New Treatment Modalities For Dry ARMD

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Age-related macular degeneration is the primary cause of blindness and visual disability for adults over 60 years in industrialised countries. AMD can be classified as wet (neovascular) or dry (atrophic). Although wet AMD constitutes less than 20 % of all AMD cases, it is responsible for the majority (80 %) of the AMD related blindness. On the other hand, in dry AMD visual acuity loss occurs gradually over several years, the most severe manifestation being geographic atrophy. Over the last few years various new treatment modalities have emerged to treat dry AMD. These can be broadly classified as:-

* Anti-inflammatory intervention;
* Complement inhibition;
* Trophic factor supplementation;
* Drugs to prevent oxidative stress;
* Reduction of retinal toxins; and
* Other therapeutic Drugs

Anti-inflammatory Intervention

Inflammatory mediators have been found in association with drusens and geographic atrophy. This has created interest in evaluation of various anti-inflammatory agents in dry AMD.

Sirolimus (Rapamycin)

Sirolimus has the ability to inhibit the mammalian target of rapamycin (mTOR), a serine/ threonine kinase that regulates cell growth, proliferation, motility and survival. Wide therapeutic actions of Sirolimus include inhibiting inflammation, angiogenesis, fibrosis, and hyperpermeability.

Sirolimus also inhibits the translation and activity of hypoxia-inducible factor-1 alpha (HIF-1a), a stress activated protein that mediates the activity of numerous survival proteins involved in angiogenesis and hyperpermeability. Since HIF-1a is a potent vascular endothelial growth factor (VEGF) stimulator; its inhibition affects both VEGF production and activation at the receptor level.

Dose: 20 µl of subconjunctival injection

Glatiramer acetate (Copaxone)

Glatiramer acetate (Copaxone) is an immunomodulatory agent approved for the treatment of multiple sclerosis that induces specific suppressor T-cells and down-regulates inflammatory cytokines. Subcutaneous Glatiramer acetate in patients with dry AMD has shown to reduce the drusen area, eliminate plaque formation and induce neuronal survival.[12]

Complement Inhibition

Polymorphic variants in genes encoding complement factor H (CFH), complement component 3 (C3), and age-related maculopathy susceptibility 2 (ARMS2) confer significant risks for developing both wet and dry AMD.

There is evidence that the complement cascade plays an important role in AMD pathogenesis, leading to the possibility that complement inhibitors could 'neutralize' the response toward inflammatory sites in early AMD.

POT-4

POT-4 is a derivative of cyclic peptide compstatin. It can inhibit the complement activation system by inhibiting C3, a component upon which all known complement activation pathways converge. POT-4 is designed as an intravitreal gel that functions as a depot, allowing slow and sustained drug release.

ARC-1905

ARC-1905 is a selective factor C5 inhibitor. This drug is comprised of a chain of nucleic acids called an aptamer. This drug inhibits the cleavage of C5a and C5b, thus blocking downstream complement cascade. C5 is a downstream complement cascade mediator that mobilizes key terminal fragments responsible for tissue pathology: C5a, a proinflammatory fragment, and the membrane attack complex (MAC), which initiates cell lysis and releases pro-angiogenic molecules, such as platelet derived growth factor and VEGF. Unlike monoclonal antibodies, aptamers are synthetic and generally do not elicit an immune response.

Eculizumab/ Soliris

Eculizumab is a recombinant humanized monoclonal IgG antibody derived from a murine anti-human C5 antibody. It is approved by the FDA for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), a rare acquired form of complement induced hemolytic anemia. Like ARC-1905, eculizumab binds to the complement protein C5 with high affinity, inhibiting its cleavage to C5a and C5b and preventing terminal complement complex generation.

Trophic factor supplementation

NT- 501

Ciliary Neurotrophic Factor (CNTF/NT-501) is a cytokine member of the IL-6 family and a potent neuroprotective agent. CNTF receptors in a device have been identified on Muller glial membranes as well as rod and cone PR. Designated as NT-501, human RPE cells designed to produce neurotrophic factor are encapsulated in an implant measuring approximately 5mm × 1mm with a semipermeable polymer outer membrane.

Brimonidine Intravitreal Implant

Brimonidine is a a-2 receptor agonist. Brimonidine tartrate intravitreal implant is currently available as an ophthalmic solution. The implant delivers the drug to retina for a period of 3 months. Brimonidine stimulates the production of neurotrophic factors and has been shown to protect the photoreceptors. Currently implant being used for geographic atrophy is either 200 or 400 µg.

Drugs to prevent oxidative stress

Another strategy for dry AMD focuses on reducing the oxidative stress of the retina. Interest in the development of antioxidative therapies increased when carboxyethyl pyrrole-modifed proteins (CEP adducts) were identifed in Bruch's membrane and drusen obtained from AMD tissues. CEP adducts and autoantibodies are also elevated in plasma in those with AMD. CEP modifcations are generated by covalent adduction of primary amino groups with an oxidation fragment derived uniquely from phospholipids.

OT-551

OT-551 also known as 4-cyclopropanoyloxy-1-hydroxy-2,2,6,6- tetramethylpiperidine HCl, is a small lipophilic molecule that readily penetrates the cornea when applied as a topical medication. OT-551 is converted by ocular esterases to TEMPOL-H (TP-H), the active metabolite that is a potent free-radical scavenger and antioxidant that does not penetrate the cornea.] The drug OT-551 was shown to possess anti-inflammatory, antiangiogenic as well as antioxidant properties. OT-551 also was shown to protect against oxidative damage in vitro, to protect against light damage in vivo, to suppress PR cell death in animal models, and to block angiogenesis stimulated by growth factors.

AL-8309A

AL-8309A is a serotonin receptor agonist shown to protect the retina from light damage. It reduces CEP biomarker levels in rat retinas and plasma, and lower CEP autoantibody levels. Because CEP adducts and autoantibodies are elevated in AMD patients, they may be causal in the disease process, making AL-8309A potentially useful in reducing CEP modifcations in dry AMD. This drug is currently being used as 1% and 1.75% ophthalmic solution.

Reduction of retinal toxins

It has been seen that in patients of AMD there is an accumulation of cellular debris, or lipofuscin, within the RPE cells. Lipofuscin is an autofluorescent material composed of lipids, proteins, and vitamin A derivatives that form during daily phagocytosis of photoreceptor outer segments.

The most abundant autofluorescent compounds in AMD tissues are bisretinoid compounds such as N-retinyl-N-retinylidene ethanolamine (A2E). All-trans retinal (ATR), a retinoid formed in the retina during light exposure, is the precursor for A2E and related molecules. Various therapeutic trials in AMD are directed towards reducing ATR levels, including the one aimed at reducing the rate of retinoid metabolism in the RPE by targeting key visual cycle enzymes.

ACU-4429

ACU-4429 is an orally dosed small non-retinoid molecule that targets RPE. It inhibits the conversion of all-trans-retinyl ester to 11-cis retinol via inhibition of the isomerase, RPE. Since it acts as an enzyme inhibitor, it has a longer lasting effect than other drugs which act by reducing the availability of precursor. Dose related side effects are dyschromatopsia and delayed dark adaptation. The drug effects on ocular retinoid metabolism can be seen by electroretinography and is well tolerated upto a dose of 75 mg.

Fenretide

Fenretinide is an oral synthetic retinoid derivative which competes with retinol for binding to RBP and cause dose-dependent and reversible reductions in circulating retinol. Fenretide limits the accumulation of toxic retinal fluorophores by preventing the delivery of vitamin A to the RPE, thus downregulating the photoreceptor metabolism. Retinol enters the eye as a tertiary complex with retinol binding protein (RBP) and transthyretin (TTR) and is taken into the RPE through a receptor-mediated process. Fenretide is currently being used in doses ranging from 100-300 mg/day for geographic atrophy.

Other Therapeutic Drugs

It has been seen with the help of Doppler flowmetry that blood flow through RPE/ choroid complex is reduced in patients of AMD. This reduction in blood flow in patients of AMD has been found to be more pronounced in patients with increasing severity of AMD. Thus, the drugs which improve choroidal circulation and protect against ischaemia may promote survival of photoreceptors and the RPE.

Alprostadil

Alprostadil is a naturally occurring PGE1 with vasodilatory and antithrombotic properties. It was initially approved for the treatment of erectile dysfunction and is currently being used in various vascular disorders. Studies are on to assess if alprostadil can improve choroidal blood flow and improve visual acuity in early geographical atrophy. The drug is delivered as an i.v. infusion over a 15 day period.

MC-1101

It is a topical agent which increases the mean choroidal blood flow. It has been also shown to possess anti-inflammatory and anti- oxidant properties. Studies have found increased choroidal blood volume and velocity in MC-1101 treated eyes. The most common side effect in these studies was treatment related transitory ocular hyperaemia.

Trimetazidine

This drug is currently approved for the treatment of angina pectoris. It improves myocardial glucose utilisation by stopping fatty acid metabolism and is believed to have cytoprotective effect in ischaemic conditions. Ongoing studies are using this drug to slow the conversion of dry AMD to wet AMD. It is available as 35 mg tablet.

Conclusion

As is evident from the above discussion, a large number of investigative therapies have been developed targeting

many of the potential pathways implicated in the pathophysiology of Geographic atrophy. Results from ongoing studies are encouraging and show that one or more of these may achieve success over the next few years and provide cure to this important cause of irreversible blindness.

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