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Visual Acuity Loss and Associated Risk Factors in the Retrospective Progression of Stargardt Disease Study (ProgStar Report No. 2)

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Purpose: To examine the association between characteristics of Stargardt disease and visual acuity (VA), to estimate the longitudinal rate of VA loss, and to identify risk factors for VA loss.

Design: Retrospective, multicenter cohort study.

Participants: A total of 176 patients (332 eyes) with molecularly and clinically confirmed Stargardt disease enrolled from the United States and Europe.

Methods: Standardized data report forms were used to collect retrospective data on participants' characteristics and best-corrected or presenting VA from medical charts. Linear models with generalized estimating equations were used to estimate the cross-sectional associations, and linear mixed effects models were used to estimate the longitudinal VA loss.

Main Outcome Measures: Yearly change in VA.

Results: The median duration of observation was 3.6 years. At baseline, older age of symptom onset was associated with better VA, and a longer duration of symptoms was associated with worse VA. Longitudinal analysis estimated an average of 0.3 lines loss ($P < 0.0001$) per year overall, but the rate varied according to baseline VA: (1) eyes with baseline VA $\geq$20/25 (N = 53) declined at a rate of approximately 1.0 line per year; (2) eyes with VA between 20/25 and 20/70 (N = 65) declined at a rate of approximately 0.9 lines per year; (3) eyes with VA between 20/70 and 20/200 (N = 163) declined at a rate of 0.2 lines per year; and (4) eyes with VA worse than 20/200 (n = 49) improved at a rate of 0.5 lines per year. Older age of onset was associated with slower VA loss: Patients with onset age >30 years showed 0.4 lines slower change of VA per year ($P = 0.01$) compared with patients with onset age $\leq$14 years.

Conclusions: Given the overall slow rate of VA loss, VA is unlikely to be a sensitive outcome measure for treatment trials of Stargardt disease. However, given the faster decline in younger patients and those with no or mild visual impairment, VA may be a potential outcome measure for trials targeting such subgroups of patients. These observations will need to be assessed in a prospective study bearing in mind the inherent limitations of retrospective datasets. *Ophthalmology 2016;■:1–11 © 2016 by the American Academy of Ophthalmology.*

*Supplemental material is available at www.aaojournal.org.

Stargardt macular dystrophy 1 (STGD1) (Online Mendelian Inheritance in Man: 248200) is the most common macular dystrophy with a prevalence of 10 to 12.5 per 100 000 persons[1] and is inherited as an autosomal recessive trait.[2] It is characterized by the appearance of yellowish-white lesions called "fundus flecks" at the level of the retinal pigment epithelium and by the development of atrophic lesions. Patients with STGD1 experience progressive impairment of visual acuity (VA) that often begins in the first or second decade of life, but some patients may maintain good VA until the fourth or fifth decade of life.[3] Currently, there is no approved treatment for the disease, with ongoing phase I/II clinical trials based on gene, stem cell, and pharmacologic therapy.

There are limited data documenting the rate of change of VA in STGD1. Several studies have reported average VA measured at 2 study visits[4–6]; however, these analyses did not take into consideration the variable length of follow-up of the study participants. Rotenstreich et al[7] estimated the time to reach VA of 20/200 and its association with age among participants with VA of 20/40 or better, or VA between 20/50 and 20/100, at their first study visit.[7] Oh et al[8] compared the time to vision loss of 20/200 VA among different clinical phenotypes. More recently, the

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longitudinal analysis from Testa et al[9] estimated the yearly progression rate of best-corrected VA in patients with STGD1 with an age of onset less than 30 years.

To better understand visual function loss in STGD1 and to help assess the appropriateness of VA as an outcome measure for future treatment trials, we analyzed data from the retrospective multicenter study on "the natural history of the Progression of Atrophy Secondary to Stargardt Disease (ProgStar)." Our specific purposes were to examine the cross-sectional relationship among participant demographic, clinical characteristics, and baseline VA; to estimate the yearly rate of VA loss using the longitudinal data; and to identify participant demographic and clinical characteristics associated with yearly VA change rate. We identified that the rate of VA loss in the entire cohort was too slow to be an effective clinical trial outcome measure. However, a faster decline in younger patients and those with no or mild visual impairment (VI) at baseline suggests that VA may be a potential end point in these patient subgroups and is worthy of assessment in a prospective study bearing in mind the inherent biases of retrospective data.

Methods

Data for this analysis are derived from the retrospective ProgStar study, which has been described in detail by Strauss et al.[10] In brief, from March of 2013 to December of 2014, eligible participants were identified and enrolled through retrospective review of medical charts at 9 participating sites, including 6 sites from the United States and 1 site each from the United Kingdom, France, and Germany. The members of the ProgStar study group are listed in Appendix 1 (available at www.aaojournal.org). Inclusion criteria were as follows[10]: (1) presence of at least 1 well-demarcated area of atrophy with a minimum diameter of 300 μm, with the total area of all atrophic lesions being $\leq$12 mm^2 at the most recent visit; (2) presence of at least 2 likely disease-causing variants in *ABCA4* or 1 likely disease-causing variant associated with at least 1 eye with flecks at the level of the retinal pigment epithelium typical for STGD1; (3) sufficient quality of images or psychophysical tests; (4) age at least 6 years at the most recent visit; (5) follow-up for at least 2 visits over a period of at least 24 months, up to 60 months between single visits, and must have had at least 1 test of the following completed at each visit for the same eye(s): fundus autofluorescence obtained with a Heidelberg Engineering (Heidelberg, Germany) instrument (e.g., HRA2) and/or spectral domain optical coherence tomography obtained with the Heidelberg Spectralis and/or microperimetry (MP) obtained with the Nidek (Tokyo, Japan) MP-1.

Exclusion criteria were (1) presence of ocular disease in either eye that may confound assessment of the retina morphologically and functionally; (2) intraocular surgery in the study eye(s) within 90 days before any eligible visit; (3) current or previous participation in a clinical trial to treat STGD1; and (4) current participation in or participation within the last 6 months in any drug trial.

Before data collection, site investigators and study coordinators received training from the data coordinating center in chart review, reporting of VA, and data entry using the Research Electronic Data Capture system (http://www.project-redcap.org/cite.php). A standardized clinical report form (CRF), designed by the data coordinating center, was used at all sites to record information on VA, results from the biomicroscopy of the anterior segments and dilated fundus examination, and use of vitamin A supplementation at each study visit. Participant's age at enrollment, gender, race, and age of symptom onset were identified from chart review and recorded in a standardized demographic form. For each participant, data of up to 4 visits were collected.

Monocular VA was measured using Snellen or Early Treatment of Diabetic Retinopathy Study charts,[11] and the measurements extracted from chart review were entered into the CRF. A participant may have multiple types of VA captured at a visit, including best or presenting VA with correction (BPC VA), uncorrected (SC = sine correctione [without correction]) VA, and pinhole VA. Up to 2 types of VA were recorded in the CRF for each eye at each visit. Because BPC VA constituted the major type of VA measurement, all downstream analyses used BPC VA.

The retrospective ProgStar study was approved by the Western Institutional Review Board, the local institutional review boards, and the Human Research Protection Office of the U.S. Army Medical Research & Materiel Command. The study was registered at www.clinicaltrials.gov (Identifier NCT01977846). If required by the local institutional review board, participants' consent was obtained before data collection.

Statistical Analysis

Participant demographic and clinical characteristics at the first study visit (baseline visit) were summarized. Baseline data of study eyes were used to explore the cross-sectional association of VA with demographics including age ($\leq$18, >18−50, 50+ years), gender, and race (white vs. nonwhite), and clinical characteristics including age at symptom onset ($\leq$14, 15−20, 21−30, 30+ years) and duration of symptoms (0−2, >2−6, >6−11.5, and >11.5−53 years).

The VA measures were converted to logarithm of the minimum angle of resolution (logMAR) scale, and univariate linear models with generalized estimating equations (GEEs) were used to estimate the unadjusted cross-sectional associations while accounting for between-eye correlation, followed by multivariate linear models with GEE to estimate the adjusted associations adapting for variables associated with VA in univariate analyses with $P < 0.1$. In addition, the variables of baseline age and age of onset and duration were modeled as continuous variables.

Linear mixed effects model (LMM) was used on the longitudinal data to estimate the yearly change rate of VA as described in Appendix 2 (available at www.aaojournal.org). To further identify baseline variables associated with VA change rate, LMMs were used by including each variable and its interaction with time. Baseline variables examined included the aforementioned demographics and clinical characteristics, with baseline VA also categorized on the basis of the World Health Organization's International Classification of Diseases, 10th revision,[10,12] as (1) VA $\geq$20/25 (logMAR $\leq$0.1) (i.e., no VI); (2) worse than 20/25 to 20/70 (logMAR 0.1−0.54) (i.e., mild VI); (3) worse than 20/70 to 20/200 (logMAR 0.54−1.0) (i.e., moderate VI); (4) worse than 20/200 to 20/400 (logMAR 1.0−1.3) (i.e., severe VI); and (5) worse than 20/400 (logMAR >1.3) (i.e., blindness). The univariate association of each variable with VA change rate was first estimated. Because VA progression rate was shown to differ significantly by baseline VA, adjusted associations were estimated using multivariate LMMs including variables that were significantly associated with baseline VA at $P < 0.1$.

All analyses were conducted in SAS 9.3 (SAS Institute Inc, Cary, NC), and 2-sided P values from Wald tests were reported. For the cross-sectional analysis using GEE models, model fit was assessed using aggregated residuals,[13] and for the longitudinal