

The vitreoretinal community will remember 2016 as the year that unfavorable anti-platelet-derived growth



Seenu M. Hariprasad
Practical Retina
Co-Editor

factor (anti-PDGF) clinical trial results ended the development of Fovista (pegpleranib; Ophthotech, New York, NY) and Rinucumab (Regeneron, Tarrytown, NY). The failure of these trials reaffirmed how important the innovations made in

2006 with anti-vascular endothelial growth factor (anti-VEGF) were to our field and our patients.

Evan N. Dunn, MD, and **Veeral S. Sheth, MD**, were tasked with analyzing and dissecting the anti-PDGF clinical trials — beginning with the basic science behind anti-PDGF. They will also review novel, multitarget approaches to our diseases, as well as unique routes of delivery such as topical and suprachoroidal administration.

Reading this article leads one to appreciate how high the anti-VEGF class of molecules has set the bar for the treatment of vitreoretinal disease. Although recent clinical trial results have been a disappointment to our community (and our patients), we should be reassured by the fact that many development programs are strongly underway investigating novel approaches to treat back-of-the-eye disorders. Drs. Dunn and Sheth's insights will be highly valued by our community.

An Overview of the Fovista and Rinucumab Trials and the Fate of Anti-PDGF Medications

by Evan N. Dunn, MD; Veeral S. Sheth, MD



Evan N. Dunn



Veeral S. Sheth

Intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections have remained the standard of care for neovascular age-related macular degeneration (AMD) since the landmark ANCHOR and MARINA studies published in 2006, which demonstrated the superiority of ranibizumab (Lucentis; Genentech, South San Francisco, CA) over photodynamic or sham therapy, respectively.^{1,2} Since then, trials such as VIEW 1 and VIEW 2 have brought us new anti-VEGF agents such as aflibercept (Eylea; Regeneron, Tarrytown, NY).³ Other trials, such as CATT and TREX-AMD, have demonstrated the effects of alternate dosing and, ultimately, the superiority of monthly ranibizumab and bevacizumab (Avastin; Genentech, South San Francisco, CA) dosing over less-frequent dosing intervals.^{4,5} Studies such as HORIZON have demonstrated that switching from monthly dosing to less-frequent, investigator-determined, as-needed

dosing resulted in disease destabilization, with 19.6% of patients initially treated with anti-VEGF in ANCHOR or MARINA losing 15 letters or more.⁶ Even with monthly dosing, VIEW 1 and VIEW 2 demonstrated that fewer than 46% of patients achieved 20/40 or better vision whether they were treated with ranibizumab or aflibercept.³

There are a handful of conclusions that can be made during this decade of innovation. First, anti-VEGF therapies have changed the landscape of ophthalmology and our ability to impact our patient's lives in a meaningful way. Second, despite this leap forward in quality of care, there have been no new-in-class medications since the advent of anti-VEGFs. Third, although a very large unmet need was filled with the anti-VEGFs, serious gaps still exist in our ability to manage patients with neovascular AMD. These gaps include the existence of patients subop-

tunately responding despite recurrent injections and marginally acceptable durability of the anti-VEGF class of drugs (especially in year 1) in many patients.

Ultimately, the question is why newer, more novel therapeutics have not become available during the past decade despite the remaining unmet need. The answer is not due to a lack of investment into research and development on the part of pharmaceutical companies and researchers. In fact, despite numerous clinical trials underway the community has been disappointed with repeat failures of highly publicized drugs — most notably the anti-platelet-derived growth factors (anti-PDGFs). Despite these failures, hope remains given numerous other clinical trials underway to fill the remaining unmet needs from the anti-VEGFs.

THE BASIC SCIENCE BEHIND ANTI-PDGF

The process of choroidal neovascularization (CNV) is not solely mediated by VEGF. Rather, it occurs as a result of a complex biological orchestra of activity with a number of growth factors involved. As a result, a monotherapeutic approach with anti-VEGFs may lead to incomplete or ineffective treatment of neovascular AMD.⁷ In the laser-induced CNV model, laser injury promotes the migration and proliferation of pericyte-like cells into the site of CNV formation, where they express markers for smooth muscle actin and PDGF receptor beta.⁸ These pericyte-like cells form a scaffold before infiltration of endothelial cells and subsequent formation of new blood vessels. Researchers have demonstrated that targeting these PDGF receptors in combination with VEGF receptors could potentially inhibit the formation of the pericyte-like scaffold, with resulting attenuation of CNV.^{8,9} Therefore, theoretically, treatment with the combination of anti-VEGF and anti-PDGF should provide a more complete and effective way of treating neovascular AMD.

EARLY, PROMISING RESULTS CREATE HOPE

In 2012, Ophthotech announced its phase 2B data using the anti-PDGF Fovista (pegpleranib; Ophthotech, New York, NY) in combination with ranibizumab at the American Academy of Ophthalmology Retina Subspecialty Day.¹⁰ The company demonstrated that patients receiving the combination of Fovista and ranibizumab gained 10.6 letters versus 6.5 letters in patients receiving ranibizumab monotherapy at 24 weeks. This was the first trial to show statistical superior efficacy over ranibizumab monotherapy; for the first time since 2006, a new in class therapeutic for the treatment of neovascular AMD seemed tangible.

This success, coupled with other pharmaceutical companies having potential anti-PDGF molecules, caused a boom in research and development targeting this receptor. Regeneron's rinucumab (an anti-PDGR receptor beta co-formulated with aflibercept) and Allergan's multi-VEGF/PDGF designed ankyrin repeat protein (DARPin) are examples of molecules being explored by some of the larger players in the industry. In addition, smaller companies are looking at applying the multitarget approach to different delivery systems. With its agent, X-82, Tyrogenix is looking at an oral anti-VEGF/PDGF formulation that demonstrated positive results in a phase 1 study.¹¹ Clearside Biomedical is developing axitinib, a compound targeting VEGF and PDGF receptors, for injection into the suprachoroidal space for the treatment of wet AMD. The company is planning to submit an investigational new drug application in early 2017 followed by phase 1 and 2 clinical trials.¹² OHR Pharmaceutical's phase 2 IMPACT study of topical Squalamine Eye Drops (anti-VEGF/PDGF/basic fibroblast growth factor) demonstrated an improvement in visual acuity when used in combination with an anti-VEGF agent versus anti-VEGF monotherapy. Patients receiving combination therapy achieved a mean vision gain in visual acuity of 10.5 letters compared to 5.4 letters in anti-VEGF monotherapy.¹³ With all of this activity, it seemed as though anti-PDGF medications were well on their way.

2016: ANTI-PDGF REALITY HITS

In 2016, the anti-PDGF momentum finally started to stall. The first clues that there may be some difficulty moving the anti-PDGF story forward came in September of 2016. Regeneron released the phase 2 CAPELLA results, which looked at Regeneron's combination anti-PDGF rinucumab/aflibercept versus aflibercept monotherapy. The combination drug failed to meet the primary endpoint of an improvement in best-corrected visual acuity (BCVA) at 12 weeks. Patients receiving combination therapy showed a 5.8-letter improvement in BCVA at 12 weeks, whereas patients receiving monotherapy with aflibercept showed a 7.5-letter improvement in BCVA at 12 weeks.¹⁴ If anything, this study confirms the efficacy of Regeneron's aflibercept.

In November 2016, the data from the phase 2 Ophthotech study were published confirming the statistically significant vision gains in the combination Fovista/ranibizumab cohort over the ranibizumab monotherapy group.¹⁵ However, optical coherence tomography (OCT) findings demonstrated no meaningful or statistically significant differences between the groups receiving the combination versus mono-

TABLE
New Medications in the Pipeline

Compound	Mechanism	Sponsor	Delivery	Phase	Highlights
X-82	Anti-VEGF/PDGFR	Tryogenix	Oral	2	In the phase 1 study, 15 of 25 patients who completed 24 weeks on X-82 required no intravitreal injections of anti-VEGF and had a mean visual acuity improvement of +5.3 letters.
CLS-1002 (Axitinib)	Anti-VEGF/PDGFR	Clearside Biomedical	Suprachoroidal	IND to be submitted in 2017	Drug administration through the suprachoroidal space of triamcinolone acetonide was well tolerated in phase 2 study by Clearside Biomedical for the treatment of noninfectious uveitis and macular edema secondary to RVO.
OHR-102 (Squalamine)	Anti-VEGF/PDGFR/bFGF	OHR Pharmaceutical	Topical	3	The phase 2 study reported in patients with classic CNV, 44% of patients receiving Squalamine combination therapy achieved a three-line vision gain at 9 months, compared to 29% in the ranibizumab monotherapy group. Similar gains were seen in occult CNV.
Abicipar	DARPin-based Anti-VEGF	Molecular Partners/Allergan	Intravitreal	3	Phase 2B data suggest abicipar could be administered every 12 weeks following loading doses, compared to every 4 weeks for ranibizumab. Phase 3 clinical trials started in 2015 and results are expected in 2018.
Nesvacumab	Anti-ANG2, co-formulated with aflibercept	Regeneron and Bayer	Intravitreal	2	Phase 1 data suggest improvement in vision and retinal morphology with nesvacumab/aflibercept at all dose levels for both AMD and DME.
RG7716	Anti-VEGF-A/ANG2	Hoffman-La Roche	Intravitreal	2	Phase 1 data evaluated patients with wet AMD with prior exposure to multiple anti-VEGF injections and suboptimal response. The 6 mg RG7716 group demonstrated a median BCVA increase of 7.5 letters and decrease in central subfield thickness of 117 μm from baseline.
HI-con1 (ICON-1)	Factor VII-IgGfc chimeric protein that targets TF	ICONIC Therapeutics	Intravitreal	2	Phase 1 data demonstrated an improvement in visual acuity, reduced retinal thickness, and regression of neovascularization. The phase 2 clinical trial will compare ICON-1, ICON-1 plus ranibizumab, and ranibizumab alone. Phase 2 is fully enrolled.

VEGF = vascular endothelial growth factor; PDGFR = platelet-derived growth factor receptor; bFGF = basic fibroblast growth factor; IND = Investigational New Drug; CNV = choroidal neovascular membrane; RVO = retinal vein occlusion; AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; DARPin = designed ankyrin repeat protein; ANG = angiopoietin; IgGfc = immunoglobulin G fragment crystallizable; TF = tissue factor

therapy. This vision-OCT disconnect caused concern in that biological plausibility for the vision gains seemed to be missing in the phase 2 data.

On December 12, 2016, the largest setback to anti-PDGF story occurred. Ophthotech announced results from its pivotal phase 3 trials that investigated Fovista in combination with ranibizumab versus ranibizumab monotherapy for neovascular AMD. The two clinical trials (OPH1002 and OPH1003) were international, multicenter, randomized, double-masked, controlled phase 3 studies evaluating the safety and efficacy of Fovista and enrolled 1,248 patients with neovascular AMD.

In OPH1002, patients receiving Fovista/ranibizumab combination therapy gained a mean of 10.74 ETDRS letters of vision compared to a mean gain of 9.82 ETDRS letters in patients receiving ranibizumab monotherapy ($P = .44$). In OPH1003, subjects receiving Fovista/ranibizumab combination therapy gained a mean of 9.91 ETDRS letters of vision at 12 months, compared to a gain of 10.36 ETDRS letters in patients receiving ranibizumab monotherapy ($P = .71$).¹⁶

In the pooled analysis of the data, 24.2% of patients receiving Fovista/ranibizumab combination therapy gained 20 or more ETDRS letters from baseline at month 12, compared to 22.1% of patients receiving ranibizumab monotherapy. In this analysis, 12.1% of patients receiving Fovista/ranibizumab combination therapy lost five or more ETDRS letters from baseline at month 12, compared to 11.2% of patients receiving ranibizumab monotherapy. In addition, in the pooled analysis, 13.5% of patients receiving Fovista/ranibizumab combination therapy achieved visual acuity of 20/25 or better at month 12, compared to 13.9% of patients receiving ranibizumab monotherapy.

Preliminary analysis of the safety data demonstrated that both combination and monotherapy were well-tolerated after 1 year of treatment. There were more frequent reports of ocular adverse events in Fovista/ranibizumab combination therapy, mainly related to the injection procedure, which was performed as two separate intravitreal injections. The incidence of reported serious systemic adverse events was similar between the two groups.

The Ophthotech data combined with the earlier Regeneron data make the previous inevitability of anti-PDGF success much less probable. Since the phase 3 Ophthotech data were announced, the company has terminated other phase 2 studies investigating Fovista. OPH1005, investigating Fovista in combination with bevacizumab, ranimizumab, and aflibercept in patients with neovascular AMD with subretinal fibrosis, has been terminated.¹⁷ In addition, OPH1006,

which was investigating Fovista in combination with bevacizumab, ranimizumab, and aflibercept to evaluate the potential reduction in treatment burden for neovascular AMD patients, has also been terminated.¹⁸

CONCLUSION

With the increasing prevalence of advanced AMD, the search for therapeutic advancements must continue.¹⁹ The anti-PDGF results to date have been a disappointment, demonstrating no vision or anatomic advantages to combination therapy over monotherapy. Subgroup analyses of the later-stage anti-PDGF data and imaging may illuminate which specific groups of neovascular AMD patients may benefit from the addition of an anti-PDGF agent. Studies looking at alternate routes of delivery such as Tyrogenix's oral delivery, Clearside Biomedical's suprachoroidal delivery, and OHR's topical delivery may demonstrate that anti-PDGF or other molecules can still play a role in decreasing the injection burden and improving outcomes for patients. Furthermore, these recent anti-PDGF disappointments have helped refocus the effort on anti-angiopoietin 2 and other potential targets. The latest data and ongoing research efforts have helped put into perspective how important the leaps in innovation made in 2006 have been to our field and our patients. Anti-VEGF molecules have set the bar high, and countless patients have benefited from the current standard of care.

REFERENCES

1. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med.* 2006;355(14):1432-1444.
2. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med.* 2006;355(14):1419-1431.
3. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. *Ophthalmology.* 2012;119(12):2537-2548.
4. Busbee BG, Ho AC, Brown DM, et al. Twelve-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology.* 2013;120(5):1046-1056.
5. Wykoff CC, Croft DE, Brown DM, et al. Prospective trial of treat-and-extend versus monthly dosing for neovascular age-related macular degeneration: TREX-AMD 1-year results. *Ophthalmology.* 2012;119(12):2514-2522.
6. 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.
7. Spaide RF. Rationale for combination therapy in age-related macular degeneration. *Retina.* 2009;29(6 Suppl):S5-S7.
8. Strittmatter K, Hayley P, Marneros AG. Targeting platelet-derived growth factor receptor $\beta(+)$ scaffold formation inhibits choroidal neovascularization. *Am J Pathol.* 2016;186(7):1890-1099.
9. Mabry R, Gilbertson DG, Frank A, et al. A dual-targeting PDGFR-

- beta/VEGF-A molecule assembled from stable antibody fragments demonstrates anti-angiogenic activity in vitro and in vivo. *MAbs*. 2010;2(1):20-34.
10. Positive Results from Phase 2b Study of Ophthotech's Novel Anti-PDGF Combination Agent Fovista to be Presented at AAO Retina Subspecialty Day. Ophthotech website. <http://www.ophthotech.com/news/positive-results-from-phase-2b-study-of-ophthotech-novel-anti-pdgf-combination-agent-fovista-to-be-presented-at-aa-retina-subspecialty-day>. Published October 24, 2012. Accessed December 21, 2016.
 11. Tyrogenex Presents Final Results from Phase 1 Study of X-82 for Wet AMD at the 2015 Annual American Academy of Ophthalmology Meeting. PR Newswire website. <http://www.prnewswire.com/news-releases/tyrogenex-presents-final-results-from-phase-1-study-of-x-82-for-wet-amd-at-the-2015-annual-american-academy-of-ophthalmology-meeting-300178524.html>. Published November 13, 2015. Accessed December 21, 2016.
 12. Focused Pipeline of CSC Treatments for Multiple Blinding Eye Diseases. Clearside Biomedical website. <http://clearsidebio.com/product-portfolio>. Accessed December 21, 2016.
 13. OHR-102 (Squalamine). OHR Pharmaceutical website. <http://www.ohrpharmaceutical.com/product-portfolio/squalamine>. Accessed December 21, 2016.
 14. Regeneron Announces Phase 2 Study of Aflibercept Co-Formulated with Rinucumab (anti-PDGFR-beta) Shows No Benefit Over Aflibercept Alone in Neovascular Age-Related Macular Degeneration. PR Newswire website. <http://www.prnewswire.com/news-releases/regeneron-announces-phase-2-study-of-aflibercept-co-formulated-with-rinucumab-anti-pdgr-beta-shows-no-benefit-over-aflibercept-alone-in-neovascular-age-related-macular-degeneration-300337055.html>. Published September 30, 2016. Accessed December 22, 2016.
 15. Jaffe GF, Ciulla TA, Ciardella AP, et al. Dual antagonism of PDGF and VEGF in neovascular age-related macular degeneration. *Ophthalmology*. 2016 Oct 28. pii: S0161-6420(16)31636-0. [Epub ahead of print]
 16. Ophthotech Announces Results from Pivotal Phase 3 Trials of Fovista in Wet Age-Related Macular Degeneration. Ophthotech website. <http://investors.ophthotech.com/releasedetail.cfm?ReleaseID=1003651>. Published December 12, 2016. Accessed December 22, 2016.
 17. Phase 2A Open Label Safety Study of Fovista (Anti-PDGF BB) Regimen Administered in Combination With Anti-VEGF Therapy to Study Sub-Retinal Fibrosis in Neovascular AMD. ClinicalTrials.gov website. <https://clinicaltrials.gov/ct2/show/NCT02214628>. Published August 5, 2014. Updated December 19, 2016. Accessed December 22, 2016.
 18. An 18 Month Phase 2a Open Label, Randomized Study of Avastin, Lucentis, or Eylea (Anti-VEGF Therapy) Administered in Combination With Fovista (Anti-PDGF BB Pegylated Aptamer). ClinicalTrials.gov website. <https://clinicaltrials.gov/ct2/show/NCT02387957>. Published March 9, 2015. Updated December 19, 2016. Accessed December 22, 2016.
 19. Jager RD, Mieler WF, Miller JW. Age-related macular degeneration. *N Engl J Med*. 2008;358(24):2606-2617.

Evan N. Dunn, MD, can be reached at the University of Illinois at Chicago, Department of Ophthalmology & Visual Sciences, 1855 West Taylor Street, Chicago, IL 60612; email: edunnmd@gmail.com.

Veeral S. Sheth, MD, MBA, FACS, can be reached at 15947 West 127th Street, Suite E, Lemont, IL 60439; email: vsheth@uretina.com.

Seenu M. Hariprasad, MD, can be reached at the Department of Ophthalmology and Visual Science, University of Chicago, 5841 S. Maryland Avenue, MC2114, Chicago, IL 60637; email: retina@uchicago.edu.

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