Recent Update in Pathogenesis and Newer Therapies for Wet Age Related Macular Degeneration

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Age related macular degeneration (AMD) affects the elderly, a demographic that spends its free time reading, writing and in other activities requiring near vision. The abnormalities of this disorder range from discrete drusen deposits and pigmentary changes in early AMD to geographic atrophy and/or choroidal neovascularization (CNV) in the advanced forms causing substantial vision loss. Patients with age related macular degeneration thus, report it as one of their most distressing medical problems. Although a number of therapies for AMD have been introduced, such as nutritional supplements for dry AMD and anti-VEGF therapy for exudative AMD the disease continues to be the leading cause for irreversible blindness worldwide[1]. Identification of risk factors and preventive measures are to be undertaken for tackling this growing public health problem.

This review will focus on the recent updates in the understanding of molecular pathways involved in the genesis of neovascularisation in wet AMD and newer treatments.

RECENT UPDATE ON MOLECULES INVOLVED IN ANGIOGENESIS

A) The VEGF family (VEGF-A, VEGF-B, VEGF-C, VEGF-D, and VEGF-E and the placental growth factor (PGF)) are proteins of approximately 40 kDa. The discovery of anti- VEGF agents continues to be the most significant contribution in the treatment of wet AMD[2].

B) Platelet derived growth factor- PDGF- The process of choroidal neovascularization (CNV) is not solely mediated by VEGF. It is a complex 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. Vascular 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. These pericyte-like cells form a scaffold before infiltration of endothelial cells and subsequent formation of new blood vessels[3].

C) Thromboospondin-1, a component of platelet alpha granules in monocytes and macrophages is an anti-angiogenic factor. It is localized in the RP, Bruch membrane, choriocapillaris and the choroidal vessel walls. Data suggests that the decrease in thrombospondin concentration promotes neovascularization[4].

D) The integrin family of cell adhesion molecules mediates homeostasis, signal transduction, and various other interactions between the cell and the extracellular matrix. Integrins are type-1 transmembrane glycoproteins and are expressed in choroidal cells and RPE cells and are pro-angiogenic[5].

E) Angiopoietin-2 (ANG2) is essential for retinal vascular development and causes disruption of the blood-retinal barrier thereby increasing vascular permeability. ANG2 is upregulated in retinal and choroidal neovascularization since its production is upregulated by hypoxia[6]. ANG2 is significantly elevated in the vitreous of patients with retinal vascular pathologies, Tie2 tyrosine kinase, a receptor of the angiopoietin family of proteins is inhibited which in turn causes the upregulation of ANG2 and there is an increase in angiogenesis. Conversely, angiopoietin 1 (ANG1) binds and activates Tie2, which stabilizes blood vessels. ANG2 competes with ANG1 for Tie2 binding, thus increasing the retinal vessels to react to VEGF and promotes vascular leakage and neovascularization. On the contrary, ANG1 reduces responsiveness to VEGF and reduces vascular leakage. Therefore, either inhibiting ANG2 or activating Tie2 can both be potential strategies to treat wet AMD[7].

Recent update on molecules studied in the treatment of Wet AMD

Brolucizumab (RTH258, ESBA1008) is a humanized single chain antibody fragment with high affinity to all VEGF-A isoforms. It has a low molecular weight of 26 kDa that makes it possible to prepare higher molar concentrations and administer up to 6 mg of the drug in 0.05mL intravitreal injection. This leads to longer duration of action, and better ocular tissue penetration[8].

It is administered as 3.0-6.0 mg intravitreal injection q4w-q12w.

OSPREY was a phase II trial that compared the safety and efficacy of 6mg brolucizumab to 2mg aflibercept in subjects with treatment- naive active choroidal neovascularization due to AMD. Both Brolucizumab and Aflibercept groups received 3 monthly loading doses and were then treated every 8 weeks and assessed up to 40 weeks. The mean BCVA change from baseline with brolucizumab was comparable to aflibercept. The brolucizumab group received fewer injections and had more stable central subfield fluid thickness reductions. A greater proportion of brolucizumab treated eyes also had resolved intraretinal and subretinal fluid compared with the aflibercept group[9].

Since the knowledge of the role of PDGF in the stabilization of neovascular membranes was established, targeting PDGF receptors in combination with VEGF receptors was tried.

In 2012, Ophthotech announced phase 2B data using

the anti-PDGF Fovista (pegpleranib; Ophthotech, New York, NY) in combination with ranibizumab[10]. Rinucumab (an anti-PDGRβ co-formulated with aflibercept) was another potential molecule. X-82, Tyrogenix was an oral anti-VEGF/PDGF formulation that demonstrated positive results in a phase 1 study[11].

In 2016, results from studies of Fovista showed that although there was an apparent gain in vision in phase 2 studies, there were no statistically significant changes on optical coherence tomography (OCT). After phase 3 data came out, trials were terminated owing to inferior anatomic and functional outcomes and increasing reports of ocular adverse effects mainly related to the injection procedure[12].

The failure of the anti- PDGF trials reaffirms the immense contribution of the discovery of anti- VEGF molecules in the field of vitreoretina.

Abicipar pegol (MP0112), a designed ankyrin repeat protein (DARPin), is a genetically engineered antibody mimetic protein that is used as an intravitreal anti- VEGF agent. Results of initial studies demonstrate that MP0112 decreases mean retinal thickness and leakage area in patients with neovascular AMD. Currently, two independent phase III studies are ongoing[13].

Squalamine lactate is one of the few topical agents for wet AMD and is known to inhibit angiogenesis by entering into activated endothelial cells and then binding to calmodulin to limit neovascularization. Data from the IMPACT study demonstrates that, after 9 months of treatment, patients with combination therapy of ranibizumab and squalamine lactate had a mean gain of 11 letters versus a gain of 5 letters in the ranibizumab monotherapy arm[14]. Presently, a phase III trial of squalamine lactate is underway.

Single-chain antibody fragment VEGF inhibitor RTH258 has been tested in a phase I/II trial in AMD related subfoveal CNV. Changes in BCVA and mean central subfield thickness were comparable between RTH258 and ranibizumab[15] Phase III studies are now underway to compare the efficacy and safety of RTH258 to Aflibercept.

Small interfering RNAs (siRNAs) are small strands of RNA of about 21 nucleotides that bind specifically to target mRNA an influence the expression of VEGF. Bevasiranib a siRNA anti- VEGF was studied in phase I and II trials[16]. Phase III studies were inconclusive and thus were discontinued. A second alternative is the use of siRNA that targets the VEGF receptor 1 (VEGFR-1). The preclinical studies in animal models have shown encouraging results.

Anti-Integrin Therapies. Three classes of integrin inhibitors have been studied: monoclonal antibodies that target the extracellular domain of the integrin protein, comprising of triple amino-acid sequences;Arginine- glycine-aspartate(RGD) motif containing peptides and peptidomimetics that mimic the RGD sequence[17]. Mouse models have been studies and these ischemic retinopathy models have shown that anti- integrins have beneficial effects in the inhibition of retinal VEGF.

Resveratrol (3, 4, 5 - trihydroxy-stilbene) is a polyphenolic antioxidant commonly found in grape skin and seeds. It has antioxidant effects against peroxide-induced oxidative stress and reduces the UVA-induced aberrant activation in RPE cells, and also reduces MAPK activation and the expression of cyclooxygenase-2 in RPE cells in vitro[18]. Small case series, using resveratrol, have shown improvement in retinal structure and function[19].

Rabinizumab Port Delivery System: The Ranibizumab Port Delivery System (RPDS) is a refillable reservoir system designed to gradually release ranibizumab. It is placed under the conjunctiva, fixed to the pars plana, and is sutureless. The subconjunctival implant refilled with ranibizumab as needed (estimated every 4-6 months). It is currently under phase 2 trials[20].

Aflibercept Hydrogel Depot is a hydrogel-based drug delivery depot that gradually dissolves and releases aflibercept for up to 6 months

Nesvacumab (REGN-910-3): Human IgG1 monoclonal antibody directed against ANG2 that blocks its interaction with the Tie2 receptor as mentioned in the mechanism of angiopoietin above. It is given as an intravitreal injection every 4 weeks.

A phase I study including 20 patients with wet AMD and diabetic macular oedema (DME) showed no significant adverse effects and good functional and anatomical outcomes[21]. Nesvacumab has also been tried in combination with aflibercept.

ALTERNATIVE TARGETS

ICON-1 (hI-con1): this is a chimeric protein designed to bind to and inhibit Tissue Factor (TF) with higher affinity than monoclonal antibodies. This, in turn, triggers natural killer-cells to selectively destroy overexpressing TF tissues, such as pathologic neovascularisation[22]. It is given as a 0.3mg intravitreal injection.

The EMERGE study was a phase II trial that used ICON-1 monotherapy, ranibizumab monotherapy or combination treatment. There was central retinal thickness reduction and BCVA gain which was comparable in the ICON-1 combination and ranibizumab groups, although it was maintained with fewer treatments from month 3 to 6 with ICON-1 combination[23].

Carotuximab (DE-122, TRC105) is a chimeric antibody to endoglin, a transmembrane glycoprotein that is expressed on proliferating endothelial cells and functions as a co-receptor of the transforming growth factor ß (TGF-ß) superfamily. that promotes angiogenesis. It is administered as an intravitreal injection. A phase II trial has begun recruiting patients in July 2017 (NCT03211234)[24].

CONCLUSION

Intravitreal injections, the current standard of care, are invasive and involve frequent patient monitoring. It is also a significant economic burden. Complement pathway modulators, gene therapy and cell implants,are promising future breakthroughs. Most of the molecules described in this update work at a sub-cellular level influencing various pathways involved in angiogenesis. Research is moving towards simultaneous inhibition of various pro-angiogenic pathways to nip the vascular network at the bud.

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