Invited Commentary

Adopting the Results of Everest II Into Practice
A Clearer View From a Higher Level Study

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Polypoidal choroidal vasculopathy (PCV), an oddity shown at fluorescein conferences 35 years ago, is now recognized as a common cause of neovascular maculopathy among those older than 50 years.[1] Its prevalence has not increased, but new imaging techniques have revealed its features and ophthalmic consciousness has been raised. Randomized clinical trials that compare treatments, rather than case series, are now feasible.

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Whether PCV is a form of neovascular age-related macular degeneration (nAMD) or a distinct entity is controversial,[1,2] but the prevailing notion is that PCV is a subtype of nAMD. Both affect older people and lack systemic associations, yet PCV shows a male predominance that is not present in nAMD,[3] the natural history of PCV seems better than that of NAMD with less subretinal fibrovascular proliferation, and PCV responds to photodynamic therapy better than nAMD. In PCV, drusen are absent or sparse in the fellow eye, but these are typically present in nAMD. Polypoidal choroidal vasculopathy constitutes up to 55% of cases of nAMD in Asian people,[4] 14% in white people,[5] and an unknown percentage in people of African ancestry, although it is probably high.[1]

In this issue of *JAMA Ophthalmology*, Koh and colleagues[6] reported the 12-month results of the EVEREST II randomized clinical trial that compared combined intravitreal ranibizumab (IVR) and PDT with IVR monotherapy among Asian people. The combined therapeutic approach was associated with greater improvement in best-corrected visual acuity (BCVA), more polyp closure, and fewer injections than IVR monotherapy. Using PDT did not increase hemorrhagic complications,[7] nor were there other increased adverse effects in the combined arm. Combined IVR+PDT, as performed by the investigators, was better than IVR monotherapy for PCV among Asian people. Moreover, because of the pivotal roles of indocyanine green angiography (ICGA) and PDT in the study, the clinical importance of these procedures has been enhanced.

Clarification of 3 aspects of the retreatment regimen would help clinicians to adopt the results into practice. Retreatment occurred after the mandatory 3 monthly injections if BCVA dropped relative to the previous visit or if there was any evidence of disease activity on spectral-domain optical coherence tomography (SD-OCT). Conventional interpretation would suggest that a threshold for BCVA of change of 5 letters would be used, and that was what was used in EVEREST, but what was actually used in the EVEREST II? For the SD-OCT criterion, conventional interpretation would be that any intraretinal or subretinal fluid implied activity and a need to retreat; was that the criterion used in the clinical trial? Also, because in PCV many SD-OCT changes involve the subretinal pigment epithelial features, did these enter into the criteria for retreatment?

The diagnosis of PCV is tricky and requires ICGA. The definition is early focal hyperfluorescence on ICGA plus 1 of the following: nodular polyps on a stereoscopic viewing, a hypofluorescent halo around a nodule, a branching vascular network, pulsatile nodule on dynamic ICGA, an orange subretinal nodule on color fundus photography results, or subretinal hemorrhage that was 4 disc diameters or more.[8] The EVEREST II protocol projected a screen fail rate of 20%, but the actual rate was 34%. It would be helpful to know what led to the screen fails. If it was because investigators diagnosed PCV but the reading center disagreed, that would signal how difficult the diagnosis can be and emphasize scrutiny of ICGA for polyps and branching vascular networks and SD-OCT for tall, peaked, and notched pigment epithelial detachments and the double layer sign.

The results of EVEREST II suggest that all Asian people older than 50 years with a serosanguinous maculopathy should have ICGA to help determine if PCV is the cause. If the definition is met, combined IVR+PDT as described in Koh et al[6] offers better outcomes than serial IVR monotherapy. If typical nAMD without these features is found instead, serial intravitreal antivascular endothelial growth factor therapy without PDT is assumed, but not known, to be a better option.

What about serosanguinous maculopathy in older patients from other racial/ethnic groups? The results of EVEREST II cannot be generalized to these patients without additional research, but there is reason to suspect that they might also apply to these racial/ethnic groups. Thus, baseline ICGA in all cases of serosanguinous maculopathies to look for PCV is rational, and if PCV is present, combined therapy in these subgroups is worth considering.

To apply the results of EVEREST II, ICGA also needs to be done during follow-up if the BCVA drops compared with the previous visit or if the optical coherence tomography results show disease activity and it has been more than 3 months since the last PDT. In the aftermath of EVEREST II, the use of ICGA and PDT by retina specialists may increase.

What about combined therapy in which aflibercept or bevacizumab are substituted for ranibizumab? EVEREST II does not address this issue, and clinicians will need to use their own judgment if IVR is unavailable or economically impractical. Further comparative effectiveness studies of these combined approaches will need to be done.

What should the clinician do who lacks ICGA or PDT and is confronted with an Asian patient with active PCV? Serial IVR produces good results, if not as good as combined IVR+PDT. If PDT is available but not ICGA, it may be tempting to apply

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PDT with a large spot size without ICGA guidance, but the clinician would be venturing into uncharted waters. In EVEREST II, the PDT spot needed to encompass all polyps and branching vascular networks, which cannot be discerned without ICGA.

During the second 12 months of EVEREST II, the protocol specifies that the patients in the IVR monotherapy arm for the first 12 months will be converted to combined IVR+PDT. The 24-month results will help clinicians understand whether a delay in instituting PDT compromises the outcomes at 24 months.

There are several questions that are prompted by EVEREST II. What does a cost-effectiveness analysis show regarding compared treatments? Does the race/ethnicity of the patient matter regarding natural history and the response to treatments? Is the initial 3 times monthly IVR a necessary component of the regimen, or would equally good outcomes be obtained without the 3 initial mandatory injections if intraretinal and subretinal fluids were absent? How would the results of intravitreal bevacizumab plus PDT compare with IVR+PDT? How would serial intravitreal aflibercept therapy compare with IVR+PDT or to intravitreal aflibercept and PDT? Do responses to combined therapy depend on any baseline factors, such as choroidal thickness? Can swept-source optical coherence tomography results diagnose PCV as well as ICGA and remove an invasive part of the diagnostic and management regimen at less expense? Are there any differences in the ensemble of single-nucleotide polymorphisms that cluster with PCV compared with NAMD? Earlier work indicates that they are similar, but as differences in phenotype and optimal treatments emerge, will deeper study reveal a genetic basis for these distinctions?

EVEREST II followed EVEREST, a smaller comparison study with a 6-month end point. The conclusions of the 2 studies differed regarding changes in BCVA but were consistent regarding polyp closure. The differences reflect how important an adequate sample size, long enough follow-up, and high retention rates are to reach reliable conclusions in randomized clinical trials.

The ophthalmology community is indebted to the EVEREST II investigators for designing a sound study and executing it well. Perhaps the network that they have developed can be leveraged to learn more about a disease that is of increasing global significance.

ARTICLE INFORMATION

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