Visudyne®
verteporfin for injection

Management of Persistent Fluid and Worsening Visual Acuity in a Patient With Resistant Neovascular Age-related Macular Degeneration

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Age-related macular degeneration (AMD) is a progressive, chronic disease and one of the leading causes of blindness globally. Neovascular AMD is characterized by pathologic choroidal neovascularization that breaks through Bruch's membrane into the subretinal pigment epithelium space and/or the subretinal space. This can lead to exudation, hemorrhage, retinal fluid, pigment epithelial detachment (PED), and fibrous scarring, which can have a serious adverse impact on visual acuity.[1]

Because vascular endothelial growth factor (VEGF) is a key component in promoting neovascularization, intravitreal anti-VEGF agents have greatly improved vision outcomes since their addition to the clinical armamentarium over a decade ago.[2] Even when there are clinical improvements in vision, neovascular AMD does not completely resolve after long-term therapy. Real-world therapeutic goals, including minimizing treatment burden and cost, and maximizing ocular and systemic safety, remain unmet in this patient population.[3-5]

The following case report describes a patient with bilateral neovascular AMD who received anti-VEGF injections for 2 years in the right eye. Despite treatment, the patient continued to experience worsening visual acuity and persistent fluid. After undergoing photodynamic therapy (PDT) with VISUDYNE® (verteporfin for injection), the patient required fewer anti-VEGF injections, had improved visual acuity, and remained fluid free as of the last follow-up in this case study.

Case Report: Photodynamic Therapy in a Patient With Persistent Fluid in Neovascular Age-related Macular Degeneration

BACKGROUND: A 67-year-old female was diagnosed with bilateral neovascular AMD. Despite treatment with anti-VEGF therapies, she experienced progressive vision loss.

DIAGNOSIS: The diagnosis of neovascular AMD was based on optical coherence tomography (OCT) and fluorescein angiography (FA) imaging in 2016, and the patient started receiving anti-VEGF treatment in 2017.

In November 2018 when I took over the patient's care, the imaging was reviewed and was felt to be consistent with AMD. The pattern on OCT (***Figure 1***) and FA (***Figure 2***) was not consistent with an alternative diagnosis such as central serous chorioretinopathy given the absence of a thickened choroid. Indocyanine-green angiography was not performed.

At this time, the vision in the right eye was 20/200 and vision in the left eye was reduced to hand motion. The IOP was 13 mm Hg and 16 mm Hg in the right and left eye, respectively. The vitreous was clear in both the eyes, though the right eye had a grade 2+ nuclear sclerosis cataract.

Indication

VISUDYNE® (verteporfin for injection) therapy is indicated for the treatment of patients with predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration, pathologic myopia or presumed ocular histoplasmosis. There is insufficient evidence to indicate VISUDYNE for the treatment of predominantly occult subfoveal CNV.

Important Safety Information

- VISUDYNE (verteporfin for injection) is contraindicated for patients with porphyria or known hypersensitivity to any component of this preparation.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information here.

TREATMENT: In February 2017, the patient's vision in her right eye was 20/40, and she was initially treated with intravitreal injections of bevacizumab, as needed (PRN). She was then transitioned to monthly bevacizumab due to a decline in vision to 20/80. By January 2018, her vision progressively declined to 20/200, and she was transitioned to aflibercept, once every 4 weeks.

But by November 2018, despite the monthly regimen of aflibercept injections, there was little improvement in best corrected visual acuity (BCVA) and more importantly, there was persistent fluid. OCT taken at the time showed pigment epithelial detachment and intraretinal fluid present (***Figure 1***).

The FA of the patient's right eye indicated the presence of early hypo- and hyperfluorescence, with late macular leakage (***Figure 2***).

After discussing treatment options with the patient, I suggested that PDT with VISUDYNE® may be an option. PDT with VISUDYNE® is indicated for the treatment of patients with predominantly classic subfoveal choroidal neovascularization due to AMD, pathologic myopia, or presumed ocular histoplasmosis.[6]

I explained to the patient that PDT therapy is a two-step process performed in the office that requires administration of verteporfin via intravenous infusion followed by activation of the drug with a light from a nonthermal diode laser.[6]

I advised the patient that her skin would be sensitive to bright light and direct sunlight for 5 days after therapy.[6]

The patient agreed and returned on December 4, 2018, for PDT treatment. At this time, her BCVA was 20/80. An OCT scan of the right eye was taken prior to treatment, confirming the presence of a persistent PED and intraretinal fluid (***Figure 3***). The patient tolerated the PDT treatment without reported treatment-related adverse effects.

Important Safety Information (cont.)

- Standard precautions should be taken during infusion of VISUDYNE to avoid extravasation, including but not limited to:
  - » A free-flowing intravenous (IV) line should be established before starting VISUDYNE infusion and the line should be carefully monitored.
  - » Due to the possibly fragility of vein walls of some elderly patients, it is strongly recommended that the largest arm vein possible, preferably the antecubital, be used for injection.
  - » Small veins in the back of the hand should be avoided.
- Extravasation of VISUDYNE, especially if the affected area is exposed to light, can cause severe pain, inflammation, swelling or discoloration at the injection site. Necrosis at the injection site following extravasation has been reported. If extravasation does occur, the infusion should be stopped immediately. The extravasation area must be thoroughly protected from direct light until swelling and discoloration have faded in order to prevent the occurrence of local burn, which could be severe. Cold compresses should be applied to the injection site. Oral medication for pain relief may be administered.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information here.

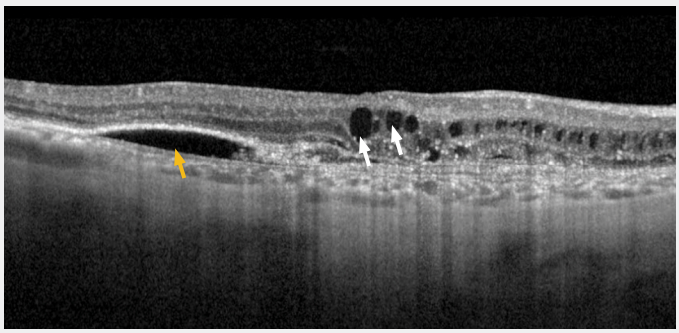

Figure 1. Heidelberg spectral domain OCT (SD-OCT) of the right eye. The OCT cross section at presentation shows pigment epithelial detachment (yellow arrow) and intraretinal fluid (white arrows).

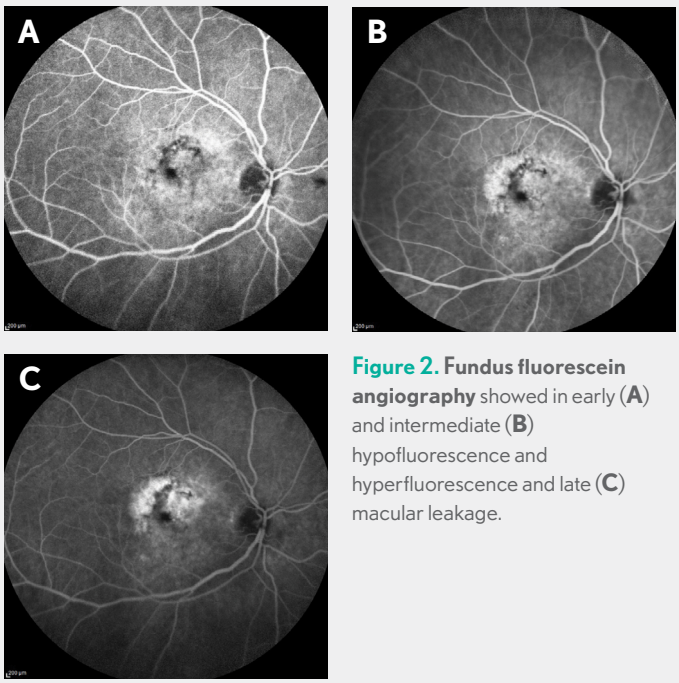

Figure 2. Fundus fluorescein angiography showed in early (**A**) and intermediate (**B**) hypofluorescence and hyperfluorescence and late (**C**) macular leakage.

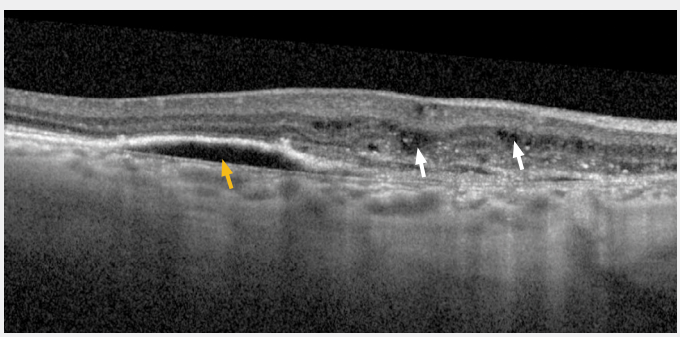

Figure 3. Heidelberg SD-OCT of the right eye, on the day of PDT, prior to treatment. OCT cross section shows the presence of persistent pigment epithelial detachment (yellow arrow) and intraretinal fluid (white arrow).

WHY VISUDYNE®?

The goal of disease management in patients with neovascular AMD is to stabilize vision and prevent further vision loss. Anti-VEGF therapy remains a mainstay of AMD treatment, but some patients who respond initially can experience a slow loss of efficacy.[1]

For example, in the TREND study, patients with neovascular AMD were randomized to either treat-and-extend (T&E) or monthly regimens of anti-VEGF for 12 months, yet approximately 50% of those patients in both treatment arms still had persistent intraretinal or subretinal fluid at the end of the study.[7*]

Given these data, it was apparent that my patient fell into this category. She had persistent fluid despite changing her therapy from bevacizumab PRN to monthly injections of aflibercept.

Both the patient and her family were concerned given that the affected eye was her better seeing eye, and they wanted to try an additional therapy that might slow the disease process, as VISUDYNE® has been shown to do.[6,8]

FOLLOW-UP: The patient returned for her first post-PDT follow-up in January 2019. Her BCVA initially declined to 20/200, and OCT showed the presence of subretinal fibrosis, atrophy, and the notable absence of the previous PED and intraretinal fluid (***Figure 4***). No anti-VEGF treatment was administered.

At the next follow-up in February 2019, the patient's BCVA was 20/200. An OCT was performed and showed the absence of previous PED and that intraretinal fluid was maintained (***Figure 5A***). An injection of aflibercept was administered. Vision then improved to 20/100 and although it fluctuated as is typical with neovascular AMD patients, it was consistently better than her pre-laser vision, averaging around 20/60 with fewer injections than before her PDT treatment. The patient returned for a follow-up in December 2019 for another injection (BCVA 20/50). In 2020 the patient had 8 follow-up visits. At her April (***Figure 5B***) and June (***Figure 5C***) visits she had BCVA of 20/50 in her affected eye. At her September (***Figure 5D***) and November (***Figure 5E*** and ***Figure 6***) visits she had BCVA of 20/60. She was treated with an injection of aflibercept at all 4 of these visits.

For the patient's last visit outlined in this case (November 2020), OCT scans indicated the absence of intraretinal or subretinal fluid, or the presence of PED. However, geographic atrophy was noted (***Figure 6***).

The following table outlines the patient's post-PDT right eye course of treatment

Date	BCVA	Image	Treatment
January 2019	20/200	Figure 4	None
February 2019	20/200	Figure 5A	Aflibercept injection
December 2019	20/50	Not Available	Aflibercept injection
April 2020	20/50	Figure 5B	Aflibercept injection
June 2020	20/50	Figure 5C	Aflibercept injection
September 2020	20/60	Figure 5D	Aflibercept injection
November 2020	20/60	Figures 5E + 6	Aflibercept injection

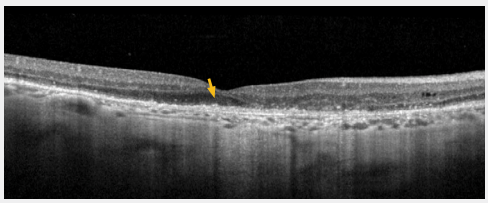

Figure 4. Heidelberg SD-OCT of the right eye, 1-month follow-up. Post-PDT follow-up without anti-VEGF injection. OCT cross section demonstrates the absence of previous pigmented epithelial detachment and intraretinal fluid and presence of subretinal fibrosis (yellow arrow) and atrophy demonstrated by hypertransmission.

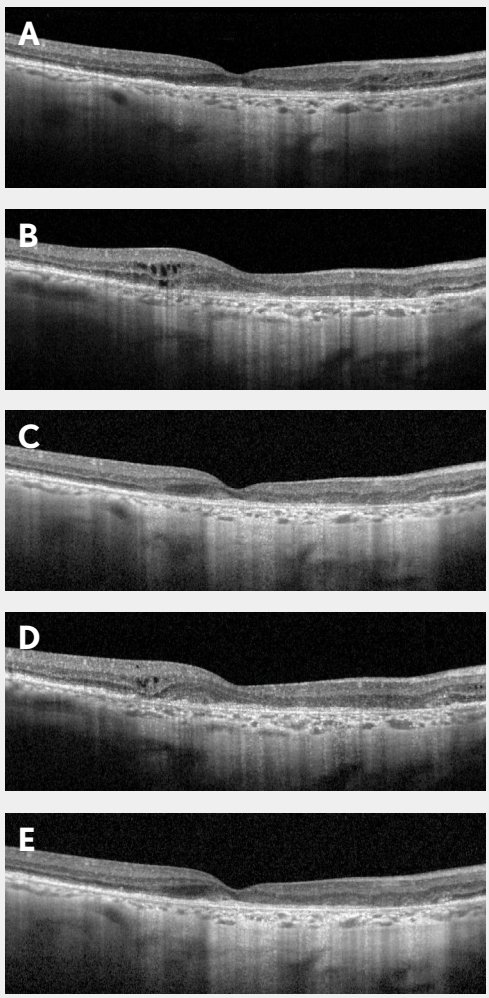

Figure 5. Heidelberg SD-OCT of the right eye at follow-up visits. 2 months after PDT treatment (**A**); 4 months after PDT treatment (**B**); 6 months after PDT treatment (**C**); 9 months after PDT treatment (**D**); and 11 months after PDT treatment (**E**). OCT images demonstrate sustained fluid-free retina and absence of PED after PDT treatment and anti-VEGF injections at each follow-up visit.

CONCLUSIONS

This case involved a patient diagnosed with neovascular AMD in 2016 who was treated with anti-VEGF treatments in her right eye for a 2-year period. Despite a change in treatment regimen during this period, she had persistent intraretinal fluid and subjective decline in her visual acuity. Because of the persistent activity, the patient was treated with PDT with VISUDYNE® (verteporfin for injection) in her right eye. After PDT treatment, she remained fluid free and maintained BCVA as of the last follow-up appointment in this case study. This case nicely demonstrates both the safety and efficacy of PDT with VISUDYNE®.[6,8]

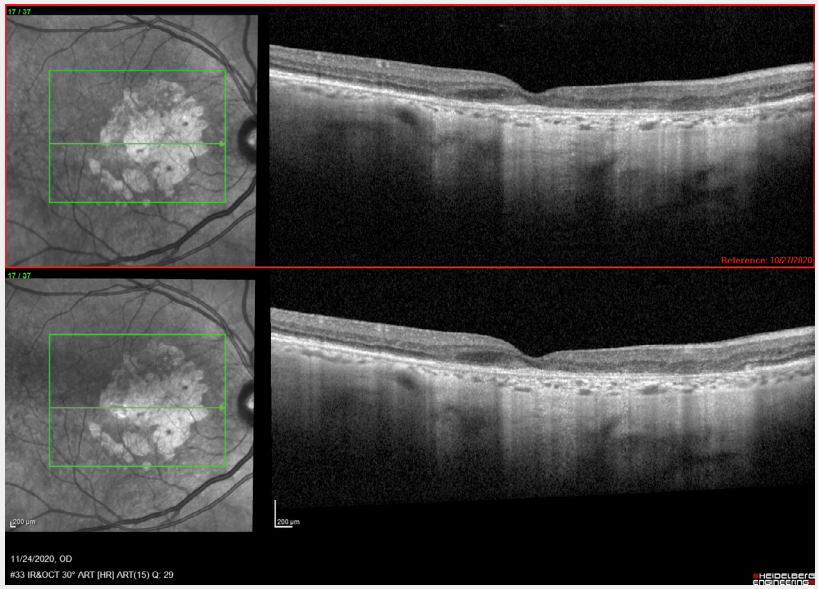

Figure 6. Heidelberg SD-OCT of the right eye, post-PDT follow-up (November 2020). OCT en face structural and cross section images shows the presence of geographic atrophy and absence of intraretinal, subretinal fluid or the presence of PED.

*__Study Design:__ In a 12-month, multicenter, randomized clinical trial, 650 patients with neovascular AMD were randomized 1:1 to receive ranibizumab 0.5 mg T&E or monthly. Primary outcome was to show noninferiority of ranibizumab 0.5 mg T&E versus monthly regimen, as assessed by the change in BCVA from baseline to the end of the study. Secondary objectives included change in retinal central subfield thickness from baseline to the end study, treatment exposure, and safety.

Important Safety Information (cont.)

- Following injection with VISUDYNE, care should be taken to avoid exposure of skin or eyes to direct sunlight or bright indoor light for 5 days. If emergency surgery is necessary within 48 hours after treatment, as much of the internal tissue as possible should be protected from intense light.
- Patients who experience severe decrease of vision of 4 lines or more within 1 week after treatment should not be retreated, at least until their vision completely recovers to pretreatment levels and potential benefits and risks of subsequent treatment are carefully considered by the treating physician.
- Cases of anaphylactic reactions have been reported. Immediately discontinue VISUDYNE and initiate appropriate therapy if anaphylactic or other serious allergic reactions occur during or following therapy.
- The most frequently reported adverse events (occurring in approximately 10%-30% of patients) were injection site reactions (including pain, edema, inflammation, extravasation, rashes, hemorrhage, and discoloration), and visual disturbances (including blurred vision, flashes of light, decreased visual acuity, and visual field defects, including scotoma).

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information here.

References: 1. Yang S, Zhao J, Sun X. Resistance to anti-VEGF therapy in neovascular age-related macular degeneration: a comprehensive review. *Drug Des Devel Ther*. 2016;10:1857-1867. **2.** Homayouni M. Vascular endothelial growth factors and their inhibitors in ocular neovascular disorders. *J Ophthalmic Vis Res*. 2009;4(2):105-114. **3.** Cousins S. The role of imaging in clinical decision making. *Retinal Physician*. 2010;Jan/Feb:1-7. **4.** Wykoff CC, Clark WL, Nielsen JS, Brill JV, Greene LS, Heggen CL. Optimizing anti-VEGF treatment outcomes for patients with neovascular age-related macular degeneration. *J Manag Care Spec Pharm*. 2018;24(2-a Suppl):S3-S15. **5.** Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Maguire MG, Martin DF, et al. Five-year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration: the comparison of age-related macular degeneration treatments trials. *Ophthalmology*. 2016;123(8):1751-1761. **6.** VISUDYNE Prescribing Information. Bausch & Lomb Incorporated. **7.** Silva R, Berta A, Larsen M, Macfadden W, Feller C, Monés J; TREND Study Group. Treat-and-extend versus monthly regimen in neovascular age-related macular degeneration: results with ranibizumab from the TREND study. *Ophthalmology*. 2018;125(1):57-65. **8.** 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(2):198-207.

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