Anti-PDGF Combination Therapy in Neovascular Age-related Macular Degeneration: Results of a Phase 2b Study

BY PRAVIN U. DUGEL, MD

There is no doubt that anti-VEGF monotherapy is effective in the treatment of neovascular age-related macular degeneration (AMD). There is equally no doubt that anti-VEGF monotherapy induces disease resistance in neovascular AMD.

Long-term visual outcomes of anti-VEGF monotherapy in the clinical setting, however, are disappointing. The HORIZON extension study[1] analyzed patients with choroidal neovascularization (CNV) secondary to AMD who had received ranibizumab (Lucentis, Genentech) every 4 weeks for 2 years as participants in phase 3 trials of the drug. When patients who received 2 years of monthly therapy in the original trials were subsequently treated on an as-needed (prn) basis for an additional 2 years in HORIZON, their mean visual acuity returned almost to baseline. Similar limitations in the long-term outcomes of patients treated with anti-VEGF therapies have been observed in other trials such as the SECURE and SEVEN-UP studies.[2,3]

More recently, in the CATT study[4] comparing ranibizumab and bevacizumab (Avastin, Genentech) with monthly and prn dosing schedules, the 2-year results showed similar insights. Patients in the crossover arms of this study received monthly anti-VEGF treatment—whether ranibizumab or bevacizumab—and were then switched to prn treatment after 1 year. In the second year of the study, the response in these patients was similar to the response of those who had been treated prn from the beginning of the study.

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In other words, these studies suggest that anti-VEGF monotherapy does not result in disease modification: ie, it induces no structural advantage in neovascular AMD. It may be that patients with CNV secondary to AMD would need anti-VEGF monotherapy indefinitely—perhaps forever. Why is this? What is the reason for this apparent anti-VEGF resistance?

ROLE OF PDGF

Compelling evidence for anti-VEGF resistance has been identified in the oncology literature for more than a decade. It has to do with pericytes, a type of cell that intimately covers and protects the neovascular complex as new vessels develop and mature. Pericytes supply VEGF and other cell survival factors to the proliferating endothelial cells and confer anti-VEGF resistance.[5]

Platelet-derived growth factor (PDGF) is responsible for pericyte recruitment, survival and maturation.[6,7] Studies in the oncology literature have shown that PDGF-deficient mice lack microvascular pericytes, and they form microaneurysms that rupture in late gestation.[7] Conversely, PDGF overexpression in melanoma cells leads to increased pericyte proliferation and tumor growth.[8]

These insights from the oncology literature are crucial for our understanding of neovascularization in AMD. The growth of a neovascular complex is not random, but rather specifically directed by a group of specialized cells known as tip cells.[9] These tip cells are the only unprotected endothelial cells in the neovascular complex; they express PDGF, which stimulates the maturation and recruitment of pericytes that cover the neovascular complex.

Anti-VEGF monotherapy is typically effective in obliterating only these unprotected tip cells. The pericytes that have been recruited form a protective armor around the rest of the neovascular complex, allowing it to remain in place. When anti-VEGF therapy is stopped, the tip cells become active and mitotic again, leading to continuation of disease progression.

This physiologic process is suggested by the results of clinical studies of anti-VEGF agents in neovascular AMD. The familiar curve showing visual acuity improvement is remarkably consistent among these studies. An initial improvement in visual acuity in the first 3 or 4 months of treatment is followed by a plateau that persists through the study, and seemingly indefinitely. This pattern correlates well with the time course of anti-permeability induced by VEGF antagonists. The pathophysiology of neovascular membrane growth explains the shape of the curve. Anti-VEGF monotherapy acts primarily on fenestrated and unprotected endothelial cells in the first few months of treatment, causing a decrease in exudation and initial improvement in visual acuity. Thereafter, however, the rest of the neovascular complex is protected by the pericyte armor, resulting in the plateau. As soon as anti-VEGF monotherapy is withdrawn, the tip cells regrow, the neovascular complex increases in size, and disease progression with leakage continues.

To summarize, chronic anti-VEGF treatment causes PDGF upregulation, leading to pericyte recruitment and neovascular membrane maturation. This concept is well known in the oncology literature, where the role of VEGF as a negative regulator of pericyte function and vessel maturation have been well described.

In what may be a related finding in ophthalmology, Pachdaki et al[10] recently described submacular surgery and excision of neovascular membranes in an eye with CNV that was unresponsive to bevacizumab treatment. The membrane displayed well-formed neovascular units consistently exhibiting pericytes, the authors reported.

ANTI-PDGF THERAPY

If pericytes are the source of resistance to anti-VEGF therapy in neovascular AMD, then there is a physiologic rationale for a combination of anti-PDGF and anti-VEGF therapies. The objective would be for the anti-PDGF agent to chemically bind to and strip pericytes from the neovascular complex, rendering the CNV more vulnerable to anti-VEGF treatment.

Ophthotech has developed a PDGF inhibitor, (Fovista, formerly E10030), a PEGylated DNA aptamer. Preclinical work has shown that this agent binds to PDGF and strips pericytes from CNV, and that the combination of this agent with an anti-VEGF agent is more effective than anti-VEGF therapy alone in multiple animal models of neovascularization.[11]

In an uncontrolled dose-ranging phase 1 study with a small sample size (N=22), the safety profile of this anti-PDGF agent was excellent, with no dose-limiting toxicities observed.[12] Despite the severity of disease in patients recruited for the study, a number of patients gained significant vision. A number of patients also showed significant regression of neovascular complex.

PHASE 2 COMBINATION STUDY

Based on these encouraging results, a large phase 2b study was conducted (clinicaltrials.gov NCT01089517). The results of this study were presented at the American Academy of Ophthalmology Annual Meeting last year.[12] The goal of the study was to assess the safety and efficacy of a combination of the anti-PDGF agent E10030 plus ranibizumab compared with ranibizumab monotherapy in patients with CNV secondary to AMD. Patients were randomly assigned to 1 of 3 treatment groups: 0.3 mg E10030 plus ranibizumab 0.5 mg, 1.5 mg E10030 plus ranibizumab 0.5 mg, or ranibizumab 0.5 mg monotherapy.

Two things are notable about the study design. First, this was a very large, randomized phase 2 study, resembling a phase 3 study. Investigators recruited 449 patients, making this the largest phase 2 superiority study in retina. Second, unlike other recent studies in this area, it was a superiority study, not a noninferiority study.

The primary endpoint was mean change in visual acuity from baseline to week 24. Secondary endpoints included mean change in visual acuity at week 12, the proportion of patients gaining 15 or more letters of

visual acuity at week 12 and week 24, and mean change in the area of occult CNV at week 24 as defined by fluorescein angiography. The baseline demographics of all 3 arms were comparable.

The prespecified superiority primary endpoint of improvement in visual acuity at week 24 was met by both combination groups. The 1.5 mg combination group showed mean improvement of 10.6 letters of vision, the 0.3 mg combination group showed improvement of 8.74 letters, and the ranibizumab monotherapy group showed improvement of 6.52 letters ($P = .019$ for ranibizumab only in comparison with each combination group).

It is notable that both combination groups met their prespecified primary endpoint of superiority. In fact, in the 1.5 mg combination arm there was a 62% additional benefit compared with ranibizumab monotherapy. There was a classic dose-response curve that showed early and sustained superiority. There was also improvement over time, meaning that the curves were most divergent at the end of the study.

To determine whether any particular subgroup of patients drove these positive study results, numerous prespecified subgroup analyses were conducted.

For baseline lesion size, an arbitrary segregation point of 4 disc areas was chosen. Results in the combination arms were superior for lesion sizes both greater than and less than or equal to 4 disc areas. Additionally, whether the median lesion size of 1.21 disc areas or the mean lesion size of 1.78 disc areas was used as the segregation point, again the combination arms were superior.

The effect of baseline visual acuity was also examined. For relatively good visual acuity of 20/60 to 20/80 or relatively poor visual acuity of 20/160 or worse, the combination arms were superior. When the results were focused to patients who gained 15 or more letters of visual acuity, again, regardless of whether initial visual acuity was relatively good at 20/60 to 20/80 or relatively bad at 20/160 or worse, the combination arms were superior.

Clinically relevant subgroups were also examined. In patients who gained 3, 4, and 5 lines of visual acuity, the combination arms were always superior to the monotherapy arm, with 27%, 71%, and 190% relative benefits, respectively. In patients who lost 5 letters or more or 10 letters or more, the combination regimens were protective.

Overall change in visual acuity from baseline was also analyzed, but no matter how the data were sliced—3-, 4-, or 5-line gainers, patients with final visual acuity of 20/40 or better or 20/25 or better—the combination arms were always superior. In patients who had visual acuity loss or poor visual outcome, whether they were segregated by greater than 1 or 2 line loss, worse than 20/125, or worse than 20/200, again across the board the combination regimens were always protective.

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Biomarkers including optical coherence tomography (OCT) and fluorescein angiography were also examined. On OCT, of particular interest was subretinal hyperreflective material (SHRM), the thickness of which appears to correlate with visual function. Resolution of SHRM at week 24 showed a clear dose-related response, based on masked reading center assessment. This clear dose-response effect was also seen in patients who gained 3 lines of visual acuity or more. When the relationship of visual acuity with central retina thickness (CRT) on OCT was analyzed, whether in relatively thin CRT of less than 316 µm or relatively thick CRT of greater than 480 µm, across the board the combination arms were superior.

On fluorescein angiography, there was a clear correlation across the board between lesion regression and visual acuity gain, whether in patients with 3, 4, or 5 lines of visual acuity gain, with superior results in the combination arms. In patients who lost vision, there was a clear correlation with growth of the neovascular membrane, and again the combination regimens were protective. This relationship was seen in patients who lost vision, whether they had growth of the entire neovascular membrane, growth of the classic component of the neovascular membrane, or growth of the entire lesion.

Regarding safety, there was no difference in ocular adverse events or systemic serious adverse events among the 3 treatment groups. There was also, importantly, no difference in mean intraocular pressure among the groups, despite requiring 2 injections in the combination arms.

CONCLUSIONS

In this large phase 2 clinical trial of E10030 anti-PDGF agent in combination with an anti-VEGF agent, both combination arms met their prespecified primary endpoint of superiority over anti-VEGF monotherapy

(Continued on page 71)

(Continued from page 67)

(P = .019). Results showed a 62% additional benefit of combination therapy over monotherapy, a classic dose-response profile at all time points, diverging efficacy curves over time, and a marked increase in extreme visual acuity gain (4- and 5-line gain, 20/25 or better visual outcome) with combination treatment. Data were consistent across all clinically relevant prespecified subgroups. There was marked reduction in visual acuity loss with combination treatment, and biomarkers were confirmatory.

Lessons from the oncology literature suggest that it makes good physiologic sense to combine anti-PDGF and anti-VEGF therapies. If the results of this large phase 2b trial are confirmed in a planned pivotal phase 3 trial, this combination therapy modality has the potential to dramatically and profoundly change our treatment model for patients with neovascular AMD. ■

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1. Singer MA, Awh CC, Sadda S, et al. HORIZON: an open-label extension trial of ranibizumab for choroidal neovascularization secondary to age-related macular degeneration. *Ophthalmology*. 2012;119(6):1175-1183. doi: 10.1016/j.ophtha.2011.12.016.
2. Silva R, Axer-Siegel R, Eldem B, et al; SECURE Study Group. The SECURE Study: Long-Term Safety of Ranibizumab 0.5 mg in Neovascular Age-related Macular Degeneration. *Ophthalmology*. 2013;120(1):130-139.
3. Bhisitkul RB, Rofagha S, Boyer DS, Sadda S, Zhang K. Year 7 outcomes for ranibizumab-treated subjects in ANCHOR/MARINA: a multicenter, prospective cohort study. Paper presented at: Association for Research in Vision and Ophthalmology Annual Meeting; May 8, 2012; Fort Lauderdale, FL.
4. Martin DF, Maguire MG, Fine SL, et al; Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration. *Ophthalmology*. 2012;119(7):1388-1398. doi: 10.1016/j.ophtha.2012.03.053.
5. Reinmuth N, Liu W, Jung YD, et al. Induction of VEGF in perivascular cells defines a potential paracrine mechanism for endothelial cell survival. *FASEB J.* 2001;15(7):1239-1241.
6. Benjamin LE, Hemo I, Keshet E. A plasticity window for blood vessel remodelling is defined by pericyte coverage of the preformed endothelial network and is regulated by PDGF-B and VEGF. *Development*. 1998;125(9):1591-1598.
7. Lindahl P, Johansson BR, Levéen P, Betsholtz C. Pericyte loss and microaneurysm formation in PDGF-B-deficient mice. *Science*. 1997;277(5323):242-245.
8. Furuhashi M, Sjöblom T, Abramsson A, et al. Platelet-derived growth factor production by B16 melanoma cells leads to increased pericyte abundance in tumors and an associated increase in tumor growth rate. *Cancer Res*. 2004;64(8):2725-2733.
9. Gerhardt H, Golding M, Fruttiger M, et al. VEGF guides angiogenic sprouting utilizing endothelial tip cell filopodia. *J Cell Biol*. 2003;161(6):1163-1177.
10. Pachydaki SI, Jakobiec FA, Bhat P, et al. Surgical management and ultrastructural study of choroidal neovascularization in punctate inner choroidopathy after bevacizumab. *J Ophthalmic Inflamm Infect*. 2012;2(1):29-37. doi: 10.1007/s12348-011-0050-x.
11. Jo N, Mailhos C, Ju M, et al. Inhibition of platelet-derived growth factor B signaling enhances the efficacy of anti-vascular endothelial growth factor therapy in multiple models of ocular neovascularization. *Am J Pathol*. 2006;168(6):2036-2053.
12. Dugel PU. Anti-Platelet Derived Growth Factor: Where Do We Stand? Paper presented at: American Academy of Ophthalmology Annual Meeting; November 10, 2012; Chicago.