Inhibiting Platelet Derived Growth Factor: The Next Step in the Treatment of Exudative Age-Related Macular Degeneration

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The intravitreal administration of drugs that block the actions of Vascular Endothelial Growth Factor (VEGF) has completely revolutionized the treatment of exudative Age-related Macular Degeneration (AMD) over the past 7 years. Injections of bevacizumab (Avastin®, Genentech, S. San Francisco, CA, USA/Roche, Basel, Switzerland), ranibizumab (Lucentis®, Genentech, S. San Francisco, CA, USA/Roche, Basel, Switzerland), and aflibercept (Eylea®, Regeneron, Tarrytown, NY, USA) into eyes with subfoveal or juxtafoveal Choroidal Neovascular Membranes (CNVM) result in visual improvements which average +6.9 letters to +11.3 letters [1-4]. Furthermore, vision is stabilized in most eyes, with severe loss of vision (>15 letters) occurring in only 5% of patients. Since physicians around the world rapidly adopted this therapeutic strategy, rates of blindness in industrialized nations have already fallen significantly [5]. The unqualified success of anti-VEGF therapy juxtaposes sharply with the deficiencies associated with previously available treatments (thermal laser photoagulation, photodynamic therapy, transscleral thermotherapy, and macular translocation surgery) [6-9]. These therapies were indicated for only a small percentage of affected patients, were followed by frequent neovascular recurrences, were plagued by unacceptable complication rates, and rarely improved the visual acuity.

Much of what we know about both the benefits and limitations of anti-VEGF therapy is derived from pre-clinical studies with bevacizumab and aflibercept. These drugs impressively suppress the growth of orthotopic tumors in various animal models, and phase 1 and 2 trials in humans with advanced solid tumors demonstrated that the drugs were reasonably well tolerated. Unfortunately, monotherapy produced limited improvements in progression-free and overall survival for most patients [10]. The only human tumor currently treated with anti-VEGF monotherapy is glioblastoma, whereas for all other tumors, anti-VEGF agents are combined with multi-drug chemotherapeutic regimens.

Though newly developed anti-VEGF drugs possess stronger VEGF binding affinities than their predecessors (bevacizumab < ranibizumab < aflibercept) [11], they have not resulted in greater visual improvements for patients with exudative AMD. Thus it appears that anti-VEGF monotherapy for AMD may have hit a therapeutic "ceiling". Based on these observations, some investigators have suggested that further improvements in the treatment of AMD will require combination therapy (similar to the experience with tumors). Different treatment modalities (photodynamic therapy, radiation therapy) have already been combined with anti-VEGF pharmacotherapy, but these offer no additional advantage in efficacy (maximum number of letters gained) and little advantage in durability (duration of treatment effect) [12-14]. Intravitreal corticosteroids decrease VEGF synthesis, and stabilize cell membranes and tight junctions, but provide little additional benefit when used with anti-VEGF drugs, or used as triple therapy (combined with both anti-VEGF drugs and photodynamic therapy).

Recently, however, the quest for effective combination pharmacotherapy for exudative AMD may have yielded positive results. A 6-month phase 2 trial demonstrated that co-administration of ranibizumab and E10030 (foviast, Ophthotech, New York, NY), an aptamer which inhibits the actions of platelet derived growth factor (PDGF), increased visual improvements by 60% over ranibizumab monotherapy (+10.6 letters vs. +6.5 letters) [15]. Throughout the trial, the visual acuity differences between the 2 groups increased at each successive time point (suggesting that combination therapy may have been even more effective had the trial been extended) and the sizes of the CNVM steadily decreased. These results are impressive and encouraging but they must be viewed with healthy skepticism. Most other anti-VEGF trials have produced average visual improvements substantially greater than +6.4 letters, thereby making one question the composition of the control group. Nonetheless, no trial produced a group whose visual acuity improvement exceeded that from ranibizumab by 4 letters (the aflibercept 2 mg q4week arm in the VIEW 1 exceeded ranibizumab by 2.8 letters).

Why should this drug work so well in combination therapy? The answers to this question can be teased from our current understanding of angiogenesis. New blood vessel growth begins when localized tissue hypoxia and inflammation upregulate the synthesis of VEGF. Isomers of VEGF-A, principally VEGF165, bind to the extracellular domains of VEGFR2, causing receptor dimerization, activating intracellular tyrosine kinase moieties, and initiating a biochemical cascade along several pathways. These dissolve the intercellular matrix (by upregulating matrix metalloproteinases), amplify the VEGF effect (by plasmin-mediated cleavage of sequestered VEGF-A isomers), release tight junctions (by phosphorylating intercellular proteins), and produce new vascular endothelial cells (via mitosis and the recruitment of endothelial cell progenitors). Vascular buds originate from pre-existing vessels at areas of highest VEGF concentrations, elongate into tubules, and mature into full vascular loops [16]. These newly formed, immature vascular complexes leak and bleed, and only when covered by a sheath of pericytes (mature vessels have endothelial cell: pericyte populations of 1:1) do they become fully competent. Pericyte proliferation, migration, and survival depend upon PDGF, thereby prompting some authors to metaphorically state that ‘PDGF is VEGF for pericytes’. Furthermore, once pericyte coverage of new vessels becomes complete, the vessels are no longer VEGF-dependent. For CNVM associated with AMD, this represents disciform scarring that is unresponsive to anti-VEGF drugs. Therefore, interrupting the actions of PDGF prevents vessel maturation, and prolongs the interval during which the neovascular complex is sensitive to anti-VEGF therapy.

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But the clinical effects of anti-PDGF therapy go well beyond potentiating anti-VEGF therapy. Though anti-VEGF drugs stop exudation and prevent CNVM expansion, they do little to shrink membranes. In the CLEAR-IT 2 trial, aflibercept decreased the average area of CNVMs by only 20% [17]. A resecting CNVM restores the normal photoreceptor/retinal pigment epithelium/choriocapillaris relationship, improves the intercellular transfer of nutrients and waste products, and presumably results in improved vision. PDGF inhibition in this phase 2 trial led to a steady contraction of the CNVM, presumably through death of pericytes, with secondary loss of endothelial cells. So, PDGF suppression may be the "magic bullet" that causes dissolution of CNVM.

Though anti-PDGF therapy has emerged as the first pharmacologic therapy that leads to CNVM regression, it may not be the only one. CNVMs anchor to surrounding tissues via integrins and a phase I study with voloxicimab, an integrin inhibitor, resulted in modest CNVM regression.

Unfortunately, history is replete with promising drugs that failed when subjected to the increased experimental rigor of a phase III trial. Now that PDGF suppression in combination with anti-VEGF therapy appears promising, questions regarding the future immediately come to mind. Will these results be reproducible in a phase III trial? Though aptamer technology is elegant, physicians were disappointed with the clinical results obtained with pegaptanib (Ophthotech’s anti-VEGF aptamer) [18]. However, important differences between VEGF and PDGF biochemistry (heparin binding sites, multiple biologically active isomers) suggest that pegaptanib’s inherent weaknesses will not translate to fovista. Will the results of combination therapy apply equally to the use with other anti-VEGF agents? After all, most physicians prefer bevacizumab as the initial therapy for exudative AMD [19] and, since its approval by the FDA, aflibercept use has been more than double what was initially expected. Several industry analysts have questioned whether Ophthotech will co-formulate fovista with ranibizumab; a close working relationship with Genentech/Roche could be lucrative for Ophthotech, but this would require another phase 2 trial and would push back market approval (already approximately 5 years in development) to the future) by another 2 years. Does fovista need to be administered for Ophthotech, but this would require another phase 2 trial and would push back market approval (already approximately 5 years in development) to the future) by another 2 years. Does fovista need to be administered twice-weekly for AMD? What is the correct dosing regimen for AMD? A phase II trial demonstrated increasing efficacy of fovista through 6 months but results of CLEAR-IT 2, a phase 2 study of vascular endothelial growth factor trap-eye dosed as-needed after 12-week fixed dosing. Ophthalmology 118: 1098-1106.

We must now await formal publication of the phase 2 fovista results and completion of the phase 3 trial, but this drug may represent the next evolutionary step in the treatment of exudative AMD. For the health of our patients I hope that this drug fulfills the lofty expectations that have now been set.

References
4. Regeneron. Bayer and Regeneron report positive top-line results of two phase 3 studies with VEGF trap-eye in wet age-related macular degeneration.

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