing Phase III study of 323 patients, to determine whether verteporfin retreatments six weeks after initial therapy versus the standard three months is more beneficial.

Following the first verteporfin treatment at baseline, all patients are receiving retreatments at three months and six months. Half are randomly selected, however, to receive verteporfin six weeks and four and a half months after the initial infusion.





Left: Predominantly classic subfoveal choroidal neovascularization prior to PDT. Right: A fluorescein angiogram nine months after a third session of PDT.

The study is based on the rationale that 80 percent of vision loss in verteporfin-treated patients who lose visual acuity occurs in the first six months after treatment when abnormal blood vessels rejuvenate and advance the disease. "So if we can treat the abnormal blood vessels when they first come back to life, we should be able to limit vision loss in patients," says Louis A. Lobes, Jr., MD, partner of Retina Vitreous Consultants and clinical associate professor at the University of Pittsburgh Medical School. "The other theory is if we treat the lesions more frequently, we can limit the size of the final active lesion and, therefore, decrease the amount of visual damage." One-year results of the 24-month trial are expected early in 2004.

Occult with No Classic CNV

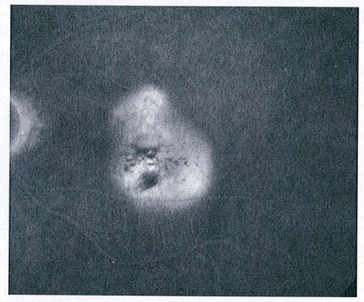
The need for an FDA-approved treatment for occult CNV in the United States has spurred researchers to begin the Visudyne in Occult (VIO) trial—a 24-month, multicenter study that's analyzing a subset of patients with occult lesions who participated in the Visudyne in Photodynamic Therapy (VIP) study. The latter showed positive visual-acuity outcomes in verteporfin-treated patients with occult CNV.

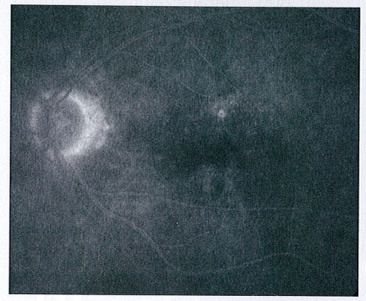
The VIO trial will include 360 patients, age 50 and older, who will be enrolled at 30 centers in the U.S. and 11 sites in Canada, according to researcher Kevin J. Blinder, MD, a vitreoretinal specialist at Barnes Retina Institute, and assistant professor of ophthalmology at Washington University School of Medicine in St. Louis.

"The VIO trial is essentially identical to the VIP study, but it incorporates what we've learned from the VIP trial, namely that smaller lesions respond better to Visudyne treatment," says Dr. Kaiser, the VIO-study chairman. "The FDA liked the results [of the VIP trial], but it wants more proof that patients with small occult lesions respond better to treatment."

Results from a retrospective subgroup analysis of the VIP trial, which followed the disease course of occult CNV, showed that patients with occult lesions less than or equal to 4 MPS (Macular Photocoagulation Study) disc areas and baseline visual-acuity scores worse than 20/50 benefited most from verteporfin therapy and immediate treatment.

"Due to these results, a lot of physicians are not waiting for the results of the VIO trial but are using PDT to treat occult lesions off label," says Dr. Kaiser. "Instead of sitting around and watching patients lose vision, treatment is instituted."





Left: Fluorescein angiogram of an occult with no classic CNV lesion prior to PDT therapy. Right: The same occult lesion six months after a single session of verteporfin.

Based on the VIP subgroup analysis, researchers raised an important question: Should ophthalmologists promptly treat patients with occult with no classic lesions greater than 4 MPS disc areas and who have visual acuity scores of 20/50 or better as well or take the watch-and-wait approach until they convert to a predominantly classic composition that may benefit from treatment?

According to Dante J. Pieramici, MD, a retinal specialist with the California Retina Consultants in Santa Barbara, Calif., and co-director of the California Retina Research Foundation, physicians should watch and wait. The reason: Patients with larger lesions and higher levels of visual acuity are less likely to benefit from verteporfin treatment—as evidenced in the VIP trial. So they should be monitored for conversion or for vision loss, at which time they may be considered for possible verteporfin therapy.

"It's unclear why these patients didn't benefit from verteporfin treatment," says Dr. Pieramici. "Perhaps, they represent a subgroup of patients who have foveal photoreceptors that are relatively resilient to the effects of subfoveal CNV. Or, they may have what some have termed 'a survivor lesion' that manifests more benign pathophysiology."

In the Verteporfin with Altered (Delayed) Light in Occult (VALIO) study, researchers delayed non-thermal laser-light application for 30 minutes and for the standard 15 minutes after initiating a verteporfin infusion in patients with occult lesions. Sixty patients (median age 78) were equally randomized to the 15- or 30-minute treatment arm.

Six-month data show that patients in the 30-minute group lost 1.3 lines of vision compared with those in the 15-minute treatment arm who lost two to

three lines, says principal investigator Jason S. Slakter, MD, clinical professor of ophthalmology at New York University School of Medicine, and surgeon director at Manhattan Eye, Ear and Throat Hospital in New York City.

One-year results of the trial are expected late this year.

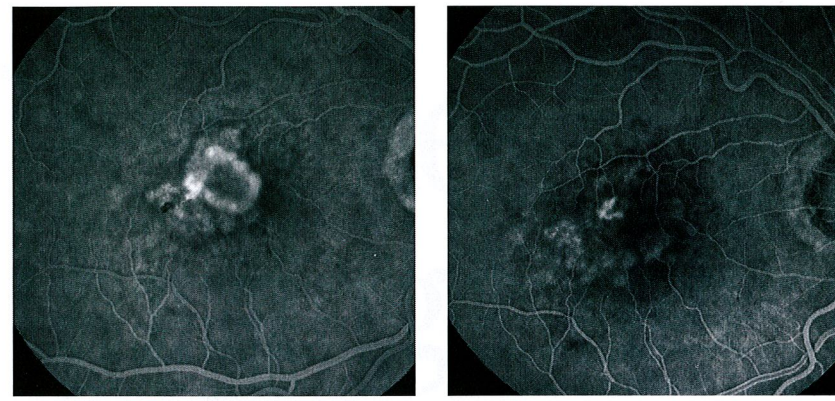
Researchers are encouraged by these results in that there's potential "for manipulation of the [standard] treatment regimen to provide better visual outcomes," says Dr. Slakter.

The theory behind delaying light application for an additional 15 minutes after administering a verteporfin infusion comes from previous clinical trials that have shown higher closure rates in occult lesions as a result. "Because of certain flow characteristics inherent in occult vessels, verteporfin builds up within [diseased] blood vessels while at the same time decreases in the surrounding normal tissue [as time progresses]. The end result is more drug in the target tissue and less drug in the normal tissue. So, theoretically, you get a more selective treatment," says Dr. Slakter.

Minimally Classic CNV

Retrospective subgroup analyses of the TAP investigation and VIP trial, led by Susan B. Bressler, MD, professor of ophthalmology at Johns Hopkins University School of Medicine in Baltimore, suggest that lesion size is an important predictor of treatment benefit for minimally classic and occult lesions.

Based on her data, Dr. Bressler suggests treating minimally classic and occult with no classic CNV when lesions are equal to or less than 4 MPS disc areas and to continue treating predominantly classic blood vessels regardless of size. Further, she recommends that physicians treat smaller lesions regardless of blood-vessel composition and consider undertaking larger lesions if a poor natural history exists



Left: A fluorescein angiogram of a minimally classic CNV lesion. Baseline visual acuity is 20/200. Right: The classic component of the neovascular membrane is much smaller three months following one verteporfin treatment, although the occult membrane remains visible. Visual acuity is 20/60.

Will Verteporfin Soon Have Competition?

Verteporfin is the only weapon in the ophthalmologist's armamentarium that's been approved by the U.S. Food and Drug Administration to treat wet age-related macular degeneration. But will it continue to be the only photosensitizing drug on the market?

Miravant Medical Technologies in Santa Barbara, Calif., the maker of the lipophilic photosensitizer drug Photopoint SnET2, plans to file its first New Drug Application for marketing approval. The decision came after two randomized Phase III clinical trials showed positive visual-acuity results in a significant number of patients treated with the drug.

Visual stability in the SnET2-treated patients with predominantly classic and minimally classic lesions was statistically significant versus those who received placebo. The studies also showed that the drug is safe and well-tolerated and may be used for a broader population of wet AMD patients than verteporfin (Visudyne, Novartis AG), which is only approved for predominantly classic choroidal neovascularization in the United States.

Like Visudyne, SnET2 is a light-activated drug designed to target abnormal blood vessels beneath the macula.

"There's a big question mark as to whether SnET2 will be FDA-approved," says Carl D. Regillo, MD, professor of ophthalmology at Wills Eye Hospital, Thomas Jefferson University in Philadelphia. "It seems to be showing that it stabilizes vision. The safety profile after two years of follow up seems to be favorable. But the big question is how well does it work? It's a matter of finding out how useful it will be in treating the various forms of AMD."

One photosensitizing drug that was recently in the clinical-trial pipeline but has since been pulled is Lu-Tex/Optrin (lutetium texaphyrin, Pharmacyclics, Sunnyvale, Calif.). "The preliminary rates of closure and the side effects such as paresthesia seen at higher doses suggested that [the drug] wasn't going to be as useful a vessel-closure agent as verteporfin," says Mark S. Blumenkranz, MD, chairman of the department of ophthalmology at Stanford Medical Center in Stanford, Calif.

Combining the Best of Both Worlds

Verteporfin may slow the progression of vision loss in most patients with age-related macular degeneration, but it doesn't stop disease recurrence or restore lost vision permanently. So researchers are conducting clinical trials combining verteporfin (Visudyne, Novartis AG) therapy with angiogenesis inhibitors, drugs that prevent blood-vessel growth, such as rhuFab V2 (ranibizumab, Genentech) and triamcinolone acetonide (Kenalog) in hopes of curing the disease.

"Antiangiogenesis drugs used with verteporfin offer the best theoretical opportunity for optimal visual outcomes," says Louis A. Lobes, Jr., MD, partner of Retina Vitreous Consultants and clinical associate professor at the University of Pittsburgh Medical School. "We know that patients on verteporfin alone continue to lose vision, so we need to add something to it. Verteporfin will be the foundation, and the antiangiogenesis drugs will block the VEGF stimulus that may result in better visual outcomes."

Here are the angiogenesis inhibitors currently being combined with verteporfin therapy in clinical trials.

RhuFab V2

RhuFab V2, or Lucentis, is an anti-VEGF (vascular endothelial growth factor) antibody fragment that's administered by intravitreal injection. It binds and inhibits VEGF, a protein that plays a critical role in ocular angiogenesis, thus blocking new blood-vessel growth.

Improvements in visual-acuity scores in previous Phase I/II trials after using rhuFab V2 have prompted researchers to introduce multiple Phase III studies this year.

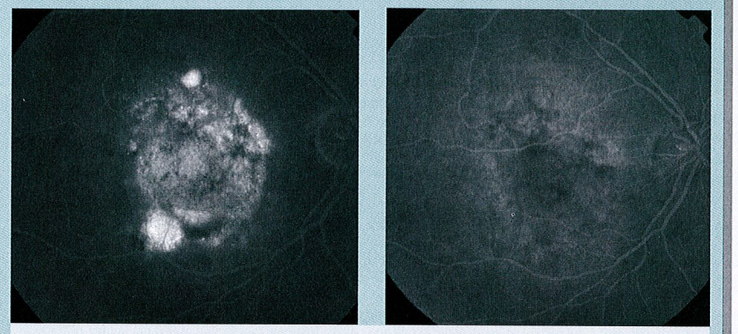
A dose-comparison, open-label clinical trial, called the Focus study, is under way to determine if injections of rhuFab V2 into the eye in combination with verteporfin is a safe, effective and tolerable treatment for patients with predominantly classic choroidal neovascularization secondary to AMD. Researchers will compare the combination therapy to a verteporfin-only regimen.

Two other trials are also in progress: The Marina study is recruiting 720 patients with minimally classic and occult CNV to compare rhuFab V2 injections alone to placebo. The Anchor trial is pitting rhuFab V2 alone against verteporfin therapy in 400 patients with predominantly classic lesions, says Ted McCluskey, MD, PhD, medical director and senior clinical scientist at Genentech, Inc., in San Francisco.

Triamcinolone Acetonide

Previous studies have shown that the corticosteroid triamcinolone acetonide improves visual acuity in patients with CNV when combined with verteporfin. The studies included a limited number of patients, but the positive visual-acuity outcomes and lack of fluorescein leakage have prompted a team of New York researchers, led by Richard F. Spaide, MD, partner of Vitreous-Retina-Macula Consultants of New York, to begin a multicenter, randomized phase II trial later this year that will again assess the effectiveness of Kenalog intravitreal injections following verteporfin treatment.

During the three-year study, patients will receive either verteporfin followed by a sham injection or verteporfin combined with a Kenalog injection, says Jason S. Slakter, MD, clinical professor of ophthalmology at New York University School of Medicine, and surgeon director of Manhattan Eye, Ear and Throat Hospital in New York City. Researchers will assess visual acuity and CNV closure rates to determine the number of retreatments needed for optimal visual outcomes.



Left: Leakage in an occult lesion following two prior PDT sessions. Right: Cessation of leakage three months following PDT combined with Kenalog injections.

Anecortave Acetate

Called an angiostatic steroid, anecortave acetate (Alcon) inhibits blood-vessel growth and is delivered by juxtascleral injection. Presently, no studies are under way combining the drug with verteporfin. But a recently completed six-month trial compared anecortave acetate and verteporfin therapy to PDT alone.

In the placebo-controlled, double-masked trial, 136 patients were randomized to receive a single 15-mg, 30-mg, or placebo injection of anecortave acetate one week following verteporfin therapy. Visual acuity stabilized in 78 percent of patients who received the combination treatment compared to just 67 percent of those treated with PDT alone. Recruitment for a Phase III study is under way to compare anecortave acetate alone to verteporfin for the treatment of wet AMD.

Macugen

Eyetech recently launched a phase II/III, randomized, multicenter trial to establish the safety and efficacy of intravitreal injections of the anti-VEGF agent Macugen (pegaptanib sodium) in patients with CNV due to wet AMD.

The two-year comparative study will determine if Macugen alone or combined with verteporfin will stabilize or improve vision. Approximately, 1,200 patients have been enrolled in 117 medical centers around the world. Researchers will measure visual-acuity outcomes as their primary endpoint.

(i.e., predominantly classic vessels).

These recent findings astounded one physician who, like many others, couldn't figure out why verteporfin therapy wasn't working for minimally classic CNV. "[That study] is an amazing story," says Dr. Lobes, "because there was no clear understanding why predominantly classic and occult lesions were responding but minimally classic CNV was not. It was a counterintuitive result you might say."

Lawrence J. Singerman, MD, FACS, president of Retina Associates of Cleveland, and clinical professor of ophthalmology at Case Western Reserve University, says "Lesion size is the most important determinant in visual outcome, and we finally have the data that show that clearly. Small lesions benefit from verteporfin no matter what the lesion composition, and if we can get that understood and sold to the FDA it would simplify things, bring clarity to doctors on how and when to treat their patients, and it would also allow more people to benefit from PDT."

Promising new data from the ongoing Visudyne in Minimally Classic (VIM) trial bolster the finding that small lesion size is a prime factor in successfully treating minimally classic lesions.

Participants in the Phase II, 24-month trial have minimally classic lesions equal to or less than 6 MPS disc areas—a significant difference from the lesion sizes of patients in the TAP investigation that ranged in size up to 9 MPS disc areas, which may explain why verteporfin therapy showed no benefit for these patients, says Philip J. Rosenfeld, MD, PhD, associate professor of ophthalmology at Bascom Palmer Eye Institute in Miami.

In the study, researchers are looking at the potential benefit of verteporfin therapy using a reduced or standard fluence (laser-light intensity) rate com-

pared to placebo in 117 patients with minimally classic CNV. Twelve-month preliminary findings show that 39 patients in the standard fluence group lost a mean of eight letters on the Early Diabetic Retinopathy Study visual-acuity chart compared with 38 people who lost a mean of five letters in the reduced fluence treatment arm. Patients receiving placebo in both fluence groups lost a mean of 14 letters.

"For the first time, we've been able to show a treatment benefit for minimally classic CNV," says Dr. Rosenfeld. "Patients treated with verteporfin have a reduced risk of vision loss and an increased chance of stable or improved vision."

The VIM study also showed that verteporfin-treated patients with minimally classic lesions were less likely to convert to predominantly classic CNV.

Yet, according to a retrospective subgroup analysis of patients with minimally classic CNV who were given placebo in the TAP investigation, researchers found that 40 percent of minimally classic lesions converted to a predominantly classic component over a 24-month period, with most of the conversions occurring in the first three months. Additionally, visual acuity and lesion size at the time of conversion in many patients were within a range where verteporfin therapy may reduce the risk of further vision loss.

Based on this data, investigators suggest that physicians monitor patients with minimally classic CNV closely within the first year of diagnosis if they're not receiving verteporfin therapy. That way, if they convert to predominantly classic CNV, they may be eligible for treatment.

Facing the Future

With the wealth of research under way and plans to conduct additional studies in the future, researchers are optimistic and particularly enthusiastic about the possibility of establishing new and effective therapies for their patients. "This is a very exciting time for us in retina," says Dr. Blinder. "We're dealing with a disease that we don't fully understand yet and have not had effective treatment modalities for in the past. But I think the next few years will show us a multitude of treatments for our patients."

Dr. Kaiser agrees. "I think all the research is very exciting for ophthalmologists. There are a lot of clinical studies going on and each one seems to be better than the one before."

The race to develop effective treatments for AMD, says Dr. Rosenfeld, is analogous to a sporting event. "We're all looking for that edge that will give our patients a performance advantage. Any gains or progress we make will come from making modifications to the PDT protocol. We're only looking at incremental gains at this point, but those are important."