

Sight-Savers in Future near: New Drugs in Horizon for Vitreo-Retinal Pathologies

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Editorial

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Abbreviations: OCT: Optical Coherence Tomography; DME: Diabetic Macular Edema; ARMD: Age-Related Macular Degeneration; CNVM: Choroidal Neo-Vascular Membrane; RVO: Retinal Vascular Occlusions; VMT: Vitreo-Macular Tractions; MIVS: Micro Incision Vitrectomy System; FA: Fluocinolone Acetonide; IOP: Intraocular Pressure; TKI: Tyrosine Kinase Inhibitor

Editorial

Vitreo-retinal pathologies have remained the Achilles' heels for the ophthalmologists since time immemorial. Changing lifestyles, enhanced longevity and better access to specialist ophthalmic care heralded an era of non-communicable ocular diseases. Precise diagnostic modalities viz. optical coherence tomography (OCT) and OCT-angiography have simplified the diagnostic algorithm of entities like diabetic macular edema (DME), age-related macular degeneration (ARMD), choroidal neo-vascular membrane (CNVM), retinal vascular occlusions (RVO) and vitreo-macular tractions (VMT). While the diagnostic improvisations managed to answer the "why's" successfully, the "wherefores" still remain unanswered as far as visual outcomes are concerned. Micro incision vitrectomy system (MIVS) on the surgical front and intravitreal dexamethasone, bevacizumab, ranimizumab and ocriplasmin as novel drugs provided the much required armamentarium against these intractable conditions. GALILEO to COPERNICUS have all hailed these advents. What next- the obvious question arises? A glimpse into what the future therapies behold would be worth-while.

ILUVIEN® (licensed to Alimera Sciences, Inc.) is an injectable, non-biodegradable, fluocinolone acetonide (FA), intravitreal implant approved by the U.S. Food and

Drug Administration (FDA) for the treatment of chronic DME considered insufficiently responsive to available therapies for patients who did not have a significant rise in intraocular pressure (IOP) when treated with a course of corticosteroids. It utilizes pSivida's proprietary third generation Durasert™ Technology and is designed to release the corticosteroid for up to three years with a single intra-vitreous injection. Surrounded by an inert coating, the implant elutes drug only from its ends, giving it the near zero-order kinetics that allow it to last for such a long time. Iluvien clinical trials showed that Iluvien can actually reverse vision loss in many DME patients [1].

Durasert™ Bioerodible TKI is supposed to be a sustained-release bioerodible device containing a tyrosine kinase inhibitor (TKI) for treatment of wet AMD [1].

GrayBug is a polymer-drug biomolecular conjugate for the treatment of wet age-related macular degeneration and other neovascular diseases. Candidates such as Rhopressa (netarsudil ophthalmic solution 0.02%) are being evaluated with Gray Bug [1].

Neurotech Pharmaceuticals is developing Encapsulated Cell Therapy (ECT), a genetically engineered ocular implant, for the treatment of idiopathic parafoveal macular telangiectasia in the MacTel Project and for the treatment of wet macular degeneration [2].

Clearside Biomedical is developing suprachoroidal administration of CLS-TA, a proprietary formulation of triamcinolone acetonide, alone and combined with Eylea (afibercept, Regeneron) and PDGF inhibitors for the treatment of macular edema associated with noninfectious uveitis and retinal vein occlusion. Clinical

trials are in progress or in the planning stages with various formulations [2].

Smaller anti-VEGF products for treating AMD is a brilliant idea, hypothesizing that small anti-VEGF products will have a stronger binding affinity, improved efficacy, and longer duration. Also, they may be able to be packaged into a sustainable drug delivery device, which would obviate the need for frequent injections. Alcon (Fort Worth, Texas) and Novartis (Basel, Switzerland) are jointly developing RTH258, a small, humanized anti-VEGF antibody fragment that inhibits all its forms of VEGF-A. Allergan is developing an anti-VEGF DARPIn (abicicparpegol), a small, engineered protein that mimics the action of an antibody with high specificity and binding affinity [3].

The anti-platelet derived growth factors (anti-PDGF) promise a better vision salvage. The anti-PDGF agent Fovista (Ophthotech, New York) is currently in phase 3 clinical trials, being developed to work in combination with anti-VEGF agents to combat neovascularization. Anti-PDGFs bind and strip pericytes, cells that serve as an armor for neovascular membranes. Once the pericytes are gone, anti-VEGF can attack the naked endothelial cells, so the combination is particularly powerful. The phase 2 trial of Fovista, the largest ever done in retina, showed that the combination of Fovista and Lucentis had a 62% increase in efficacy from baseline over Lucentis treatment alone [3].

MC-1101, a topical agent developed by MacuClear, aims to stop dry AMD from progressing to wet AMD. A Phase Ib trial found it to be safe and well tolerated. It relaxes the epithelial lining of the vasculature, dilates choroidal blood vessels by stimulating nitric oxide production, and increases choroidal blood circulation. The drop is administered with a novel delivery system (the VersiDoser, developed by Mystic Pharmaceuticals) that employs unit-dose, micro-pump "blisters" that are inserted into a small handheld pump sprayer to deliver a preservative-free uniform spray dose to the ocular surface [4].

The LADDER study is evaluating the safety and efficacy of the ranibizumab port delivery system (RPDS) for the sustained delivery of Lucentis (ranibizumab, Genentech) in the treatment of wet AMD [5].

Based on the phase 3 MYRROR study, the National Institute for Health and Care Excellence has given final positive recommendation for Eylea (aflibercept) for the treatment of visual impairment due to myopic choroidal

neovascularization, according to a Bayer press release. September 25, 2017

A global Spectriphase 3 study is in progress for evaluation of lampalizumab (10mg every 4 or 6 weeks by intravitreal injection) for geographic atrophy [6].

Zimura (Ophthotech), a complement factor C5 inhibitor will begin an open-label phase 2a clinical trial for patients with wet age-related macular degeneration. Zimura (avacincaptadpegol) will be administered in combination with Lucentis (ranibizumab, Genentech) in patients who have not previously been treated with anti-VEGF drugs [7].

Two additional trials of Zimura, one as monotherapy for Stargardt disease and the second as a phase 2a study evaluating it in combination with anti-VEGF therapy for idiopathic polypoidal choroidal vasculopathy are expected to yield promising results.

These agents of vision offer us a glimpse of promising vitreo-retinal disease management. Many of these aforementioned drugs would be available for clinical usage pretty soon. Though the quest for the elixir for posterior segment pathologies will continue, with these molecules at our disposal we can infallibly step into the future hailing "fiat lux".

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