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Invited Commentary

Treatment for a Subtype of Exudative Macular Degeneration—Another Mountain Climbed

Gregg T. Kokame, MD, MMM; Judy E. Kim, MD

Polypoidal choroidal vasculopathy (PCV) is a subtype of exudative age-related macular degeneration (AMD) that is most prevalent in Asian populations but is becoming increasingly recognized in populations around the world.[1-3] The importance of recognizing PCV is that it is a subtype of exudative AMD that has been associated with resistance to antivascular endothelial growth factor (anti-VEGF) injections, which has become standard treatment for most cases of active exudative AMD.[1,2] Therefore, finding a good treatment option for PCV would benefit many patients around the world.

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Trial results at 2 years of EVEREST II (a 24-month, phase IV, randomized, double-masked, multicenter study of the effect of ranibizumab monotherapy or ranibizumab in combination with verteporfin photodynamic therapy on visual outcome in patients with symptomatic macular polypoidal choroidal vasculopathy) are published in this issue.[4] This trial compared treatment starting with a combination of verteporfin photodynamic therapy (vPDT) and intravitreal ranibizumab injections with treatment starting with ranibizumab monotherapy for PCV. EVEREST II clinical trial of 322 individuals performed at 42 centers across 7 Asian countries followed a carefully designed protocol. Although other, smaller trials have examined the role of other anti-VEGF agents and 1 other large randomized clinical trial to date, Aflibercept in Polypoidal Choroidal Vasculopathy (PLANET),[5] evaluated aflibercept monotherapy vs aflibercept monotherapy plus rescue vPDT as needed, the EVEREST II trial compared anti-VEGF monotherapy with anti-VEGF combined with vPDT when initiating treatment for PCV. One strength of this study is that a central reading center in Singapore confirmed the diagnosis of PCV in all cases based on indocyanine green angiography (ICGA), which is considered the gold standard imaging mode for diagnosis of PCV, using predetermined grading criteria.

However, there are substantial clinical implications when diagnosing PCV using ICGA. It is an invasive test and not readily available in many practices in the US and elsewhere around the world. In addition, the interpretation of ICGA for diagnosing PCV is not taught in many training programs. In many treatment centers for retinal diseases, all patients with exudative AMD initially receive anti-VEGF monotherapy; if there is a poor response to treatment, the possible diagnosis of PCV is considered and further testing is ordered. Because of the potential difficulty of accessing ICGA and of diagnosing PCV with ICGA, other more commonly obtained noninvasive diagnostic tests have been evaluated to make the diagnosis of PCV, including fundus photography, optical coherence tomography (OCT),[6] en face OCT,[7] and OCT angiography.[8] Chaikitmongkol and colleagues[6] showed that highly suggestive signs of PCV

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on fundus photographs and OCT can make the diagnosis of PCV with high sensitivity and specificity without ICGA. En face OCT is a widely available method of evaluating a potential PCV lesion, which is visualized as a dilated, irregular vascular structure with hyperechogenic borders and polypoidal vascular dilations similar to what is seen on ICGA.[7] In the study by Kokame and colleagues,[7] en face OCT was better than ICGA at identifying the full extent of the PCV complex in 44% of patients with PCV. OCTA was evaluated by de Carlo and colleagues[8] and was highly specific for diagnosing PCV, but the sensitivity was lower than ICGA. OCTA was not as successful at imaging the polypoidal lesions, possibly because of slower blood flow through these aneurysmal lesions.

At 2 years, the EVEREST II study[4] found that the combination therapy group with vPDT and intravitreal ranibizumab injection compared with the monotherapy group with intravitreal ranibizumab injection had more visual acuity improvement (9.6 letters for combination therapy vs 5.5 letters for monotherapy), better anatomic closure of polypoidal lesions (56.6% vs 26.7%), and less treatment burden (6 injections vs 12 injections). These results are promising because this type of result is the goal of any new developing technology for the treatment of exudative AMD.

Of note, participants in the monotherapy group were allowed to switch to combination therapy in year 2 for ethical reasons to obtain the potential increased treatment benefit of combination therapy noted after knowing the primary outcome results at year 1. This switched group also showed improved closure of the polypoidal lesions at the end of year 2 (47.5%) compared with the monotherapy group (26.7%).

A concern of vPDT has been the potential sudden vision loss that can occur because of choroidal ischemia, acute inflammation, retinal vascular damage, or subretinal hemorrhage. An important difference in vPDT protocol for PCV in EVEREST II was that the treatment spot was based only on the polypoidal lesions deemed to be active as imaged on ICGA. This treatment spot is more localized than the previously used spot size for typical exudative AMD, which included the entire area of leakage on the fluorescein angiogram plus 1000 µm in greatest linear dimension. In the EVEREST II study, no severe or sudden vision loss was reported after vPDT treatment among any participant in the study, which included 143 patients in the combination group and 14 patients in the switched group, some of whom received more than 1 application of vPDT. In addition, the results suggested reduced incidence of submacular hemorrhage greater than 4 disc area in size in the combination group during 2 years than in the monotherapy group. PCV has been associated with a thick choroid, which may be a factor in decreasing the risk of choroidal ischemia after vPDT treatment, whereas typical AMD was more often associated with a thin choroid and a potentially higher risk of choroidal ischemia after vPDT.

The results of EVEREST II, a multicentered trial of high caliber and careful scientific design with statistically significant and clinically relevant results at 2 years, are compelling to consider combination of vPDT and intravitreal ranibizumab injections as an initial therapy for eyes with the PCV subtype of exudative AMD. Switching to a combination treatment with vPDT and ranibizumab also suggested an improvement in PCV even after previous treatment for 1 year with ranibizumab monotherapy, although the study was not designed to determine whether such switching should be considered routinely. The results support further research into considering combination therapy in eyes being treated with anti-VEGF monotherapy, especially those with a poor response. This was to be evaluated in PLANET,[5] although in that trial, the benefits of adding PDT could not be elucidated because most participants responded to aflibercept monotherapy and only approximately 13% of the eyes in each group warranted protocol-defined rescue. Additional studies would be needed to confirm whether combining aflibercept with vPDT when initiating treatment for PCV is superior to aflibercept monotherapy and analogous to combination therapy with ranibizumab being shown to be superior to ranibizumab monotherapy in EVEREST II. In addition, without a clinical trial, it would be difficult to know which anti-VEGF agent would be more efficacious for PCV.

Implementing the results of EVEREST II, however, may be challenging because of the lack of awareness of distinguishing PCV in many countries and difficulties in diagnosing PCV with ICGA as the criterion standard or with other alternative diagnostic modalities. The lack of availability of vPDT treatment also is a challenge with limited vPDT treatment centers still available, especially because of the absence of the commercial availability of new vPDT lasers in many countries, including the US.

Despite these challenges, combination of vPDT and anti-VEGF injection, at least with ranibizumab for now, may be associated with an important improvement in the treatment results for patients with exudative AMD with the PCV subtype, both as initial therapy and potentially as adjunctive therapy with antiangiogenic drug injections for patients with anti-VEGF–resistant disease. Improved vision with a better anatomic result and with fewer treatments with the combination therapy supports increasing the awareness of PCV in all populations, including white populations in many different countries, such that PCV can be best detected and treated for an improved outcome.

ARTICLE INFORMATION

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