

Editorial

Looking Ahead to Happier Days

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When “the Fonz” (aka Henry Winkler) speaks, people listen. At least that seems to be the goal of Apellis Pharmaceuticals for its new geographic atrophy (GA) therapy Syfovre[®] (pegcetacoplan injection). Geographic atrophy (GA) is a chronic progressive degeneration of the macula as part of late-stage age-related macular degeneration (AMD). Mr. Winkler’s messaging is focused on raising awareness about the disease and its warning signs. Within Apellis’ short lead time of about one year, Iveric Bio also recently entered the market with its newly launched drug Izervay[™] (avacincaptad pegol intravitreal solution).

Along with macular degenerations, neurodegenerative diseases affecting the visual system also encompass glaucoma, retinopathies, and inherited genetic disorders such as retinitis pigmentosa.

The World Health Organization estimates the global prevalence of the most common degenerative eye diseases to be age-related macular degeneration (8 million), glaucoma (7.7 million), and diabetic retinopathy (3.9 million).¹ Particularly concerning is that these conditions, resulting in irreversible vision loss, have considerable socioeconomic impact involving direct medical costs, indirect medical costs, productivity, and wellbeing. So, the Fonz’s well-articulated “public service message” surrounding the critical need for timely diagnosis and treatment of GA prompted me to take a broad look at investigative next generation therapeutics for degenerative retinal disease.

On World Sight Day 2022, Retina International presented data from its study into the socioeconomic impact of late-stage age-related macular degeneration (AMD). In the U.S. the total economic impact of late-stage AMD was estimated at \$49.1 billion, \$27.5 billion being attributed to neovascular AMD, and \$22.06 billion attributed to GA. Most of the costs for both conditions could be attributed to productivity i.e., job loss or job reduction due to the condition: 46% of the total figure for neovascular and 36% for GA. Further highlighting the significant and far-reaching effects of the disease, Retina International cited poor psychological health, worse overall health outcomes, and the substantial economic, physical, and emotional burden on caregivers.²

Also leading to progressive and historically irreversible visual impairment are inherited retinal diseases (IRDs), including retinitis pigmentosa (RP), Leber congenital amaurosis, choroideremia (CHM), achromatopsia (ACHM), Leber’s hereditary optic neuropathy, Usher syndrome (USH), X-linked retinoschisis, and Stargardt disease. These are a clinically and genetically heterogeneous group of diseases that cause vision loss due to abnormal development or due to the dysfunction or degeneration of the photoreceptors or the retinal pigment epithelium. They have a

prevalence of approximately 1:1380 individuals, with 5.5 million people expected to be affected worldwide, the most common being Retinitis Pigmentosa.³

The current treat armamentarium for this diverse array of sight-robbing conditions includes small molecule drugs, biologics, or gene therapies, most of which are administered topically as eye drops or as injectables. Of all approved ophthalmic therapies, over 75% are administered topically, and nearly 80% are small molecule therapeutics.⁴ As effective as these may be, they do not come without potential limitations and adverse effects such as achieving desired concentrations at the target site, retinal detachment and endophthalmitis. Thus, the development of new therapeutic strategies must focus on prolonging drug release, delivering site specific medication with reduced systemic exposure, and improving patient compliance and safety.

Nanomedicine in topical ocular therapeutics is aimed at bringing advanced drug delivery systems in the form of nanoparticles, thermogels and hydrogels, liposomes, niosomes, and viral and nonviral vectors. Nanoparticles can encapsulate glaucoma medications, protecting them from degradation and extending their release over time. This controlled release allows for sustained drug delivery, reducing the need for frequent eye drops, potential side effects, and improving patient compliance.⁵ Also holding promise are engineered technologies such drug delivering contact lenses, surgically implanted, and injectable devices.

Therapeutic investigation for inherited retinal disorders is centered around cell and gene-based therapies. A significant milestone was reached in 2017 with FDA approval of Luxturna[®] (voretigene neparvovec-rzyl), a novel gene therapy to treat patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy that leads to vision loss and may cause complete blindness in certain patients. Biallelic RPE65 mutation-associated retinal dystrophy affects approximately 1,000 to 2,000 patients in the U.S. Defects in this gene lead to several types of autosomal recessive retinal dystrophies, including subtypes of retinitis pigmentosa and Leber congenital amaurosis. Luxturna works by delivering a normal copy of the RPE65 gene directly to retinal cells, using a naturally occurring adeno-associated virus, which has been modified using recombinant DNA techniques, as a vehicle to deliver the normal human RPE65 gene to the retinal cells to restore vision. It is administered via sub-retinal injection and patients are treated with a short course of oral prednisone to limit the potential immune reaction.⁶

Finally, stem cell therapy holds great importance as a means of regenerating the damaged retina. In fact, human embryonic stem cell (hESC)-derived RPE cell suspensions

have been successfully transplanted subretinally into eyes with Stargardt disease, demonstrating survival, long-term safety and improved visual outcomes in early clinical trials. Furthermore, success in generating induced pluripotent stem cells (iPSCs) directly from somatic cells offers a promising alternative to overcoming ethical concerns around the use of hESCs.⁷

Thankfully, with the therapeutic horizon looking so robust we, along with our patients, can look forward to happier days.

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