Inherited retinal diseases (IRDs) are a heterogeneous group of dystrophies that produce a spectrum of visual impairment and blindness. Before modern treatments became available, management of these diseases was focused on diagnosis, genetic counseling, and teaching patients to cope with and use their remaining vision. Modern therapies now allow physicians to address complications, including cystoid macular edema and choroidal neovascularization, independent of the underlying genetic malfunction. Advances in technology, pharmacology, molecular biology, and whole genome sequencing have provided a plethora of avenues for delaying and even preventing devastating manifestations of these IRDs. This article takes a look at some of these emerging treatment avenues.

**MEDICAL DEVICES**

Medical devices (eg, implants) have been developed with the aim of treating patients with advanced and end-stage retinitis pigmentosa (RP), especially those with profound loss of visual acuity. Implants have been designed that sit on the retinal surface or underneath the retina and interface with an external camera mounted on a pair of spectacles to provide vision. A feature common to these devices is the aim to stimulate the remaining intact nerve fibers to provide vision. The Argus II Retinal Prosthesis System (Second Sight) is approved by the US Food and Drug Administration for use in patients with RP with bare light or no light perception. A favorable safety profile was reported in patients with functional implants. Vision-related tasks were improved in a statistically significant manner when performed with the device in the on position, compared with tasks performed with the device in the off position, in those with functional implants.

Drawbacks to the implant approach include the need for patients to have had adequate sight at one point and to receive training to provide a context for the novel manner of stimulation of the visual cortex. Focus groups have revealed that, although these technologies can provide useful vision, there may be aesthetic concerns with the associated bulky external hardware.

In addition, the niche characteristics and multidisciplinary rehabilitation team requirements of these devices mean that they are mainly available at tertiary eye care or academic centers, which may create challenges for some patients with regard to long-term maintenance and management of late complications associated with the implant. Practically, it would be difficult to use the currently available implants in a large population of patients and to leverage the skills of clinicians external to these centers. Despite these hurdles, there have been an additional 132 implant surgeries in Europe, the United States, Canada, and the Middle East since the completion of the Argus II Retinal Prosthesis Study.

**DRUGS**

The focus of pharmacologic approaches has been on the disease states of RP and Stargardt macular dystrophy.

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**AT A GLANCE**

- New therapies for inherited retinal diseases present new opportunities but also challenges.
- Recent advances in treatment revolve around medical devices, pharmaceutical options, gene therapy, and stem cell therapy.
- Successful collaborations will be necessary to usher these new modalities of treatment into practice.
A promising approach involves use of the topical glaucoma medication unoprostone isopropyl 0.15% (Rescula, Sucampo Pharmaceuticals), which has been reported to have neuroprotective effects on retinal neurons in vitro and in vivo. It is believed that these effects are related to increased retinal and choroidal blood flow secondary to partial blockage of endothelin-1 vasoconstriction of the choroidal vessels. In a phase 3 clinical study, there was a statistically significant difference in visual acuity between the unoprostone isopropyl group and controls; however, a primary endpoint of the study, change in mean retinal sensitivity at four central points on 10-2 Humphrey visual field, was not met, and the study was terminated.

No drugs are approved for the treatment of RP, but several drugs, such as an intravitreal preparation of brimonidine tartrate, valproic acid, and synthetic retinaldehyde, for treatment of Leber congenital amaurosis or RP due to a deficiency in RPE65 or LRAT, are being studied.

**GENE THERAPY**

Mendelian genetics provided the framework upon which modern genomics has been built. Genes encode protein end products, which give cells the ability to perform specific functions. Genetic mutations can produce abnormal proteins or completely prevent the production of proteins. Both of these downstream genotypic effects can phenotypically manifest disease. Gene therapy via vector delivery aims to restore a functional copy of a gene directly to cells.

The first hurdle that must be overcome in this approach is the insertion of a gene copy into a cell so that it is expressed for a significant enough period of time and produces enough protein product in order to provide therapeutic benefit. Features of the eye that facilitate gene therapy include its compartmentalization, relative ease of access, and the immune-privileged separation of the subretinal space from the blood supply via the blood-retina barrier. Another important consideration is that the majority of IRDs are caused by a mutation in genes expressed at the level of the photoreceptor or retinal pigment epithelial (RPE) cells, rather than in a more general systemic manner.

Viral vectors have shown promise for the delivery of genes. Although the adeno-associated viral vector (AAV) is the predominant delivery modality being studied at this time, lentivirus vectors (LVs) are also being studied. LVs have been demonstrated to be efficient in targeting murine RPE cells but have not been as effective at photoreceptor transduction. The AAV has demonstrated successful transduction to all retinal layers including the RPE and photoreceptors. More than 100 AAV serotypes have been identified and are being studied for their utility in targeting specific cell types and retinal layers.

Retinal disease can be caused by a lack of gene production or by undesired expression of genes. In the case of the latter, certain nucleic acid sequences can repress or prevent translation.
of target genes. Termmed gene knockdown or RNA interference (RNAi), this process takes advantage of what is believed to be a rudimentary cellular immune system to protect a cell from foreign genetic material. There are a variety of RNA subtypes that are capable of performing RNAi, including micro-RNA, small—or short—hairpin RNA, or double-stranded RNA. These molecules can be delivered using viral vectors as discussed above, as well as nonviral vectors, including liposome particles and other drug delivery devices.

Last year, Spark Therapeutics announced success of the first randomized, controlled phase 3 trial of a gene therapy for IRDs. The trial involved SPK-RPE65 gene transfer using AAV2-hRPE65v2 for RPE65-mediated IRDs. The primary endpoint was met (P = .001), and improvement of functional vision was demonstrated in the active treatment group as compared with the control group. This was measured by the change in bilateral mobility testing between baseline and 1 year.

A recent gene therapy workshop sponsored by the Office of Biotechnology Activities of the National Institutes of Health identified many challenges and opportunities with new therapies, including minimizing risk of toxicity, controlling transgene expression, sharing data, and commercialization.

STEM CELL THERAPY

Cell therapy is an alternative therapeutic approach that aims to repair areas of damaged retina. It has the advantage of working independent of the underlying mutation related to the pathology. The main cell types under investigation are similar to those targeted in gene therapy: RPE cells and photoreceptors.

NT-501 (Renumus, Neurotech) is an encapsulated cell technology involving a surgically placed implant that is designed to secrete therapeutic doses of ciliary neurotrophic factor for the treatment of retinal degenerative diseases. These implants have been evaluated for safety in patients with RP, and no adverse events related to the implant or procedure have been reported. Initial studies found no therapeutic benefit in terms of the primary outcome. A total of 184 subjects have been enrolled in three phase 2 studies, and some patients are now more than 4 years postimplantation. There is also an ongoing phase 2 multicenter, randomized clinical trial of NT-501 for macular telangiectasia.

NT-501 and similar cell technologies are promising treatments, and it will require time to establish their safety and efficacy. Such technologies may be a gateway into stem cell therapy in humans, although the encapsulated cells in implant form are not integrated into the tissue of the subject. Translating stem cell therapy to regenerative tissue to treat retinal degenerations is not without concerns, two of which are the risks of mutagenesis (generating tumors) and the challenges of ethically producing clinically effective stem cells. Furthermore, at this time there are no clearly established regulations, guidelines, or quality control measures for cellular therapies.

CONCLUSION

Modern therapies for IRDs have spawned new sets of challenges and questions that must be addressed to ensure the successful integration of these treatments into practice. The commercialization of the Argus II implant has provided new hope to previously untreatable patients. Also, there are potential translatable and novel large- and small-molecule therapeutics moving downstream in the pipeline. Gene therapy and cell therapy hold great promise, potentially allowing physicians to shift focus from managing the manifestations of progressive diseases to correcting the underlying defects.

The current state of research and development for IRDs is exciting, but ushering in the age of gene and stem cell therapies will require successful collaboration among academia, industry, funding agencies, and policy makers.


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