

Stargardt Disease: Advances and Obstacles

Several treatment strategies are under investigation to assess therapeutic efficacy.

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Stargardt disease, which is the most common type of juvenile onset macular dystrophy, is caused by mutations in the ABCA4 gene.¹ Mutations in both alleles are required for the disease to manifest (autosomal recessive inheritance). Symptom onset typically occurs in the first 2 decades of life, but some patients develop symptoms later.² The hallmark clinical finding of Stargardt disease is the presence of pisciform retinal flecks. The appearance of the macula varies among patients and can include macular flecks, a beaten bronze sheen, macular granularity, areas of retinal pigment epithelium (RPE) atrophy, and a bull's eye lesion.³ Patients typically have a progressive loss of central vision and expansion of central scotoma.

PATHOGENESIS

The ABCA4 gene encodes an ATP-binding cassette transporter found in the photoreceptor disc membrane that couples ATP hydrolysis to the translocation of a visual cycle intermediate (N-retinylidene-phosphatidylethanolamine [N-ret-PE]) from the photoreceptor disc lumen to disc cytoplasm. Reduced function of this protein allows an additional molecule of all-trans-retinal to covalently and irreversibly bind to N-ret-PE to form A2PE, a toxic di-retinal pyridinium compound.⁴

The photoreceptor outer segments containing A2PE are phagocytosed by the RPE as new photoreceptive elements are added at the inner- and outer-segment junction. The phosphatidyl moiety of A2PE is removed by RPE lysosomal enzymes to produce A2E. Because A2E cannot be readily metabolized, it progressively accumulates in RPE cells, leading to lipofuscin deposition, which explains some of the characteristic features of Stargardt disease, including the presence of pisciform flecks, a dark choroid on fluorescein angiography, RPE and photoreceptor atrophy, and delay in dark adaptation.⁴

It is difficult to deduce the pathogenic contributions



Figure 1. Fundus photographs and best corrected visual acuity of patients seen at the University of Michigan, illustrating that the Stargardt disease phenotype is clinically heterogeneous, with notable variation from patient to patient.

of Stargardt disease mutations. Stargardt disease is clinically heterogeneous, with notable variation among patients. A particular ABCA4 genotype determines the severity of the disease, which can include disease phenotypes restricted to the macula, cone-rod dystrophy, and rod-cone dystrophy similar to retinitis pigmentosa. Figure 1 illustrates the variation in phenotypes seen at the Kellogg Eye Center. The ABCA4 gene spans more than 100,000 bases, and several hundred sequence variations have been identified within it.¹ As most individuals with ABCA4-associated retinal disease are compound heterozygotes, deducing the relationship between the ABCA4 genotype and the clinical phenotype becomes problematic.

TREATMENT STRATEGIES UNDER INVESTIGATION

The discovery of the genetic and molecular bases of ABCA4 retinal degenerative disease has led to investigations into possible treatments for this disease. Gene

To date, there is no agreement as to an appropriate outcome measure to evaluate therapeutic efficacy of these medications in human Stargardt disease trials.

therapy offers a promising approach to prevent or slow the onset of ABCA4-related disease. Allocca et al⁵ inserted the large 6.8 kb mouse ABCA4 gene into a chimeric rAAV vector and delivered this to the photoreceptors of ABCA4 knockout mice. Kong et al⁶ delivered the human ABCA4 gene to photoreceptors of an ABCA4 knockout mouse using a lentiviral vector. In both studies, expression of ABCA4 in photoreceptors correlated with a reduction in A2E levels in RPE cells.

The US Food and Drug Administration recently allowed Advanced Cell Technology, Inc. (Marlborough, MA), to initiate a clinical treatment trial of 12 patients with Stargardt disease using retinal cells derived from human embryonic stem cells (hESCs). The phase 1/2 trial will be a prospective, open-label study that is designed to determine the safety and tolerability of the RPE cells following subretinal transplantation to patients with advanced Stargardt disease. Lu et al⁷ demonstrated successful functional rescue using hESC-derived RPE cells in both the RCS rat and Elov14 mouse. In their study, the RPE sustained visual function and photoreceptor integrity in a dose-dependent fashion without untoward pathologic reactions. Near-normal functional measurements were recorded after 60 days survival in the RCS rats.⁷

A less invasive approach is to reduce the level of 11-cis retinal and, consequently, all-trans-retinal in photoreceptors through the application of drugs that inhibit enzymes of the visual cycle.⁸ The retinoid-based inhibitor N-(4-hydroxyphenyl) retinamide (Fenretinide; RT-101, ReVision Therapeutics) is known to reduce serum levels of vitamin A and retinylamine, an inhibitor of isomerase activity in RPE cells. It has been developed and tested in animals and shown to reduce A2E accumulation.⁹

The retina has a high concentration of omega-3 fatty acids, particularly docosahexaenoic acid (DHA). The high concentration of DHA in the photoreceptor cells (50% of the lipids of the external membrane) suggests it plays a major role in the maintenance of the structure of these cells. Animal studies have demonstrated that DHA has a protective role in the retina, preserving mitochondrial activity, increasing RPE acid

lipase activity, and having antioxidative, antiproliferative, and antiapoptotic effects.¹⁰ A small study of 20 patients with Stargardt disease found mild improvement in best corrected visual acuity (BCVA) and improvement on multifocal electroretinogram (mfERG) in four patients after 6 months of DHA supplementation. During this period, no progression was observed in any of the study patients.¹¹

ASSESSMENT OF TREATMENT EFFECT

As we enter an era of therapy initiation for Stargardt disease, important questions still must be answered before moving forward, such as which patients are the best candidates for phase 1 clinical trials, and how do we assess the effects of therapy? A clinical trial involving a retinoid analogue such as Fenretinide appears imminent. To date, there is no agreement as to an appropriate outcome measure to evaluate therapeutic efficacy of these medications in human Stargardt disease trials.

We can determine who the best candidates are for these initial trials if we can predict the clinical course for individual patients. Our experience at the Kellogg Eye Center is that a significant number of patients with Stargardt disease remain stable over many years. Accurate prediction of the pathogenic effects of specific ABCA4 genotypes will be important for the design and execution of clinical treatment trials as well as for meaningful counseling of individual patients. As in Stargardt disease and many other autosomal recessive diseases, however, it is challenging to deduce the relative pathogenic contribution of individual alleles because only a few affected individuals share the same two disease-causing variations.

DIAGNOSTIC EVALUATION

Fundus autofluorescence (FAF) is useful for evaluating the extent of Stargardt disease manifestation in an individual patient. This noninvasive imaging technique enables the visualization of A2E and other bis-retinoid components of lipofuscin in the RPE. FAF capitalizes on a fundamental property of retinal fluorophores in that they emit light in the spectral range of 500 to 700 nm when excited by short-wavelength light (less than 490 nm). The topographic distribution and density of the emitted light define regions where the lipofuscin fluorophores have accumulated above background levels (hyperfluorescence). Regions with fluorescent signal below background levels (hypofluorescence) identify regions where RPE and photoreceptor cells are presumed to have been irretrievably lost. Abnormal patterns of increased fundus fluorescence

that surround atrophic lesions may serve as prognostic markers for the future progression and expansion of the atrophic retinal lesion.¹²

The mfERG evaluates the function of the central retina corresponding to 10° of visual field. In the multifocal recording technique, small areas of the retina are stimulated simultaneously (m sequence), and local contributions to a massed electrical potential are extracted from a continuously recorded ERG. Under photopic conditions, the local waveforms appear biphasic, with negative and positive deflections similar to the a- and b-waves of the full-field ERG. The mfERG is able to detect local retinal abnormalities that would not be detected by conventional full-field ERGs.

For most mfERG amplitude parameters, there exists a test-retest variability rate of 20% to 25% in patients with Stargardt disease, making longitudinal monitoring of these amplitudes not useful. However, the test-retest reliability for the implicit time of the P1 (first positive deflection) in patients with Stargardt disease is much better than that for amplitudes, indicating that changes in timing may be a better and a more sensitive index of serial change.¹³ This hypothesis is consistent with prior research showing that the implicit time of the mfERG—not amplitude—is the more sensitive measure of damage in degenerative diseases involving loss of photoreceptor cells.¹⁴

Evaluation of the photoreceptor layer in the foveal region of patients with Stargardt disease with spectral-domain optical coherence tomography (OCT) has revealed that, in patients with central atrophy, there is a loss of photoreceptors in the foveal region and a reduction in central foveal thickness.¹⁵ Gomes et al¹⁶ elegantly compared the diameter of absent FAF to the extent of the inner- and outer-segment junction loss in the macula. They found that the diameter of absent FAF was smaller than that of the inner- and outer-segment loss. That is, the measurement of the diameter of absent FAF underestimated the extent of the inner- and outer-segment junction loss. However, when the transition zone of abnormal FAF surrounding the central area of absent FAF (ie, the region between absent AF and normal AF) was included, the diameter of abnormal FAF more closely approximated the inner- and outer-segment junction loss measurement.¹⁶ If we assume that inner- and outer-segment junction loss means that the photoreceptors are not functioning, then the finding that the region of inner- and outer-segment loss is larger than the region of absent FAF suggests that photoreceptor outer segment loss may precede RPE loss in Stargardt disease.

CONCLUSION

The discovery of the genetic and molecular bases of ABCA4 retinal degenerative disease has led to investigations into possible treatments for Stargardt disease. Current strategies being investigated include gene therapy, stem-cell therapy, and small-molecule interventions aimed at manipulating the biological effects of ABCA4 mutations. A major obstacle to evaluating the effects of these potential therapies is the lack of a standardized set of outcome measures by which to assess therapeutic efficacy in human clinical trials. Furthermore, no mechanism exists for accurately predicting disease progression, making appropriate selection of patients for inclusion in clinical trials very difficult. ■

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