

COMBINATION THERAPY FOR NEOVASCULAR AMD

Could the combination of an anti-VEGF agent and an anti-PDGF drug solve some of the issues seen with anti-VEGF monotherapy? Trial data may soon tell.

BY GLENN J. JAFFE, MD



Anti-VEGF therapy has significantly improved the care of patients with neovascular, or wet, age-related macular degeneration (AMD). However, all anti-VEGF agents approved by the US Food and Drug Administration (FDA) for the treatment of wet AMD show similar safety and efficacy profiles,¹⁻⁵ and research conducted in the past decade has highlighted

limitations of this drug class. In the CATT, despite continuous (monthly) dosing for up to 2 years, a significant proportion of patients (30-40%) did not achieve 20/40 or better visual acuity (VA), a level that is necessary for an unrestricted driver's license in regions of the United States.¹ Additionally, nearly three of four patients did not gain 3 or more ETDRS lines of VA, and approximately one in five lost vision.⁵⁻⁷ Discontinuous (ie, less than monthly or bimonthly) dosing over a similar time period resulted in worse VA outcomes compared with continuous dosing.^{1,3} Furthermore, peak efficacy of anti-VEGF monotherapy may have been reached with available agents; despite increased anti-VEGF dosages or various regimens, no additional benefit has been observed.^{2,4,5}

With longer term follow-up, although some patients retain the initial VA improvement observed during the first 1 to 2 years of anti-VEGF treatment, the VA of most patients declines to or below their baseline VA. For example, while the original ANCHOR and MARINA registration trials yielded meaningful 1-year VA improvement with monthly treatment,^{7,8} the subsequent open-label HORIZON extension trial showed insidious vision loss, yielding a net mean VA improvement of only 2 letters at 4 years after initiating treatment.⁹ Similarly, in a follow-up to the CATT study that demonstrated noninferiority of bevacizumab (Avastin, Genentech) to ranibizumab (Lucentis, Genentech), patients had a net mean loss of 3 letters 5 years after initiating anti-VEGF treatment.¹⁰

Postregistration real-world analyses reveal even worse VA outcomes compared with those seen in randomized clinical trials.¹¹⁻²⁰ In some of these analyses, within the first 4 years of treatment, VA had decreased to below baseline in a majority of patients.^{13-15,19} Causes of this long-term decreased VA in anti-VEGF-treated eyes include persistent growth

of choroidal neovascularization (CNV), geographic atrophy, and submacular fibrosis.^{21,22} In the CATT, approximately 25% of eyes developed fibrosis within 2 years despite treatment with anti-VEGF monotherapy.^{21,22}

These study findings from the past decade reveal the limitations of anti-VEGF agents and highlight the unmet need for more effective therapy. This article looks at how the addition of an anti-platelet-derived growth factor (PDGF) agent to anti-VEGF therapy might change the management of wet AMD in the future.

PERICYTES AND PDGF IN THE PATHOGENESIS OF WET AMD

Pericyte recruitment, maturation, and survival are mediated by PDGF.²³ Four PDGF isoforms (A, B, C, and D) form homo- and heterodimers. Two transmembrane PDGF receptor subunits (α and β) dimerize upon binding PDGF. These receptors are commonly expressed on cells of mesenchymal origin, such as pericytes, and include an intracellular tyrosine kinase domain.²³⁻²⁷

Although VEGFs are well-known mediators of angiogenesis and vascular permeability, many studies indicate that PDGF is an important factor that limits the efficacy of anti-VEGF



AT A GLANCE

- Although the treatment of wet AMD with anti-VEGF drugs is common practice, it is not without limitations.
- E10030 (Fovista) is a PDGF antagonist being investigated in combination with an anti-VEGF agent for the treatment of patients with newly diagnosed wet AMD.
- In a phase 2b trial, the combination of E10030 and ranibizumab had a favorable safety profile and improved VA when compared with baseline VA.

therapy for wet AMD.^{24,26,28-32} Pericytes share a common basement membrane with endothelial cells, intimately coating them.³³ Pericytes provide endothelial cells with VEGF and other growth and cell survival factors by paracrine and/or juxtacrine signaling mechanisms.³⁴ Consequently, pericytes can protect neovascular endothelial cells from anti-VEGF therapy, thereby decreasing its efficacy.

Pericytes also play a major role in wound healing and pathologic fibrosis. For example, pericytes drive renal and hepatic fibrosis.^{23,35} In the eye, multiple diseases affecting the retinal pigment epithelium (RPE)-Bruch membrane-choriocapillaris complex result in neovascularization; on histopathologic analysis, the components include granulation tissue.³⁶ Pericytes are increasingly known to play a central role in this wound healing process,²⁵ and therefore they represent a prime therapeutic target to address anti-VEGF resistance and the related pathologic sequelae of CNV. Inhibition of both the VEGF and PDGF pathways in wet AMD may provide enhanced therapeutic benefit over anti-VEGF monotherapy.

THE CASE FOR COMBINATION THERAPY

A combination anti-VEGF/anti-PDGF approach to treating wet AMD could affect multiple cell types and processes sensitive to PDGF signaling pathways and induce a variety of disease-modifying tissue responses such as regression of the neovascular complex and reduction of fibrovascular and/or fibrous scar. Studies from multiple independent labs support this concept, as described below.

First, in preclinical pathologic angiogenesis, when PDGF signaling is disrupted, pericytes are stripped from neovascular endothelial cells. The resulting endothelial-lined neovascular tubes are highly vulnerable to the effects of anti-VEGF therapy, which thereby induces neovascular regression.^{24,26,30} Second, experimental immunolabeling studies of spatiotemporal cellular events in laser CNV models suggest that pericytes also play a key role during the initial formation and growth of CNV.³⁷ Third, there is compelling evidence that pericytes play an important role in local inflammatory response by orchestrating the navigation of leukocytes within the interstitial space to sites of inflammation.³⁸ Fourth, PDGF itself is chemotactic for pericytes, RPE cells, and glial cells,^{33,39,40} all of which are known components of surgically extracted fibrovascular and fibrous CNV.³⁶ Finally, there is strong supporting evidence that PDGF-supported pericytes are an important source of myofibroblasts that deposit pathologic matrix.^{23,35} PDGF is also approved by the FDA as a recombinant dermatologic gel to promote wound healing in diabetic ulcers. Recently, the FDA approved nintedanib (Ofev and Vargatef, Boehringer Ingelheim), an agent known to involve PDGF signaling for treatment of idiopathic pulmonary fibrosis.

E10030 (Fovista, Ophthotech) is a PDGF antagonist. Specifically, it is a 32-merpegylated DNA aptamer that selectively binds to PDGF-BB and PDGF-AB homo- and

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heterodimers, respectively, thereby disrupting interaction with all of the cognate tyrosine kinase receptors (PDGF-BB with PDGFR- $\alpha\alpha$, PDGFR- $\beta\beta$ and PDGFR- $\alpha\beta$; PDGF-AB with PDGFR- $\alpha\alpha$ and PDGFR- $\alpha\beta$). Multiple cell types express both receptors in proliferative retinal diseases.^{41,42} Hence, theoretically, if PDGF is blocked at the level of the ligand or intracellular tyrosine kinase, then the multiple aforementioned mechanisms may be more effectively inhibited than if a single PDGF receptor is targeted.

In the eye, E10030-mediated PDGF inhibition significantly reduced epiretinal fibrosis in an animal model of retinal scarring.⁴³ In another preclinical model, E10030 potently stripped neovascular pericytes from underlying endothelial cells.⁴⁴ When this happens, the underlying endothelial cells are left unprotected and vulnerable, which increases their sensitivity to the effects of VEGF blockade.^{24-26,28,30}

A PROMISING PAIRING

Dual targeting of PDGF and VEGF in the treatment of patients with wet AMD has been assessed in a phase 1 clinical trial in which E10030 was administered in combination with ranibizumab; this therapeutic approach had a favorable safety profile, improved VA when compared with baseline, and caused biomarker changes supporting enhanced efficacy.⁴⁶ In a more recent phase 2b clinical trial, this same approach demonstrated a favorable safety and efficacy profile across multiple clinically relevant visual endpoints that correlated with alterations in tissue response.⁴⁷ In this clinical trial, 449 individuals diagnosed with treatment-naïve subfoveal wet AMD were randomized in a 1:1:1 ratio to one of three intravitreal treatment groups: E10030 0.3 mg in combination with ranibizumab 0.5 mg, E10030 1.5 mg in combination with ranibizumab 0.5 mg, or sham in combination with ranibizumab 0.5 mg (ie, anti-VEGF monotherapy). The drugs were administered monthly in each of the groups for a total of 24 weeks.

This study demonstrated a statistically and clinically significant VA benefit over 6 months for the combination of E10030 1.5 mg and continuous anti-VEGF therapy for wet AMD, reflected by a 62% additive improvement in mean VA from baseline to 24 weeks for patients receiving this combination. Specifically, the E10030 1.5 mg combination therapy regimen met the prespecified primary endpoint of superiority in mean VA gain compared with anti-VEGF monotherapy (10.6 ETDRS letters at week 24 for the combination vs. 6.5 ETDRS letters for monotherapy, $P = .019$). A dose-dependent benefit of E10030 combination therapy over anti-VEGF monotherapy was evident early and was sustained to the last measured time point at 24 weeks. The relative treatment benefit in the E10030 combination therapy arm, as measured by optical coherence tomography (OCT), was evident irrespective of baseline VA, lesion size, and central subfield thickness. The benefit was also seen in multiple treatment endpoints measuring VA gain and reduction of VA loss.

Biomarker changes consistent with the mechanism of action of E10030 combination therapy in wet AMD

were observed in the phase 2b study (unpublished data). Neovascular complex regression after treatment with E10030 combination therapy was evident on OCT, represented by enhanced resolution of subretinal hyper-reflective material (SHRM, referring to tissue external to photoreceptors and internal to RPE and/or Bruch membrane on OCT, thought to represent CNV components that may include fibrin, blood vessels, blood, and fibrosis), and this also correlated with improved VA. In a publication from the CATT Research Group, SHRM was a significant risk factor for scar formation.²² On fluorescein angiography, a similar CNV regression effect was suggested by separate evaluation of small and large CNV lesions at baseline. Consistent with the mechanisms highlighted in the preclinical studies cited above, this retrospective masked analysis revealed that E10030 combination therapy was more effective than anti-VEGF monotherapy in limiting the development and progression of fibrosis.

The particular strengths of this phase 2b study include its large sample size, double-masked, randomized, prospective design, prespecified ETDRS VA endpoint obtained through masked certified ETDRS VA examiners, and the involvement

OTHER ANTI-VEGF/ANTI-PDGF COMBINATION DRUGS IN THE PIPELINE FOR TREATMENT OF AMD

BY THE STAFF OF *RETINA TODAY*

VEGF and PDGF are two common and critical pathways implicated in serious retinal diseases and a combination treatment of anti-PDGF and anti-VEGF agents may prove more effective in the treatment of wet AMD than anti-VEGF monotherapy, particularly in recalcitrant disease. This avenue is being investigated by several other companies that are developing their own anti-VEGF/anti-PDGF platforms.

ABICIPAR PEGOL

Designed ankyrin repeat proteins (DARPs) provide a platform for the creation of drugs with multiple binding target proteins, and abicipar pegol (Allergan) is part of this new class of small molecule therapeutics. The company is collaborating with Molecular Partners in the development of an anti-VEGF/anti-PDGF DualDARPin that pairs VEGF-targeting abicipar with another DARPin that targets PDGF for the treatment of patients with AMD.

Two phase 3 studies initiated in 2015 will compare this DualDARPin with ranibizumab (Lucentis, Genentech). These randomized, double-masked, parallel-group, active-controlled studies consist of approximately 400 clinical study sites in roughly 30 countries.

DE-120

DE-120 (Santen) is a small molecule dual tyrosine kinase receptor inhibitor for both VEGF and PDGF signaling pathways. DE-120 belongs to a class of active small molecules that inhibit the activity of receptor tyrosine kinases involved in the angiogenic process. Several such inhibitors have been approved by the FDA and other healthcare authorities for the treatment of various cancers. As a single anti-VEGF/anti-PDGF agent, DE-120 has the potential to provide a synergic antiangiogenic effect and reduce the potential side effects associated with intravitreal injection procedures.

Santen is conducting a phase 2 clinical trial in the United States to evaluate the safety and efficacy of intravitreal DE-120 as monotherapy and along with a single injection of aflibercept (Eylea, Regeneron) in subjects with treatment-naïve active subfoveal CNV secondary to AMD.

TWO MORE BEING INVESTIGATED

Carl C. Aw, MD, and Jeffrey S. Heier, MD, discuss two other anti-VEGF/anti-PDGF combination therapies in this issue: X-82 (Tyrogenex), an orally administered small-molecule tyrosine kinase inhibitor derived from a cancer drug that inhibits VEGF and PDGF receptors on page 83; and REGN2176-3 (Regeneron), which consists of the anti-VEGF drug aflibercept (Eylea, Regeneron) and an antibody to the PDGF receptor (rinucumab, Regeneron) on page 85.

“ [T]hese findings could change the paradigm for wet AMD treatment and, as a result, improve patient outcomes.

of certified masked image readers. These design elements and primary endpoint analysis are similar to those used in phase 3 drug registration trials. Together with the multiple supporting anatomic findings that provide biologic rationale for the VA superiority observed in the E10030 1.5 mg combination therapy group, compared with the anti-VEGF monotherapy group, there is strong rationale to conduct confirmatory phase 3 registration trials. These trials are under way, comparing 1.5 mg E10030 combined with each of the three commonly used anti-VEGF agents to the respective anti-VEGF agent administered as monotherapy. Initial topline data are expected toward the end of 2016.

IMPROVED PATIENT OUTCOMES ON THE HORIZON?

If these and other ongoing clinical trials confirm a clinically meaningful and statistically significant benefit of anti-PDGF treatment added to anti-VEGF therapy when compared with anti-VEGF therapy alone, then these findings could change the paradigm for wet AMD treatment and, as a result, improve patient outcomes. ■

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