A New Era in the Treatment of Hereditary Optic Neuropathies

by Olawale Salami

Should these treatments prove to be effective and safe, they will radically transform the treatment approach to patients at risk of visual loss. Gene therapies are emerging for several inherited retinal diseases as well. These recent scientific and clinical developments may represent the beginning of an era of approved gene therapies for a wider range of neurologic diseases.

Retinal degenerative diseases are a leading cause of irreversible blindness. The central pathology in many of these conditions is retinal death, induced by a mix of genetic and environmental factors. Inherited conditions are increasingly recognized as an important component of the neuro-ophthalmic differential diagnosis of sub-acute vision loss. For these blinding conditions, innovations in gene and cell therapy approaches offer therapeutic intervention at various disease stages.

A recent review by Dr. Tatiana Bakaeva et.al from Harvard Medical School, Boston sheds light on hereditary optic neuropathies.[1]

A journey in discovery

For experts in the field, it's been a long journey towards understanding the pathophysiological pathways that underlie degenerative retinal diseases how these insights translate into the development of novel treatments. The investigators reported that: "To date, many promising treatments have been showing disappointing results in human trials. However, newer insights into the genetic basis, natural history and phenotypic heterogeneity of these conditions have set the stage for targeted therapies that are moving into clinical trials."

Leber's hereditary optic neuropathy (LHON) is an important example, in which visual loss can be severe and permanent. It is associated with three primary pathogenic mitochondrial DNA mutations, with varying degrees of penetrance, suggesting additional environmental factors. A variety of treatments have been tried in the past including systemic steroids, hydroxycobalamin and cyanide antagonists, vitamin C and riboflavin. The results were disappointing. However, a new class of drugs has shown promising results in clinical studies. These are known as CoQ10 analogues, or mitochondrial "cocktails," They interact with the mitochondrial electron transport chain to facilitate mitochondrial electron flux and bypass complex within this class, Idebenone and EPI-743 have appeared to be the most promising judging by early results from clinical trials showing a trend toward preserved acuity and RNFL thickness. However, as reported by Dr. Bakaeva and colleagues, data from larger studies are needed to validate these results.

Bridging the genetic gap

Given the unspecific nature of existing therapies for LHON Experts in the field have evaluated gene therapy as a targeted therapy that could effectively and safely prevent visual loss in high-risk but pre-symptomatic patients. The past decade has brought an exciting set of advances in gene therapy for this condition. Using genetically engineered vectors, most commonly the adenovirus[2] experts have assembled replacement genes, like the human ND4 gene, that hopefully will be efficiently expressed by the vectors and carried into the mitochondria, to replace deficient genes in the eye tissue of patients, and restore vision. Impressive results in in-vivo animal studies have led to early phase human studies at various stages of completion.

In other inherited retinal conditions, research and development in new therapeutic strategies have progressed much further. Leber's congenital amaurosis (LCA) is a spectrum of inherited retinal disorders, characterized by severe visual impairment presenting at birth or within the first few months of life, usually accompanied by roving eye movements or nystagmus, poor pupillary responses, and severely abnormal full field electroretinogram (ERG).[3] At present, there are 24 known gene mutations and the most common mutation occurs in the RPE65 gene, which accounts for approximately 16% of cases. Until recently, management of most forms of LCA has been symptomatic, but the previous decade has brought major scientific advances leading to a major breakthrough in the treatment of the specific form associated with mutations in the RPE65 gene.[4] Gene therapy for RPE65-associated retinopathy is commercially available, but prohibitively expensive, beyond the reach of many patients.[5]

Choroideremia is a rare disease characterized by progressive degeneration of the choroid, retinal pigment epithelium (RPE), and photoreceptors, starting with night childhood blindness that ultimately progresses to severe blindness. It has an X-linked recessive inheritance pattern caused by a loss of function mutation in the CHM gene that encodes REP1 (Rab escort protein 1). In other hereditary and nonhereditary retinal diseases in which gene therapy is being explored include achromatopsia, retinitis pigmentosa, X-linked retinoschisis, Usher's syndrome, Stargardt's disease, and age-related

macular degeneration, clinical studies of novel gene therapy-based treatments offer the promise of long lasting restoration of vision.

What about stem cell therapy?

Stem cell therapies are being explored extensively as treatments for degenerative eye diseases, either for replacing lost neurons, restoring neural circuits or, based on more recent evidence, as paracrine-mediated therapies in which stem cell-derived trophic factors protect compromised endogenous retinal neurons from death and induce the growth of new connections.[6] Stem cell therapy may offer an opportunity for restoring vision for patients in whom the extent of structural damage is too severe for effective gene therapy. These conditions can include chronic LHON and other acquired optic neuropathies, as well as most inherited retinal degenerations including retinitis pigmentosa.

Unlike gene therapy that is intended to enhance the function of poorly functioning existent cells, the goal of stem cell therapies is to regenerate dysfunctional tissue and restore lost cells. There have been many promising animal and preclinical studies over the past 20 years that involve the use of embryonic induced pluripotent and bone marrow–derived stem cells for retinal and neurologic diseases. Ongoing research is focused on optimizing techniques that allow safe delivery of an adequate number of cells to the recipient eye with the appropriate development of tissue structure. Several clinical trials are focused on treatment of age-related macular degeneration and other inherited retinal degenerations.

In contrast to progress being made in rigorous, well-conducted studies, patients and clinicians should be aware of an alarming trend of commercially advertised stem cell treatments that are not regulated, with substantial risk of poor outcomes including endophthalmitis, cataract progression, fibrous proliferation and tractional retinal detachment, and retinal artery occlusion following subretinal, intravitreal, and/or periocular injections of bone marrow–derived stem cells.[7]

Translation to clinical setting

LHON and other genetic causes of visual loss are important clinical entities that can cause profound visual loss. To date, therapeutic options have been quite limited. Insights into the genetic basis of these diseases and advances in the ability to deliver effective and safe gene therapy have opened the door for new therapeutics that may revolutionize the approach to treating these conditions.

While carefully conducted, controlled studies are keys to understanding the effects of these potential treatments and defining the optimal treatment populations, how do all these translate to real-world clinical setting? More importantly, the crucial first step is diagnosis. "In trying to arrive at the diagnosis, it would be helpful to examine parents and/or siblings, as many genetic conditions, though may have variable penetrance and expressivity, may have some detectable clinical manifestations," shared Dr. Manoharan Shunmugan, vitreoretina specialist in Kuala Lumpur, Malaysia.

Having a special interest in hereditary degenerative neuropathies, Dr. Shunmugam highlighted critical points on this subject matter, including genetic counseling. "For patients with hereditary conditions it is imperative that the parents receive genetic counseling so that they are aware of the possibilities of these conditions affecting any other children. It would also be prudent to ensure siblings or extended families have a routine eye examination," he explained. Furthermore, a thorough social and dietary history is necessary, according to Dr. Shunmugam. "Some modern dietary restrictions have been shown to have an impact on even normal individuals let alone those with underlying genetic conditions," he added.

Contributing Doctor

Dr. Manoharan Shunmugam is a consultant ophthalmologist, adult and pediatric vitreoretinal surgeon who trained in the United Kingdom and returned to Malaysia in 2013. He has a keen interest in research with publications in a wide range of high-impact journals and has been invited to many international conferences as a speaker. He is also a contributing author of two book chapters in vitreoretinal reference textbooks. He graduated in Scotland and subsequently undertook his Ophthalmic Specialist Training and VR Fellowship in London. En route, he further honed his skills with a Pediatric VR fellowship at the prestigious L.V. Prasad Eye Institute, Hyderabad, India – making him one of the few pediatric VR surgeons serving in the Asia-Pacific region. He is currently the Director of Clinical Services at the flagship branch of OasisEye Specialists in Kuala Lumpur, a multi-subspeciality ambulatory eye center. He continues to serve pro-bono at Hospital Kuala Lumpur and is the Honorary Secretary of the Malaysian Society of Ophthalmology (MSO) and is a member of the Asia-Pacific Vitreoretinal Society (APVRS).

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