

Angiographic Interpretation of Neovascular AMD by Different ‘Reading Centers’

This analysis suggests that VEGF is a common denominator in neovascular AMD, regardless of subtype classification.

BY MICHAEL S. IP, MD

Fluorescein angiography (FA) is widely used to characterize neovascular lesions caused by age-related macular degeneration (AMD). Regulatory approval for photodynamic therapy with verteporfin is predicated on FA assessments with only those lesions that fall in the *predominantly classic* group being eligible, as defined by the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) study.¹

A recent US study found that there was slight disagreement for both intraobserver and interobserver determinations as reflected in a mean K coefficient of 0.64 for intraobserver variation and an intraclass correlation coefficient of 0.66 for interobserver variation.²

ANTI-VEGF THERAPY SHOULD BE EFFECTIVE ACROSS FA SUBTYPE

Because vascular endothelial growth factor (VEGF) is a common denominator of all subtypes of choroidal neovascularization (CNV),^{3,4} anti-VEGF therapy may be expected to be effective, regardless of angiographic classifications as shown in the VEGF Inhibition Study in Ocular Neovascularization (VISION) trial.⁵

A retrospective analysis of submitted angiograms in the VISION trial was performed to further explore this hypothesis. The angiograms had classification

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provided by three readers — the Eligibility and Classification Quality Assurance Team (ECQAT) made up of members from the Wilmer Reading Center, the University of Wisconsin Fundus Photograph Reading Center (UW-FPRC), and the principal investigators who performed the eligibility determinations on all study participants — with regard to visual acuity outcomes.

The objective of this retrospective analysis was to assess angiographic interpretation of entry FA by different reading centers upon outcomes of multicenter, randomized clinical trials — in particular, the VISION trial outcomes.

VISION TRIAL

VISION clinical trials were concurrent, randomized, double-masked, sham-controlled, dose-ranging trials that enrolled 1,208 patients at 117 sites in the United

States, Canada, Europe, Israel, Australia and South America. Enrolled patients were aged ≥ 50 years and had subfoveal CNV secondary to AMD and a BCVA in the study eye ranging from 20/40 to 20/320. The fellow eye had to be 20/800 or better. Patients with all angiographic subtypes of disease were enrolled; however, lesions could not exceed 12 total disc areas, of which 50% had to be active CNV. No greater than 50% of the lesion could be subretinal hemorrhage.

Patients in the VISION trials were classified at entry as having predominantly classic, minimally classic or occult lesions. Study participants were randomized to intravitreal injections of pegaptanib 0.3 mg, 1 mg or 3 mg; or to receive sham injection into one eye every 6 weeks for 48 weeks, for a total of nine treatments. An identical injection protocol was used for both sham and treatment injections, with the exception of scleral penetration.

DIFFERENCES IN ANGIOGRAPHIC INTERPRETATION

For the post hoc analysis, only patients assigned to the 0.3-mg pegaptanib group or those receiving sham injections were included. Concordance in angiographic interpretation among the readers was evaluated. They were compared based on responder rates (ie, loss of < 15 letters of visual acuity from baseline to week 54) and mean changes in visual acuity from baseline to week 54.

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In 590 patients who received 0.3 mg pegaptanib or usual care, there was discordance in FA interpretation between ECQAT and UW-FPRC (24% of cases), between ECQAT and investigators (22% of cases) and between UW-FPRC and investigators (36% of cases).

Regardless of angiographic subtype or reader, responder rates were higher in patients who received pegaptanib versus usual care. Also, across all angiographic subtypes and readers, a greater mean change in visual acuity was seen in patients assigned pegaptanib 0.3 mg compared with sham.

When analyzing the mean change in visual acuity from baseline to week 54, the relative benefit of using pegaptanib 0.3 mg versus sham, applying the investigators' interpretation, was 63%, 55% and 35% for pre-

dominantly classic, minimally classic and occult lesions, respectively. The relative benefit of pegaptanib 0.3 mg versus sham applying UW-FPRC data was 31%, 62% and 42% for predominantly classic, minimally classic and occult lesions, respectively. When we employed the ECQAT data, the relative benefit of pegaptanib 0.3 mg versus sham was 54%, 52% and 43% for predominantly classic, minimally classic and occult lesions, respectively.

TREATMENT RESULTS WERE FAVORABLE

Results favoring pegaptanib treatment were also seen with regard to the proportion of patients who gained two and three lines and avoided six-line loss. A total of 133 patients received the 0.3-mg dose for 2 years and 107 patients received sham in year 1 and sham or no therapy in year 2. The proportion of patients losing < 15 letters after 2 years was higher in the pegaptanib 0.3-mg group versus sham across all subtypes and all readers.

These data suggest that angiographic interpretation of neovascular AMD varies depending on the reader or the reading center. In the VISION trial, however, the evidence of the efficacy of pegaptanib was seen across the totality of the dataset in all angiographic subgroups. This suggests that VEGF is a common denominator in neovascular AMD, no matter what subtype classification. ■

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1. TAP Study Group. Treatment of age-related macula degeneration with photodynamic therapy (TAP). *Arch Ophthalmol*. 2001;119:198-207.
2. Holz FG, Jorzik J, Schutt F, et al. Agreement among ophthalmologists in evaluating fluorescein angiograms in patients with neovascular age-related macular degeneration for photodynamic therapy eligibility (FLAP-study). *Ophthalmology*. 2003;110:400-405.
3. Matsuoka M, Ogata N, Otsuji T, et al. Expression of pigment epithelium derived factor and vascular endothelial growth factor in choroidal neovascular membranes and polypoidal choroidal vasculopathy. *Br J Ophthalmol*. 2004;88:809-815.
4. Kvantta A, Algvere PV, Berglin L, Seregard S. Subfoveal fibrovascular membranes in age-related macular degeneration express vascular endothelial growth factor. *Invest Ophthalmol Vis Sci*. 1996;37:1929-1934.
5. Gragoudas ES, Adamis AP, Cunningham ET Jr, et al. Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med*. 2004;351:2805-2816.

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