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

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Meeting presentation: Presented in part at the annual meeting of the Association for Research in Vision and Ophthalmology (ARVO), Denver (CO), May 3-8, 2015

Financial support:
The ProgStar studies are supported by the Foundation Fighting Blindness Clinical Research Institute (FFB CRI) and a grant to FFB CRI by the U.S. Department of Defense USAMRMC TATRC, Fort Meade, Maryland (grant numbers W81-XWH-07-1-0720 and W81XWH-09-2-0189).
Dr. Hendrik Scholl is supported by the Foundation Fighting Blindness Clinical Research Institute (FFB CRI) and a grant to FFB CRI by the U.S. Department of Defense USAMRMC

TATRC, Fort Meade, Maryland (grant numbers W81-XWH-07-1-0720 and W81XWH-09-2-0189); The Shulsky Foundation, New York, NY; Ocular Albinism Research Fund (Clark Enterprises Inc.); Unrestricted grant to the Wilmer Eye Institute from Research to Prevent Blindness; Baylor-Johns Hopkins Center for Mendelian Genetics (National Human Genome Research Institute, NHGRI/NIH). H.P.N.S. is the Dr. Frieda Derdeyn Bambas Professor of Ophthalmology.

Dr. Scholl is a paid consultant of the following entities (not including the National Institutes of Health): Shire; Ocata Therapeutics, Inc.; Guidepoint Global, LLC; Gerson Lehrman Group; DeMatteo Monness Consulting. Dr. Scholl is member of the Scientific Advisory Board of Vision Medicines, Inc. and of the Clinical Advisory Board of Gensight Biologics.

Dr. Scholl is member of the Data Monitoring and Safety Board/Committee of the following entities (not including the National Institutes of Health): Genentech Inc./F. Hoffmann-La Roche Ltd; Genzyme Corp./Sanofi, and ReNeuron Group Plc/Ora Inc.

Dr. Hendrik Scholl serves as a member of the Ophthalmic Devices Panel of the Medical Devices Advisory Committee, Food and Drug Administration (FDA), Silver Spring, Maryland, United States. These arrangements have been reviewed and approved by the Johns Hopkins University in accordance with its conflict of interest policies. Johns Hopkins University and Bayer Pharma AG have an active research collaboration and option agreement.

Dr. Hendrik Scholl is principal investigator of grants at The Johns Hopkins University sponsored by the following entity (not including the National Institutes of Health): QLT, Inc. and NightstaRx Ltd. Grants to investigators at Johns Hopkins University are negotiated and administered by the institution (such as the School of Medicine) which receives the grants, typically through the Office of Research and Administration. Individual investigators who participate in the sponsored project(s) are not directly compensated by the sponsor but may receive salary or other support from the institution to support their effort on the project(s). Dr. Rupert Strauss is supported by the Austrian Science Fund (FWF; Project number: J 3383-B23) and the Foundation Fighting Blindness Clinical Research Institute (USA). Dr. Artur V. Cideciyan was partially supported by NIH (EY013203) and the Foundation Fighting Blindness (USA). Dr. Michel Michaelides is supported by grants from the National Institute for Health Research Biomedical Research Centre at Moorfields Eye Hospital National Health Service Foundation Trust and UCL Institute of Ophthalmology, Fight For Sight (UK), The Macular Society (UK), Moorfields Eye Hospital Special Trustees, Moorfields Eye Charity, the Foundation Fighting Blindness (USA), and Retinitis Pigmentosa Fighting Blindness. Dr. Michaelides is a recipient of an FFB Career Development Award.

Neither the sponsor nor funding organziations had a role in the design or conduct of this research.

Financial Disclosure:

Dr. Scholl is a paid consultant of the following entities (not including the National Institutes of Health): Shire; Ocata Therapeutics, Inc.; Guidepoint Global, LLC; Gerson Lehrman Group; DeMatteo Monness Consulting. Dr. Scholl is member of the Scientific Advisory Board of Vision Medicines, Inc. and of the Clinical Advisory Board of Gensight Biologics.

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Dr. José-Alain Sahel: Grants from LABEX LIFESENSES (ANR-10-LABX-65), Banque publique d'Investissement, Foundation Fighting Blindness, during the conduct of the study; other from Pixium Vision, other from GenSight Biologics, other from Sanofi-Fovea, other from Genesignal, outside the submitted work; in addition, Dr. Sahel is founder of the companies Fovea pharmaceuticals, Ophtimalia, Streetlab, Pixium Vision, GenSight Biologics, ChronoCam, Chronolife and has a patent Methods of increasing RDCVF 1 or RDCVF 2 polypeptides in retinal cells US 8394756 B2 pending, a patent Polynucleotides encoding rod-derived cone viability factor (rdcvf) and methods of using the same. US8071745 B2 pending, and a patent Methods of treating retinitis pigmentosa using nucleic acids encoding RDCVF 1 or RDCVF 2, US 8957043 B2 pending.

Neither the sponsor nor funding organziations had a role in the design or conduct of this research.

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Supplemental materials: This article contains additional online-only material. The following should appear online-only: Supplemental text (Statistical anaylsis details), supplemental table 1, supplemental figure 1 and ProgStar study team list (available at http://www.aaojournal.org)

Acknowledgments: The ProgStar Study is supported by the Foundation Fighting Blindness Clinical Research Institute (FFB CRI) and a grant to FFB CRI by the U.S. Department of Defense USAMRMC TATRC, Fort Meade, Maryland (grant numbers W81-XWH-07-1-0720 and W81XWH-09-2-0189)

Abstract

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

Design: Retrospective, multi-center cohort study.

Participants: 176 patients (332 eyes) with molecularly and clinically confirmed Stargardt disease enrolled from the USA 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 visual acuity.

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 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: (i) eyes with baseline VA better than or equal to 20/25 (N=53) declined at a rate of ~1.0 line per year; (ii) eyes with VA between 20/25 and 20/70 (N=65) declined at a rate of ~0.9 lines per year; (iii) eyes with VA between 20/70 and 20/200 (N=163) declined at a rate of 0.2 lines per year; and (iv) 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 to patients with onset ≤14 years.

Conclusion: 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.

Introduction

Stargardt macular dystrophy (STGD1; OMIM: 248200) is the most common macular dystrophy with a prevalence of 10-12.5 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 (RPE) and by the development of atrophic lesions. Patients with STGD1 experience progressive impairment of visual acuity which 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 on-going phase I/II clinical trials based on gene, stem cell, and pharmacological therapy.

There are limited data documenting the rate of change of visual acuity (VA) in STGD1. Several studies have reported average VA measured at two study visits,[4-6] these analyses however did not take into consideration the variable length of follow-up of the study participants. Rotenstreich et al. 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 20/50-20/100, at their first study visit.[7] Oh et. al. compared the time to vision loss of 20/200 VA among different clinical phenotypes.[8] More recently, the longitudinal analysis from Testa et al, [9] estimated the yearly progression rate of best corrected VA in STGD1 patients with an age of onset younger 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 multi-center 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 between 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 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.

Participants and Methods

Data for this analysis are derived from the retrospective ProgStar study which has been described in detail elsewhere.[10] In brief, from March of 2013 to December of 2014, eligible participants were identified and enrolled through retrospective review of medical charts at nine participating sites, including six sites from the United States, and one site each from the United Kingdom, France and Germany. Inclusion criteria were:[10] (1) presence of at least one well-demarcated area of atrophy with a minimum diameter of 300 µm, with the total area of all atrophic lesions being less than or equal to 12 mm^2 at the most recent visit; (2) presence of at least two likely disease-causing variants in *ABCA4*, or one likely disease-causing variant associated with at least one eye with flecks at the level of the RPE typical for STGD1; (3) sufficient quality of images and/or psychophysical tests; (4) age at least six years at the most recent visit; (5) follow-up for at least two visits over a period of at least 24 months, up to 60 months between single visits, and must have had at least one test of the following completed at each visit for the same eye(s): FAF obtained with a Heidelberg Engineering®

instrument (e.g. HRA2) and/or SD-OCT obtained with the Heidelberg® Spectralis and/or MP obtained with the Nidek® 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 prior to 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 six months in, any drug trial.

Prior to data collection, site investigators and study coordinators received training from the data coordinating center (DCC) in chart review, reporting of VA, and in data entry using the REDCap (Research Electronic Data Capture) system (http://www.project-redcap.org/cite.php). A standardized clinical report form (CRF), designed by the DCC, 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 four visits were collected.

Monocular VA was measured using either Snellen or "Early Treatment of Diabetic Retinopathy Study (ETDRS)" 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), and pinhole VA. Up to two types of VA were recorded in the CRF for each eye at each visit. As 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 (WIRB), the local institutional review boards (IRB), and the Human Research Protection Office (HRPO) of the U.S. Army Medical Research & Materiel Command (USAMRMC). The study was registered at www.clinicaltrials.gov (Identifier NCT01977846). If required by the local IRB, participants' consent was obtained prior to 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 (<=18, >18-50, 50+ years), gender, and race (white vs. non-white), and clinical characteristics including age at symptom onset (≤14, 15-20, 21-30, 30+) and duration of symptoms (0-2, >2-6, >6-11.5 and >11.5-53 years).

VA measures were converted to LogMAR scale, and univariate linear models with generalized estimating equations (GEE) 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 adjusting for variables associated with VA in univariate analyses with $p<0.1$. Additionally, the variables of baseline age, and age of onset and duration, were also 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 the supplemental material (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 WHO's International Classification of Diseases (ICD)-10,[10, 12] as (i) VA better than or equal to 20/25 (LogMAR≤ 0.1) (i.e. no visual impairment [VI]); (ii) worse than 20/25 to 20/70 (LogMAR 0.1-0.54) (i.e. mild VI); (iii) worse than 20/70 to 20/200 (LogMAR 0.54-1.0) (i.e. moderate VI); (iv) worse than 20/200 to 20/400 (LogMAR 1.0-1.3) (i.e. severe VI); and (v) worse than 20/400 (LogMAR>1.3) (i.e. blindness). The univariate association of each variable with VA change rate was first estimated. As VA progression rate was shown to differ significantly by baseline VA, adjusted associations were also 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, and two-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 analysis using LMMs, model fit was assessed using plots of scaled residuals.

Results

Among the 251 participants enrolled in the retrospective ProgStar study, 176 participants with 332 study eyes had BPC VA measurements available for at least two visits and thereby constituted the study sample (Figure 1). There were 165 participants (94%) with at least two likely disease-causing variants in *ABCA4* (23/165 had three, and 4/165 had four disease-causing mutations). The remaining 11 participants had one likely disease-causing variant detected. The median duration of observation was 3.6 years (interquartile range [IQR] 2.7-

5.1 years), and each participant contributed data for 2 to 4 visits (Figure 1).

Table 1 summarizes the baseline demographic and clinical characteristics of these participants and the study eyes. There were 109 females (61.9%), and the majority of participants were white (71.6%). At baseline, the median age was 29.5 (IQR 20-42) years. Among participants whose age of symptom onset was available (N=140), median age of onset was 20 (IQR 14-30) years. The median duration from the age of onset to the baseline visit was 6 (IQR 2-11.5) years. The median Snellen VA at baseline was 20/115 and LogMAR was 0.76 (IQR 0.40-1.00), ranging from -0.10 to 1.40. Based on the categorized BPC VA, 53 eyes (16.1%) had no impairment, 65 eyes (19.7%) had mild impairment, 163 (49.4%) eyes had moderate impairment, and 49 eyes (14.8%) had severe impairment or were blind (Table 1 and Figure 2). Details of the excluded participants and comparisons with the included are provided in supplemental table 1 (available at www.aaojournal.org).

Cross-sectional associations of participant characteristics with baseline visual acuity

Table 2 presents the baseline VA in subgroups determined by participant characteristics and the difference of VA between subgroups. When age was modeled as a continuous variable, worsening VA was significantly associated with older age (adjusted VA LogMAR difference with every 5 years older in age: 0.04, 95%CI [0.01, 0.07], p=0.006); suggesting that the observation of worse VA associated with younger age in univariate analysis was mainly explained by earlier symptom onset in younger participants.

Figures 3A and 3B show the distribution of baseline VA by quartiles of age at onset and duration of symptoms respectively. Later symptom onset was associated with better VA in

both univariate and multivariate analyses (Table 2): compared to patients with onset age ≤14 years and after adjusting for duration since symptom onset, both patients with onset age >30 years had ~2.3 lines better VA (LogMAR adjusted difference -0.23, 95%CI -0.39, -0.06, p=0.007), and patients with onset age of 21-30 years had 1.1 lines better VA (LogMAR difference -0.11, 95%CI -0.25, 0.03, p=0.12). Longer duration since symptom onset was associated with worse VA: after adjusting for age of onset, patients who had symptoms for 6-11.5 years and patients with symptoms for over 11.5 years both had 1.8 lines worse VA (LogMAR difference 0.18, 95%CI 0.03, 0.33, p=0.002, and difference 0.18, 95%CI 0.02, 0.33, p=0.03, respectively) compared to patients with recent onset (duration ≤2years) (Table 2).

Longitudinal analysis of yearly change in visual acuity and associated risk factors

The overall yearly rate of VA change was ~0.3 lines worsening per year; LogMAR change of 0.03, 95%CI (0.026, 0.043; p<0.0001) per year. Table 3 shows the yearly VA change rate by subgroups and the differences between subgroups. The baseline VA level was significantly associated with yearly rate of VA change: (i) VA of eyes with no impairment worsened at a rate of ~1.0 line (LogMAR rate 0.096, 95%CI [0.080, 0.112]) per year; (ii) eyes with mild impairment worsened at a rate of ~0.9 lines (LogMAR rate 0.094, 95%CI [0.080, 0.107]) per year; and (iii) VA of eyes with moderate impairment worsened at a rate of 0.2 lines (LogMAR rate 0.019, 95%CI [0.008, 0.029]) per year. For eyes with severe impairment or blindness at baseline, their VA improved at an annual rate of 0.5 lines (LogMAR rate -0.047, 95%CI [-0.064, -0.031]) per year. Figure 4 shows the estimated average rates of change in these subgroups (Spaghetti plots are provided as Supplemental Figure 1, available at http://www.aaojournal.org). When comparing the annual VA change between different baseline VA groups, there were significant differences in both univariate and multivariate

analyses: the adjusted LogMAR difference in yearly VA change rate was -0.08 (95%CI [-0.11,-0.06], p<.0001) between eyes with moderate impairment and eyes with no impairment, and was -0.16 (95%CI [-0.19,-0.12], p<.0001) between eyes with severe impairment / blindness and eyes with no impairment. However, the VA loss rate was not significantly different between eyes with mild and no impairment.

Age of symptom onset was not associated with VA change in univariate analysis (Table 3). However, in the multivariate analysis that adjusted for baseline VA and symptom duration, compared to patients with age of onset ≤14 years, participants with symptom onset age >30 years had a significant 0.4 lines slower change of VA per year (LogMAR difference -0.04, 95%CI [-0.07, -0.01] per year, p=0.01). When age of onset was modeled as a continuous variable, every 5 years later in symptom onset was also associated with a significantly slower VA loss (i.e. difference in LogMAR VA change rate=-0.006, 95%CI [-0.01, -0.002] per year, p=0.005).

Longer symptom duration was significantly associated with slower VA worsening in univariate analysis (Table 3). After adjusting for baseline VA and age of onset, duration was no longer associated with VA change (Table 3).

Discussion

We have characterized the demographic and clinical characteristics and VA of a cohort of STGD1 patients enrolled from the US and Europe in the ProgStar retrospective study. Half of the participants reported onset of symptoms at age of 30 years or older, i.e. adult-onset STGD1.

In our study, over 35% of the study eyes had no or mild visual impairment at baseline, with the average BPC VA being better than that of participants enrolled in prior studies.[7, 9, 14] Nevertheless, as reported in these studies, our cross-sectional analysis also showed that a younger age of symptom onset was associated with worse VA. Additionally, as reported in Testa et al., we found that a longer duration of onset was associated with worse VA.[9] Older age groups had better VA, which was also observed in Rotenstreich et al.[7] Considering younger participants have earlier symptom onset, after adjusting for age of onset, our multivariate analysis showed that older age was associated with worse VA, which is compatible with our finding that longer duration since symptom onset was associated with poorer VA.

Our longitudinal analysis estimated a 0.3 line loss of BPC VA per year overall. A similar rate of VA change can be inferred from the survival analysis by Rotenstreich et al.[7] that reported a median time of 22 years from VA of 20/40 or better to reach VA of 20/200 or worse (i.e. ~7 lines loss in 22 years). For the group of participants with symptom onset age <30 years, we estimated the rate of VA loss to be ~ 0. 4 lines per year. The same rate was also reported in the recent study by Testa et al.[9] that focused on patients with age of onset <30 years.

We found the better the baseline VA, the faster decline over time: VA of eyes starting with no or mild impairment declined one line per year, and VA of eyes with moderate impairment declined at a significantly slower rate. Counterintuitively, eyes that already had VA worse than 20/200 at baseline showed a small but statistically significant improvement in VA over time. This may relate to the poor inherent accuracy of Snellen charts in measuring low

vision[15] Other reasons include a lack of standardization in illumination, correction for refractive errors, and contrast in the tests that generated our VA data. However, there is also a biological plausibility for observing improvement in VA, as a result of change of the fixation location of the preferred retinal locus (PRL). [16-19] This phenomenon of eccentric fixation and its better use by the patient over time is currently an area of interest for on-going research, especially in the context with reading rehabilitation.[20] In the case of STGD1, it is also possible for the PRL to move from a superior retinal locus to the peripapillary region as the central scotoma expands with disease progression.[21] Another possible explanation might be the statistical phenomenon of "regression towards the mean" that describes the observation of outliers being more likely to retest closer to their mean values. [22]

In keeping with previous findings, after controlling for baseline VA level, younger age of symptom onset was associated with faster loss of VA.[7]

Our data may have implications on selection of appropriate outcome measures for future STGD1 clinical trials. VA is an important visual function outcome directly related to participants daily activities,[23] and is the most common primary outcome measure for efficacy studies of retinal diseases.[24] Changes of at least 15 ETDRS letters are considered clinically significant.[24] Our study showed that the overall rate of VA decline was slow, thus VA is not sensitive enough to show a clinically relevant change during a treatment trial. However, we found that for the subgroup of participants with no or mild visual impairment (35% of the cohort), the VA loss rate was approximately 1 line per year; suggesting that in a trial with three to four years of follow-up a clinically significant change may be anticipated in such participants. Hence a therapy shown to be efficacious in slowing VA deterioration in this population may potentially benefit a significant number of patients with STGD1. One

limitation of this finding is that it only alludes to patients enrolled into this retrospective study who by definition have shown some degree of progression in the past..

Our study herein has further limitations. First, data were collected through retrospective review of medical records, thus VA was not measured in a standardized way over time within the same clinic and across the different study sites. Second, our longitudinal analysis used repeatedly measured best-corrected or presenting VA. As chart review often could not differentiate between best corrected VA and presenting VA, it was possible that the change observed in a participant was due to change in refraction rather than due to disease progression. Third, BPC VA was not consistently available in all participants, and only 70% had multiple visits with BPC VA data available. Comparison between participants included in and those excluded from this analysis showed comparable distributions of most participant characteristics, but there was difference in race composition and vitamin A use status (see supplemental table 1, available at www.aaojournal.org). However, such differences are unlikely to have biased the results as race and vitamin A use was not found to be associated with VA change. Lastly, information on age of symptom onset could not be retrieved for 18% of participants. However, comparisons between participants with known and those with unknown age of onset did not show significant differences in their demographics and baseline VA distributions (data not shown), thus the results regarding age of onset using available data should not have been biased.

Strengths of our study include that we assessed the associations of VA with a range of variables on demographics and clinical characteristics, some of which have not been explored previously. Additionally, our study participants were enrolled from multiple sites in

the US and Europe, increasing the generalizability of our findings. Lastly, despite being a retrospective study, data abstraction and entry was conducted in a standardized way by trained study coordinators, and the data coordinating center's monitoring visits at the participating sites ensured the data quality.

In conclusion, 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 at baseline, suggests that VA may be a potential end-point in these patient subgroups, and is worthy of assessment in the prospective study bearing in mind the inherent biases of retrospective data. It is also important to explore other potentially more sensitive outcome measures based on imaging modalities or psychophysical tests, such as spectral-domain optical coherence tomography[25] or microperimetry.[26]

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Figure legends:

Figure 1: Flowchart of the study participants

Figure 2: Illustrative examples of eyes with no impairment (A: best-corrected or presenting visual acuity (BCP-VA 20/16), mild impairment (B: BCP-VA 20/32), moderate impairment (C: BCP-VA 20/120), and severe impairment or blindness (D: 20/400) according to WHO-criteria.

Figure 3A: Best-corrected or presenting visual acuity at baseline by quartiles of age of symptom onset.

Figure 3B: Best-corrected or presenting visual acuity at baseline by quartiles of duration of symptoms.

Figure 4. Estimated average rate of change of visual acuity and its 95% confidence interval, by baseline visual acuity. (VI: visual impairment)