Drugs of the Future 2011, 36(7): 527-533

CCC: 0377-8282/2011
DOI: 10.1358/dof.2011.36.7.1673558

STARGARDT DISEASE: LIGHT AT THE END OF THE TUNNEL

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SUMMARY

Stargardt disease, also known as Stargardt macular dystrophy and fundus flavimaculatus, is a common, inherited, juvenile-onset disease that results in bilateral vision loss and macular degeneration as a result of lipofuscin accumulation in photoreceptor cells of the retina. The disease may be caused by a number of compound mutations within the ABCA4 gene that encodes for an ATP-binding cassette transporter known as RIM protein. In addition to Stargardt disease, mutations within this gene can lead to a number of other retinopathies, which can make diagnosis difficult. The disease is usually diagnosed by a combination of genetic screening, functional visual tests and ophthalmic examination of the fundus. As yet, there is no treatment available for the disease beyond minimizing light exposure, although studies in a mouse model have uncovered several potential therapies that may prove effective in humans, such as the use of retinoid analogues to inhibit the aberrant functioning of the visual cycle that leads to the accumulation of toxins. Current clinical trials are under way for viral gene therapy following the success of this method in treating other retinopathies, such as Leber's congenital amaurosis. Recent FDA approval has also been given for a phase I/II clinical evaluation of human embryonic stem cell transplant of retinal epithelial cells.

INTRODUCTION

Stargardt disease, also known as Stargardt macular dystrophy and fundus flavimaculatus, is a common, juvenile, autosomal macular dystrophy that is mostly inherited in a recessive manner, although a rarer autosomal dominant inheritance has been documented. The estimated prevalence of the disease is approximately 1 in 10,000 (1). It is characterized by early-onset (before the age of 20 years) reduced visual acuity and color vision, loss of peripheral vision, delayed dark adaptation and macular degeneration, concomitant with yellow/white, irregular-shaped flecks confined to the posterior pole of the fundus that are consistent with an accumulation of lipofuscin in the retinal pigment epithelium (RPE) of the macular region (2, 3). The disease, like a number of similar macular dystrophies, is caused by mutations in the *ABCA4* (*ABCR*) gene that maps to chromosome 1p13–p21 and that encodes a family member of the ATP-binding cassette transporters (ABC transporters) (4). The *ABCA4* gene is primarily expressed in the retinal photoreceptor rods (5, 6) and cones (7), and encodes the RIM protein (RmP), an outwardly-directing retinoid flippase, which is crucial in regulating retinoid cycling for phototransduction (6, 8, 9). The isomerization of 11-*cis*-retinal to *all-trans*-retinal occurs when rhodopsin (or cone-opsin) in the photoreceptor outer segment is activated by light photons. Following dissociation from activated opsin, *all-trans*-retinal is transported into the intradiscal space, where it combines with phosphatidylethanolamine (PE) to form *N*-retinylidene-PE (N-RPE). The *ABCA4*-encoded RmP then simultaneously mediates transport of N-RPE out of the intradiscal space into the cytoplasm of the photoreceptor outer segment, while breaking it down into *all-trans*-retinal and PE. Reduction of *all-trans*-retinal to *all-trans*-retinol (vitamin A) by *all-trans*-retinol dehydrogenases (*all-trans*-RDHs) precedes transport back into the RPE, where it is reconverted back to 11-*cis*-retinaldehyde. In the absence of RmP, N-RPE accumulates in the intradiscal space and condenses with *all-trans*-retinal, forming *N*-retinylidene-*N*-retinyl-PE (A2PE). A2PE is then hydrolyzed to form *N*-retinylidene-*N*-retinyl-ethanolamine (A2E), a major component of lipofuscin (10). The accumulation of A2E and subsequent formation of lipofuscin that results in the characteristic yellowish flecks on the fundus seen in many macular dystrophies is known to be toxic to the cells of the RPE and results in a degenerative cycle of destruction, whereby accumulation of A2E further reduces retinoid recycling, resulting in further lipofuscin deposits and associated photoreceptor loss (10-12). It is this RPE atrophy in the photoreceptor-rich perifoveal region that produces the characteristic "bulls-eye" maculopathy observed in Stargardt disease patients.

Stargardt disease can be mistaken for a number of other macular dystrophies associated with *ABCA4* mutations. For example, fundus

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flavimaculatus, which while similar and often grouped with Stargardt disease, is only seen in older individuals with less loss of visual acuity and in whom lipofuscin accumulation is not solely restricted to the posterior pole of the fundus (13). It has also been noted that first-degree relatives of patients with Stargardt disease are often diagnosed with early age-related macular degeneration (AMD) (14, 15).

The diagnosis of Stargardt disease is made by genetic screening for *ABCA4* allelic variants, functional testing of visual acuity and color sensitivity, electroretinogram (ERG)-measured field potentials, and structural examination of the retina by fluorescein angiography, ophthalmology and light microscopy. Initially, treatment for Stargardt disease was limited and focused on management rather than cure, and was mostly oriented towards slowing down macular degeneration by the use of visual aids to limit bright light and UV exposure. The use of inhibitors of the retinoid cycle has also been explored as a possible treatment for Stargardt disease.

A phase I clinical trial investigating the potential of 4-methylpyrazole to retard the production of vitamin A derivatives in Stargardt disease has been completed. With the successful advent of viral gene therapy in other retinopathies, newer therapies are being developed to replace loss-of-function mutants, including a lentiviral vector system that is currently in phase I/II clinical trials. Recent FDA approval has been given for phase I/II investigations involving the injection of human embryonic stem cells into 12 patients with Stargardt disease. Treatments involving dietary supplements such as docosahexaenoic acid (DHA) and saffron have also obtained approval for clinical evaluation in Stargardt disease.

DIAGNOSIS AND STARGARDT DISEASE PHENOTYPES

The diagnosis of Stargardt disease is primarily based on the age of onset of visual defects, functional visual assessment, fluorescein angiography, microscopic investigation of fundus architecture and genetic screening. Patients usually present with a bilateral, gradual decline in vision onset between the ages of 6 and 20 years. Visual acuity may range between 20/20 and 20/200 (16). Changes in ERG parameters include a prolonged b-wave implicit time in photopic and scotopic full-field measurements, a delayed implicit time or reduced amplitude may be observed in a focal ERG, and multifocal ERG may reveal subnormal amplitudes corresponding to the central visual field (17, 18). The mid-peripheral field may lose sensitivity, whereas the peripheral field remains unaffected (19). Color vision is affected, producing a mild red–green dyschromatopsia leading to a more pronounced acquired red and later blue dyschromatopsia (20). Initial changes in general ophthalmology include a loss of the foveal reflex of the retina, followed by the appearance of yellowish round or pisciform flecks within the RPE that are restricted to the posterior pole of the fundus but may extend as far as the mid-periphery. In later stages, a bulls-eye maculopathy may appear measuring 2 disc diameters horizontally and 1.5 disc diameters vertically, which is consistent with atrophy of the RPE. Relative central scotomata may develop in the visual field, with progression to absolute central scotomata in the late stages of the disease. Fluorescein angiography reveals faint fluorescent flecks around the fovea due to RPE atrophy and often a dark choroid resulting from increased lipofuscin accumulation in photoreceptors (21). Light microscopy reveals non-uniform cell size in RPE cells of the peri-foveal region and the presence of PAS-positive intracytoplasmic material known to be lipofuscin (22).

In a study by Cideciyan et al., six clinical stages of *ABCA4*-related retinal dystrophy were identified in Stargardt disease patients. At stage I, rod and cone sensitivities, dark adaptation kinetics and fundus architecture all appeared normal. At stage II, fluorescein analysis showed mass accumulation of lipofuscin in the fundus. At stage III, retinal regions displayed more pronounced abnormal increases in fluorescein intensities. At stage IV, further degeneration of photoreceptors and slowing of retinoid cycling was noted, along with abnormalities in all measured parameters, and was consistent with RPE loss. At stage V, there was a return of mean fluorescein intensity to normal as retinoid cycle abnormalities and photoreceptor degeneration become more pronounced. Finally, at stage VI, there was a lack of both visual function and fluorescein intensity, suggesting marked degeneration of the RPE with subsequent loss of photoreceptor cells (2).

STARGARDT DISEASE GENOTYPES

Stargardt disease is chiefly an autosomal recessive inherited disease, although 10% of cases display autosomal dominant inheritance. Mutations in the *ABCA4* gene have been associated with numerous autosomal recessive retinal dystrophy phenotypes, including retinitis pigmentosa (RP) (23) and cone-rod dystrophy (CRD) (23), and are linked to recessive inheritance in Stargardt disease type 1 (STGD1), while those related to dominant inheritance are found elsewhere on chromosomes 13q (STGD2), 6q (STGD3) and 4p (STGD4) (24-26). It is known that one of these loci (STGD3) encodes the elongation factor of very long chain fatty acids protein 4 (ELOVL4), which is employed in photoreceptor membrane synthesis (27). Unless otherwise stated, this article will concentrate on the *ABCA4* mutations associated with juvenile-onset Stargardt disease.

The initial identification of a genetic locus for STGD (28-30) and the subsequent identification of mutations in the causative gene, *ABCA4* (4, 6, 8, 31-34), which can be missense, nonsense, splice-site, frameshift or small deletion and insertion mutations, led to the development of a genetic screen for Stargardt disease. Sequence analysis of the 50 exons of *ABCA4* in 150 European families with a history of Stargardt disease found that the majority of causative mutations are represented by missense amino acid substitutions (14). The genetic heterogeneity of Stargardt disease is extensive; over 500 mutations in the *ABCA4* gene have been predicted and associated with various retinopathies, leading to diverse genotype/phenotype characteristics in distinct populations (15, 35-38). This heterogeneity further complicates the diagnosis of Stargardt disease, as even the most frequent mutations, such as G1961E, G863A/delG863 and A1038V, are only present in 10% of Stargardt disease patients and it is estimated that 30-40% of Stargardt disease-related *ABCA4* mutations are overlooked (35, 39). A patient may also present with additional complex mutations present in distinct retinopathies (14). Furthermore there is evidence to suggest that population-specific Stargardt disease mutations exist, such as those seen in Northern European (G863A/delG863) (15), German (L541P/A1038V) (40-41) or Japanese (T1428M) (42) populations. To further complicate matters, the same homozygous *ABCA4* mutation (L541P/A1038V) has been associated with Stargardt disease in one patient but CRD in another (40).

Due to the heterogeneity of *ABCA4* mutations, Maugeri et al. developed a grouping system in which mutations are classified as mild, moderate or severe, depending on how they affect transporter function (43). Additional studies have attempted to correlate phenotype, severity and genotype; for example, one study associated the G1961E variant with mild STGD in four patients (44), and another associated homozygosity for the IVS12+2T>G mutation with a severe phenotype for RP (45). A similar approach was taken by Gerth et al., who also found that genotype could be associated with different stages of clinical severity in 16 Stargardt disease patients based on assessment of fundus autofluorescence, psychophysics (color vision, kinetic and two-color dark- and light-adapted static threshold perimetry), and electrophysiology (Ganzfeld, multifocal ERG, electro-occulography [EOG]). They found that being homozygous for the *ABCA4* 5917delG mutation resulted in the earliest disease manifestation and a general CRD, whereas being heterozygous (5917delG, G1961E) exhibited a very mild phenotype. In addition, heterozygosity for the IVS40+5G>A and the C1488Y or Y362X mutation resulted in early age of onset, but only a central dysfunction. Furthermore, severity and phenotype were not solely determined by a single variant, because the effect of the 2588G>C mutation, the G1961E mutation and the complex mutation L541P-A1038V was also dependent on the mutation in the second *ABCA4* allele (46).

Expanding on these findings, Simonelli et al., attempted to uncover associations between severity and genotype in Italian Stargardt disease patients. Their findings allowed the grouping of genotypes into a mild or severe phenotype, with a statistically significant correlation found between patient age, age of onset and ERG abnormalities. *ABCA4* mutations, such as deletions, nonsense mutations and insertions, that resulted in abnormal protein function were most prevalent in the severely affected patients, concomitant with early onset of disease and severe ERG abnormalities. In contrast, patients with the G1961E/5018+2T>C variant mostly presented a mild phenotype with late onset and normal ERG responses (37).

A study to examine phenotype signs of macular degeneration, such as decreased foveal thickening and macular volume, was conducted in Hungarian Stargardt disease patients. This study found that specific clinical features of Stargardt disease could be correlated with genotype according to the three phenotype subgroups devised by Fishman et al. (44). All patients with a homozygous or a compound heterozygous IVS40+5G>A allele belonged to the phenotype III (severe: RPE atrophy) grouping, while the majority of those with a L541P/A1038V complex allele were grouped into phenotype II (moderate: numerous yellowish-white fundus lesions throughout the posterior pole) (47). Some inconsistencies arose between the grouping studies of Fishman (44) and Hargitai (47), although the authors suggest this could be due to the different methods used to assess phenotypes, in addition to the duration of disease, because patients in the Hargitai study had a longer duration of Stargardt disease than those in the Fishman study (47). Other studies have failed to find associations between quantitative measures of functional disease phenotypes, such as abnormal ERG amplitudes and specific mutations (2). The general consensus link between genotype and phenotype is that heterozygosity for *ABCA4* mutations that allows the production of a partially functioning RmP will lead to the milder Stargardt disease, whereas mutations producing only residually active or nonfunctional RmP lead to the more severe CRD or RP, respectively (38).

MICROARRAY ANALYSIS OF STARGARDT DISEASE GENOTYPE: THE ABCR400 CHIP

With the vast genetic heterogeneity associated with retinopathies and the advent of possible viral vectors to address loss-of-function mutations, it is imperative that genetic screening be carried out for all macular dystrophies, some of which are often misdiagnosed and mistaken for similar diseases caused by mutations in different genes. Advances in microarray and genome sequencing technologies are reducing the time, cost and manpower it takes to perform widespread screening, which is particularly important in diseases that manifest with an early onset. The development of ready-made microarray chips for a number of retinal dystrophies, the first of which was made for Stargardt disease (ABCR400 chip produced by Asper Ophthalmics) and contains markers for all the known mutations of the *ABCA4* gene, has allowed rapid and accurate genotyping of patient samples within 4 hours, with a high success rate. Combined with functional and ophthalmic testing, these assays can lead to accurate and specific information for tailoring treatment to the individual and selecting individuals for future clinical studies (48).

The ABCR400 chip was shown to be 54-78% effective in indentifying at least one of two Stargardt disease patient mutations, depending on the population examined (49). A study in a Portuguese cohort of Stargardt disease patients showed a 67% success rate in using the ABCR400 chip to identify Stargardt disease-associated *ABCA4* mutations. Furthermore, this study also identified the presence of a missense mutation p. Leu11Pro allele, which seemed to appear at higher frequencies in the Portuguese population (50). A degree of caution must be exercised when using microarray chips as a diagnostic tool for planning treatment regimens, because screening must be verified and assessed in other family members before passing the information onto patients to account for the confounding effect of multiple *ABCA4* mutations or the incorrect identification of mutations (51).

PRECLINICAL INVESTIGATIONS

The *ABCA4* knockout mouse: an animal model of Stargardt disease

Understanding the role of the retinal-specific ATP-binding cassette transporter in the retinoid cycle and macular dystrophies was greatly expanded by studies involving a knockout mouse, *ABCA4*$^{-/-}$. The photoresponse and photoreceptor morphology in *ABCA4*$^{-/-}$ mice appeared normal, but these mice showed a light-dependent increase in *all-trans*-retinal levels, NPE and PE in the RPE. In addition, the *ABCA4*$^{-/-}$ mice experienced light-dependent accumulation of lipofuscin within the RPE in regions of high photoreceptor density, with concomitant elevations in toxic A2E, all of which have been seen in humans with Stargardt disease, CRD and RP (10, 38). Studies in *ABCA4*$^{-/-}$ mice implied that macular degeneration associated with *ABCA4* mutations that result in compromised RmP function was exacerbated by exposure to light, suggesting that darkness or protection from UV light could be a possible treatment to slow or halt the progression of visual defects in Stargardt disease (10, 38).

Pharmacological prevention of A2E accumulation

Much of the damage to the RPE caused by Stargardt disease is due to the accumulation of toxic A2E as a result of lipofuscin accumulation and a breakdown in the retinoid cycle. Preventing the toxic accumulation of A2E in photoreceptor cells by pharmacologically inhibiting the visual cycle or limiting the supply of vitamin A to the eyes could therefore prevent the associated photoreceptor degeneration. One such intervention has used isotretinoin (13-*cis*-retinoic acid, Accutane®), a retinoid that inhibits 11-*cis* retinol dehydrogenase, the enzyme involved in the regeneration of 11-*cis*-retinal (38). In *ABCA4*$^{-/-}$ mice, used as a model of macular dystrophy, isotretinoin suppressed the accumulation of A2E and reduced the presence of lipofuscin deposits (52-54). Prolonged exposure to isotretinoin is associated with significant adverse events, preventing its useful application for the long-term treatment of Stargardt disease.

Another retinoid-based inhibitor, fenretinide (HPR), can reduce serum levels of vitamin A (55). Treatment of *ABCA4*$^{-/-}$ mice with HPR (2.5-10.0 mg/kg/day) prevented the accumulation of A2E and lipofuscin in the RPE and restored visual function at a dose known to be safe in humans (56). Lastly, mice treated with retinylamine (Ret-NH_2), a positively charged retinoid that acts as an inhibitor of isomerase activity in RPE cells, were resistant to light-induced RPE damage (57).

Viral-mediated gene transfer

Rescuing RmP function has been suggested as a strategy for the treatment of *ABCA4* mutation-related macular dystrophies and would be expected to be useful in treating Stargardt disease in which the function of RmP is partially retained. Gene therapy using viral vector delivery systems is an attractive alternative to pharmacological intervention that has been used successfully in treating other macular dystrophies, such as Leber's congenital amaurosis (LCA). In LCA, the retinoid isomerohydrolase (*RPE65*) enzyme involved in opsin cycling is nonfunctional, leading to lipofuscin deposits and macular degeneration. A recombinant adeno-associated virus (rAAV) expressing human *RPE65* was injected into an animal model of LCA (*rpe65*$^{-/-}$ mice and the briard beagle) stably improving visual function and restoring the RPE photoreceptors (58). rAAVRPE65 is now in phase III clinical trials and is proving successful and safe in restoring visual acuity in humans (59).

There is potential for a similar vector to be used in humans to restore the function of the RmP because rAAV vectors readily transduce nondividing cells, such as those in the RPE, intravitreal injections are nonimmunogenic, producing no adverse effects, and rAAV vectors support long-term expression of the transgene delivered; there are, however, limitations to this approach. Namely, the rAAV vector can only package 4.7 kb of DNA sequence, so size constraints may be an issue. Newer chimeric rAAV2/5 vectors are being developed, which would allow packaging of the 6.8-kb *ABCA4* gene (60). However, it has emerged that there have been difficulties in packaging the *ABCA4* gene into these vectors (unpublished observation by J. Bennicelli, J.F. Wright and J. Bennett, as referenced in 61). The focus for using rAAV vectors as delivery vectors for larger transgenes has now switched to the possibility that transducing one or two vectors containing fragments of the transgene may allow in vivo recombination of an entire transcript (61).

Other suggested rAAV strategies include cDNA encoding truncated functional proteins, delivery of antisense oligonucleotides for RNA interference to alter gene expression or delivery of the cDNA in segments through a "*trans*-splicing" approach, in which two separate rAAV vectors are engineered with a splice donor/acceptor to mediate splicing of the two cDNA segments within the cell (61, 62). The latter approach has been shown to be successful in a murine model using a small CMV-lacZ transgene cassette (63). Alternative viruses may be required; for example, in 2008, Kong et al. utilized an equine infectious anemia virus (EIAV)-derived lentivirus expressing the human *ABCA4* gene to restore visual function in the *ABCA4*$^{-/-}$ mouse. Toxic A2E levels in the RPE showed a dramatic reduction compared to mock- and sham-treated *ABCA4*$^{-/-}$ mice. One year following the initial subretinal injection of the vector, A2E levels were maintained at the levels observed in untreated wild-type mice, whereas those in mock-treated *ABCA4*$^{-/-}$ mice or the contralateral eye of treated animals showed three to five times higher A2E accumulation compared to wild-type mice (64). In the treatment of humans, more caution is required using lentiviral-mediated delivery due to their ability to integrate into the genome, which may cause unwanted mutagenic effects; this is usually circumvented by inserting promoter-specific sequences into the vector cassette for target-directed insertion. Current approaches to solve this include engineering lentiviral vectors that do not have the capacity to integrate.

CLINICAL INVESTIGATIONS

4-Methylpyrazole

Approval was given for the assessment of 4-methylpyrazole (15 mg/kg) in retarding the production of vitamin A derivatives in patients with Stargardt disease as a means to halt macular degeneration and prevent further visual loss (65). This study, conducted at the University of Utah in 2005, measured dark adaptation inhibition 30 minutes after drug infusion in 10 healthy adults with normal vision. The results of this investigation have not yet been published.

Dietary supplements

Docosahexaenoic acid (DHA) is a fatty acid essential for healthy brain and eye development. Approval for phase I clinical trials for the use of DHA in treating Stargardt disease was granted on the basis that DHA may prevent or slow down the progression of certain eye diseases. The trial, sponsored by the National Eye Institute (NEI) in the U.S., began in 2003 and was completed in 2007. It was a double-masked, randomized, placebo-controlled, crossover study in 22 patients with autosomal recessive or dominant Stargardt disease (66). Assessments of visual function by ERG flicker tests and improvements in general macular appearance were tested. There are currently no data available on the outcome of this study.

A second phase I/II trial investigating the use of saffron as a dietary supplement to aid vision in Stargardt disease patients (N = 30), sponsored by the Catholic University of the Sacred Heart, is currently recruiting (67). Saffron contains high concentrations of the bioactive compounds crocin and crocetin, whose multiple C=C bonds provide antioxidant potential and may act as a retinal neuroprotectant against oxidative damage. The macular cone-mediated focal flicker ERG will be employed as the main outcome variable. The secondary outcome measure will be the psychophysical cone system recovery after bleaching.

Stem cell transplant

Perhaps one of the most promising avenues of treatment is the recent announcement that FDA approval has been given to Advanced Cell Technology for subretinal injection of human embryonic stem cell-derived RPE(MA09-hRPE) cells for the treatment of Stargardt disease (68). The trial is an open-label, multicenter phase I/II study to determine the safety and tolerability that began in April 2011 and is currently in the recruitment stage. Twelve patients will be divided into 4 cohorts (receiving 50,000-200,000 cells) and assessed over a 12-month period. Inclusion criteria include males or females over the age of 18 years and consent for genotyping of *ABCA4* mutations. Patients will be excluded if there are any other eye diseases present or if individuals are in any way immunocompromised. Outcome measures other than safety include the assessment of successful implantation of the stem cells by ophthalmic investigation.

Viral gene transfer

Oxford BioMedica has been given approval for the testing of StarGen™, the company's lentiviral vector, and is currently recruiting patients in a phase I/II trial in collaboration with Sanofi (69). The trial began in June 2011 and is a multinational, open-label, dose-escalation safety study that will enroll 28 patients to assess safety and tolerability and any delay in retinal degeneration. Patients will be over 18 years of age of either gender, with at least one known *ABCA4* mutation related to Stargardt disease. Exclusion criteria include the existence of other eye diseases or participation in any ongoing trials.

CONCLUSION

The *ABCA4* gene encodes for the ABC transporter known as the RmP, which is found on the rim of the outer segment disc membranes on photoreceptor cells. RmP is a key protein in the retinoid cycle that is essential for recycling chromophores to maintain vision. Mutations in *ABCA4* result in the production of nonfunctional or compromised RmP interfering with the retinoid cycle and resulting in the accumulation of toxic A2E, lipofuscin deposits and degradation of photoreceptor cells, leading to visual impairments. Autosomal recessive Stargardt disease can be the result of a number of mutations in the *ABCA4* gene and is characterized by bilateral vision loss and macular degeneration. There are currently no therapeutic interventions available for the treatment of the disease in humans, although some success has been achieved with various agents in an *ABCA4* knockout mouse model. Such treatments altered the retinoid cycle to prevent the accumulation of A2E and replaced faulty genes by viral vector administration. Advances in genetic screening, such as the ABCA400 microarray chip, have allowed rapid screening of patients with Stargardt disease to identify the causative mutations within the individual and identify novel mutations that may have been overlooked. Genetic screening is essential as, although there have been some attempts at genotype–phenotype severity correlations, there are often no clear matches. In addition, mutations in the *ABCA4* gene are also associated with other retinopathies that have similar phenotypes to Stargardt disease, such as RP, CRD and age-related macular degeneration (AMD).

Promising therapies for the future treatment of Stargardt disease include viral gene therapy, which has been shown to be successful in animal models and in human clinical trials for another congential eye disease, LCA. There is one phase I/II trial under way to assess a lentiviral-mediated replacement of the *ABCA4* gene in 28 Stargardt disease patients. The success of rAAV vector-mediated treatment of LCA encourages the use of virus to treat other eye disease; however, due to the heterogeneity of most eye disorders, this may not be as easy as envisaged. Moreover, there are disadvantages to using viral systems, although the viral vectors themselves are being engineered to overcome problems, such as gene size constraints, random integration effects leading to silencing or mutations, sustainability of transgene expression and immunogenic reactions. In addition to viral vectors, recent approval for stem cell transplant in a small number of patients may prove to be the most promising cure for blindness in general, without the need for genetic testing and eliminating the problems caused by heterogeneity.

Much more needs to be learned about the function, structure and interactions of the RmP protein itself in order to develop more therapeutic options. In addition, the ongoing screening of patients on a global scale will uncover novel and population-specific mutations, as well as possible mutations at other gene loci that may cause Stargardt disease. This is particularly important, as the mutations responsible for Stargardt disease are not fully identified, which may lead to misdiagnosis of the disease based on functional and clinical evaluation alone. Overall treatment strategies for this common juvenile eye disease are in their infancy, but do offer hope for the future.

DISCLOSURES

The author states no conflicts of interest.

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