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Review Article

The Role of PDGF Antagonists in the Treatment of Neovascular Age-Related Macular Degeneration

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Abstract

Platelet-derived growth factor (PDGF) plays an important role in the angiogenic process of diseases such as neovascular age-related macular degeneration (NVAMD). Currently, the primary treatment for NVAMD is intravitreal anti-VEGF therapy. However, some patients experience either a lack of response or an incomplete response to anti-VEGF injections. Emerging research of PDGF antagonists suggests that this class of anti-angiogenic agents may be beneficial when administered in combination with anti-VEGF in the treatment of patients with NVAMD.

Review

Introduction

Neovascular ("exudative" or "wet") age-related macular degeneration (NVAMD) is the most common cause of blindness and ocular morbidity in Caucasian Americans over the age of 50 [1,2]. Over the last decade, VEGF (vascular endothelial growth factor) antagonists have been found to be visually and anatomically beneficial in the treatment of NVAMD [3,4]. Since 2004, when pegaptanib became the first anti-VEGF agent to receive FDA approval for the treatment of neovascular AMD, there have been multiple groundbreaking trials such as MARINA, ANCHOR, and VIEW-1/2 which have confirmed that of all therapies currently available for neovascular AMD, VEGF antagonists are superior [2]. However, it is clear that these drugs are by no means a cure-all. More often than not, patients require repeat injections. Some patients exhibit an incomplete or lack of response to treatment [5]. Additionally, some ophthalmologists believe in a phenomenon whereby patients become less responsive to treatment with repetitive exposure to the same drug [6]. Even when patients do respond to anti-VEGF therapy with resolution of intra-/sub-retinal fluid, atrophy or a disciform scar may remain and preclude visual improvement [7]. For these reasons, there has been continued pursuit of other agents that target other pathways of ocular angiogenesis. One class of agents that has shown promise is that of the platelet-derived growth factor antagonists.

Overview of platelet-derived growth factor (PDGF)

Platelet-derived growth factor (PDGF) was first isolated in the 1970s from platelet extracts [8], and has since been found to be present in multiple cell types including placenta, brain, vessels, lungs, and bone [9]. The PDGF family consists of four ligands—A, B, C, and D—which form heterodimers or homodimers of A or B polypeptide chains, or homodimers of C or D chains [10]. Platelets release PDGF which then bind tyrosine kinase cell surface receptors, α and β, which activate downstream cellular signaling via PI3K, Ras, and PLC-γ. These signaling cascades play a role in pericyte recruitment and migration, which eventually contribute to angiogenesis [11].

Platelet-derived growth factor (PDGF) plays a critical role in angiogenic signaling. While VEGF stimulates the growth of new vessels, PDGF stabilizes pericyte-endothelial interaction and also acts as a potent chemoattractant and mitogen of fibroblasts and RPE cells. Increased expression of PDGF has been observed in patients with diseases such as non-proliferative diabetic retinopathy [12], proliferative retinopathy [13] and NVAMD [4,14-16].

The interactive roles of VEGF and PDGF in ocular neovascularization were first highlighted by Benjamin, et al. in a rat model; it was observed that while VEGF drives the formation of an endothelial plexus which acts as a scaffold for pericytes to grow along, PDGF drives the recruitment of these pericytes, an important component of subsequent vessel maturation [17]. Therefore, if pericyte encapsulation of endothelial cells can be downregulated, nascent blood vessels might be more susceptible to VEGF inhibition. It is now understood that neovascular AMD is a complex disease consisting not only of angiogenesis, but also inflammation, atrophy, and fibrosis. In the CATT trial, 45.3% of NVAMD study patients had developed subretinal fibrosis at two years [18]. Platelet-derived growth factor contributes significantly to fibrosis formation which is often the culprit of irreversible visual loss even after CNV regression. Thus, it is reasonable to predict that dual therapy with anti-VEGF and anti-PDGF may be more beneficial than anti-VEGF treatment alone.

Pre-clinical studies of combined PDGF and VEGF inhibition

There have been several studies using cultured cell lines or animal models to confirm the additive effects of VEGF and PDGF inhibition. In 2006, Jo, et al. demonstrated in a mouse model that a combination of anti-VEGF and anti-PDGF aptamers was superior to anti-VEGF therapy alone in both the treatment and prevention of laser-induced CNV [19].

Liegl, et al. studied the use of a temsirolimus, a rapamycin analog currently used in the treatment of retinal cell carcinoma, *in vitro* in RPE cells. At a concentration of 12.5 μg/mL, there was no decreased viability of RPE cell cultures. Additionally, temsirolimus appeared to lead to a decrease in VEGF and PDGF, both on RNA and protein levels [20].

Similar findings have been observed by Kernt, et al. in their studies of sorafenib. Sorafenib is an oral multikinase inhibitor used to treat various cancers. The study was designed to investigate the effect of sorafenib on light-induced growth factor expression in primary human RPE cells. When RPE cell cultures were treated with sorafenib 1 μg/mL, there was a decrease in expression of VEGF, PDGF, and PlGF (placental growth factor) measured via reverse transcription-polymerase chain reactions, immunohistochemistry, and enzyme-linked immunosorbent assays [21].

Takahashi, et al. reported that 100 mg/kg of pazopanib (small molecule inhibitor of VEGFR, PDGFR, and c-Kit) delivered orally to mice suppressed the development of CNV by 93%. Treatment of established CNV between days 7 and 14 with 8, 40, or 200 mg/kg per day reduced CNV by 0%, 58%, and 71%, respectively. Similar regression of CNV was also achieved when the drug was administered via periocular injection [22].

It was recently shown in a mouse model that intraperitoneal injections of 10 mg/kg of the anti-PDGF-BB DARPin significantly suppressed laser-induced subretinal neovascularization. 1 mg/kg of anti-PDGF-BB DARPin doses had no significant effect, but when combined with 1 mg/kg/day of an anti-VEGF-A DARPin, there was greater suppression of subretinal neovascularization than that found with anti-VEGF-A DARPin alone [23]. This suggests that PDGF is a valid target in the treatment of subretinal neovascularization.

Clinical trials studying combined PDGF and VEGF inhibition

There have been multiple other studies examining the additive effects of PDGF and VEGF inhibitors, several of which are now at clinical trial stage.

- Pazopanib (Votrient™, *GlaxoSmithKline*) is a small molecular inhibitor of VEGFR, PDGFR, and c-Kit. In 2013, Robbie, et al. showed that oral pazopanib 10 mg/kg directly bound melanin and was retained within the uveal tract of rats, and reduced laser-induced CNV formation when given three days prior to induction [24].

  Pazopanib is currently being tested in a topical eye drop and oral tablet form. In the 29-day phase I/II clinical trial of 70 patients with neovascular AMD, there was a small (20 μm), non-significant decrease in retinal thickness in the higher dose groups (oral pazopanib 6 mg/day and 15 mg/day). Visual acuity was noted to improve in the high dose groups with a mean visual acuity increase of 4.3 letters compared to baseline, with most improvement noted between days 8-29 after treatment commencement. Greater visual acuity improvements were noted in patients with a T allele-carrying CFH Y402H genotype. The drug was well-tolerated, and no serious adverse events were noted [25].

  Recently-published data showed that a 12-week course of topical pazopanib eye drops (10 mg/mL) instilled four times a day in patients with previously-untreated subfoveal choroidal neovascularization due to NVAMD resulted in no significant visual or anatomic improvement [26]; this contradicts earlier findings, and further study is expected.

- E10030 (Fovista™, *Ophthotech*) is an anti-PDGF-B pe-

gylated DNA aptamer being evaluated as an adjunct to ranibizumab. E10030 has been shown both *in vivo* and *in vitro* studies that when used in combination with an anti-VEGF agent, it is effective in preventing choroidal neovascularization. Phase I trials confirmed the safety of this drug when used as monotherapy or in combination with an anti-VEGF agent. A dose-escalation model was utilized with doses ranging from 0.03 mg to 3.0 mg injected intravitreally into human eyes, and all levels were tolerated well with no reported toxicity. A significant visual improvement of ≥15 letters was seen in 59% of patients at week 12 with an overall decrease in central retinal thickness from 395μ at baseline to 229 μ at week 12 [27].

In a randomized, double-blind phase II trial, 449 patients were randomized into three groups: 0.3 mg anti-PDGF with 0.5 mg ranibizumab, 1.5 mg anti-PDGF with 0.5 mg ranibizumab, and a sham injection given in conjunction with 0.5 mg ranibizumab. The primary outcome was improvement in best-corrected visual acuity (BCVA) at week 24 compared to baseline. The mean improvement in BCVA was 10.6 ETDRS letters, 8.74 ETDRS letters, and 6.5 ETDRS letters in the 1.5 mg combination group, 0.3 mg combination group, and the ranibizumab monotherapy group, respectively ($p = 0.019$ for ranibizumab only versus each combination group). This equates to a 62% marginal benefit of using this combination therapy over monotherapy [28].

There appear to be anatomical benefits in addition to visual benefits. At the 2014 American Academy of Ophthalmology Annual Meeting, Chakravarthy and Jaffe reported that at 24 weeks, approximately twice the number of patients on ranibizumab monotherapy (54%) were noted to have progression of subretinal fibrosis compared to those in the Fovista™ (1.5 mg)-ranibizumab (0.5 mg) combination therapy group (27%). In eyes without subretinal fibrosis at baseline, subretinal fibrosis developed in 10% of patients receiving Fovista™ (1.5 mg)-ranibizumab (0.5 mg) combination therapy compared to 51% in the ranibizumab monotherapy group (*American Academy of Ophthalmology Annual Meeting, October 21, 2014. Abstract PA092*).

Ophthotech has recently secured funding for Phase III trials which will compare the effect of an intravitreal injection of 1.5 mg E10030 + 0.5 mg ranibizumab with that of an intravitreal injection of sham E10030 + 0.5 mg ranibizumab. Initial results are expected to become available in 2016.

- X-82 (*Xcovery Vision*) is an oral VEGFR/PDGRF kinase inhibitor currently undergoing Phase I/II trials. Preliminary data from Liang, et al. suggest a good tolerability profile with an oral 50 mg daily dose (<25% of the standard dose administered to oncology patients); the investigators report that a sufficient therapeutic concentration is achieved with this dose. In their rat CNV model, 10 mg/kg dosed orally once a day showed >80% inhibition of CNV (*Association for Research in Vision and Ophthalmology Annual Meeting, May 7, 2013. Abstract 3272 - A0123*).

- DE-120 (Santen Pharmaceutical Co.) is a dual kinase receptor inhibitor that blocks both VEGF and PDGF. Developed in Japan, the drug is being evaluated in patients with late-stage neovascular AMD. Phase I/II clinical trials are currently underway to study DE-120 administered as an intravitreal injection at three different doses [29].

- In early 2014, Regeneron Pharmaceuticals, Inc. and Bayer HealthCare announced that they were embarking on a joint venture to develop an antibody to PDGFR-B that would be used in combination with aflibercept for the treatment of neovascular AMD. This antibody, REGN2176-3, is actively being studied in a phase I clinical trial [29].

The potential benefit of utilizing an oral drug in conjunction with intravitreal anti-VEGF injections to treat neovascular AMD is clear. It may limit the number of office visits as well as decrease the frequency of injections and thus reduce the risks of complications associated with intravitreal injections. Even though some of these therapies remain in an injectable form, they all share the potential of bringing better visual outcomes than what would be achieved by anti-VEGF monotherapy.

Conclusion

Anti-VEGF intravitreal therapy has significantly improved the prognosis for patients with neovascular age-related macular degeneration. However, its effects are limited in some, and there is even evidence to suggest that long-term therapy with anti-VEGF can result in retinal atrophy with eventual visual decline [30]. According to the SEVEN-UP study (Seven-year outcomes in ranibizumab-treated patients in ANCHOR, MARINA, and HORIZON: a multicenter cohort), at 7.3 years after entering the ANCHOR or MARINA trial, BCVA declined by ≥15 letters in 34% of study eyes, with an overall mean decline of 8.6 letters ($p < 0.005$) [9]. Hence, there remains a need and drive to seek other vision-salvaging therapies for these patients.

PDGF antagonists have been found to inhibit vascular development and maturation as well as increase endothelial cell susceptibility to anti-VEGF [31], and therefore may have a role in the treatment of neovascular age-related macular degener-

ation. Studies have demonstrated that suppressing PDGF-B along with VEGF is more effective in inhibiting pathological angiogenesis than suppressing either individually. A combined therapeutic approach produced CNV lesion regression in 85% of eyes compared with only 20% in eyes with anti-VEGF monotherapy, and correspondingly led to superior visual outcomes in studies by Boyer and Cousins (*Boyer D, et al. Association for Research in Vision and Ophthalmology Annual Meeting, 2009. Abstract 1260; Cousins S, et al. Association for Research in Vision and Ophthalmology Annual Meeting, 2009. Abstract 1261*).

While large randomized clinical trials of PDGF/VEGF dual-inhibitors are needed before any definitive conclusions regarding their efficacy can be drawn, early studies are compelling. As some of these agents move into late-stage clinical trials, it is probable that ophthalmologists will soon have another potent therapy to add to the armamentarium of treatment options for neovascular age-related macular degeneration. The apparent ability of PDGF antagonists to suppress the development of visually-detrimental subretinal fibrosis is especially promising. The emergence of PDGF/VEGF dual-inhibitors opens the door to a new era of combination therapy for NVAMD and highlights the importance of continued advancement in investigating the many other factors (e.g., Angpt2, FGF, TNF-α, HIF-1, PlGF) [2,32,33] involved in angiogenesis.

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CYW: conception/design of study; acquisition, analysis, and interpretation of data; drafting of the manuscript; critical revision of the manuscript; administrative, technical, or material support

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