Visual Acuity Change over 12 Months in the Prospective Progression of Stargardt Disease (ProgStar) Study (ProgStar Report No 6)

Xiangrong Kong, PhD1,2,3
Rupert W Strauss MD4,5,6,7
Artur V Cideciyan, PhD8
Michel Michaelides, MD5,6,
José-Alain Sahel, MD9
Beatriz Munoz, MS3
Mohamed Ahmed, MD3
Ann M Ervin, PhD2,3
Sheila K West, PhD3
Janet K Cheetham, PharmD10
Hendrik P N Scholl, MD, MA3,7.

on behalf of the ProgStar study group.

1. School of Public Health and Health Sciences, University of Massachusetts-Amherst, Amherst, Massachusetts.
2. Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland.
3. Wilmer Eye Institute, Johns Hopkins University, Baltimore, Maryland.
4. Department of Ophthalmology, Johannes Kepler University Linz, Linz (Austria)
5. Moorfields Eye Hospital, London, UK
6. UCL Institute of Ophthalmology, University College London, London, UK,
7. Department of Ophthalmology, University of Basel, Basel, Switzerland
8. Scheie Eye Institute, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.
9. Brain Institute, University of Pittsburgh, Pittsburgh, Maryland.
10. Foundation Fighting Blindness.

Corresponding author:
Hendrik P.N. Scholl, MD, MA
Professor and Chairman
Department of Ophthalmology, University of Basel
Universitätsspital Basel
Mittlere Strasse 91, CH-4031 Basel
Switzerland
Telephone (Office): +41 61 265 86 51
Office Fax: +41 61 265 86 52
E-mail: Hendrik.Scholl@usb.ch

Keywords: Stargardt disease, visual acuity, longitudinal study, multi-center prospective study
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); Hendrik Scholl is supported by 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; Identification number: 1U54HG006542-01). Rupert W. Strauss is supported by the Austrian Science Fund (FWF; Project number: J 3383-B23) and the Foundation Fighting Blindness Clinical Research Institute. Sheila West is supported by El Maghraby professorship. Xiangrong Kong is supported by the National Institutes of Health through grant K25AI114461. 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.

Financial disclosures: The author(s) have made the following disclosure(s):
Dr. Hendrik Scholl is a paid consultant of the following entities: Astellas Institute for Regenerative Medicine (AIRM); Boehringer Ingelheim Pharma GmbH & Co. KG; Daiichi Sankyo, Inc.; Gerson Lehrman Group; Guidepoint; and Shire. Dr. Scholl is member of the Scientific Advisory Board of Gensight Biologics; Vision Medicines, Inc.; and Intellia Therapeutics, Inc. Dr. Scholl is member of the Data Monitoring and Safety Board/Committee of the following entities: Genentech Inc./F. Hoffmann-La Roche Ltd; Genzyme Corp./Sanofi, and ReNeuron Group Plc/Ora Inc. 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. These arrangements have also been reviewed and approved by the University of Basel (Universitätsspital Basel, USB) in accordance with its conflict of interest policies. Dr. Hendrik Scholl is principal investigator of grants at the USB sponsored by the following entity: Acucela Inc.; NightstaRx Ltd.; QLT, Inc. Grants at USB are negotiated and administered by the institution (USB) which receives them on its proper accounts. 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).

Janet K Cheetham is a contractor for Foundation Fighting Blindness.

Running head: Visual Acuity Change over One Year in Stargardt Disease
Abstract

Purpose: To estimate the yearly rate of change of best corrected visual acuity (BCVA) and the risk of loss ≥1 lines over one year, and to identify risk factors for BCVA loss in patients with Stargardt disease (STGD1).

Design: Multi-center prospective cohort study.

Participants: 259 patients (489 study eyes) with molecularly confirmed STGD1 enrolled at nine centers in the USA and Europe.

Methods: Participants were followed every six months, and data at baseline, six and 12-month visits were analyzed. BCVA was measured using the ETDRS protocol. Standardized reporting forms were used to collect participants’ characteristics and clinical observations. Linear mixed effects models were used to estimate the rate of BCVA loss. Linear models with generalized estimating equations were used to identify risk factors for BCVA loss ≥1 lines over one year.

Main Outcome Measures: BCVA change over one year.

Results: Cross-sectional analysis at baseline showed that earlier symptom onset and longer duration since onset was associated with worse BCVA. Longitudinal analysis showed no overall significant change of BCVA within 12 months, but the rate of BCVA change was significantly different by baseline BCVA (p<.001). BCVA of eyes with baseline BCVA better than or equal to 20/25 declined at a rate of 2.8 ETDRS letters per year (p=.10); eyes with baseline BCVA between 20/25 and 20/70 declined at a rate of 2.3 ETDRS letters per year (p=.002); eyes with baseline BCVA between 20/70 and 20/200 declined at a rate of 0.8 ETDRS letters per year (p=.08); and eyes with baseline BCVA worse than 20/200 showed a significant improvement of 2.3 ETDRS letters per year (p<.001). Overall, 12.9% eyes lost ≥1 lines, and the risk of such BCVA loss was different by baseline BCVA level (p=.016).

Smoking and vitamin A use was not significantly associated with baseline BCVA, nor with rate of BCVA loss over one year.

Conclusions: BCVA change in STGD1 over a 12 month period was small, but the change varied depending on baseline BCVA. Given the slow change during one year, BCVA is unlikely to be a sensitive outcome measure for STGD1 treatment trials with one year duration.
Introduction

Stargardt disease (STGD1; OMIM: 248200) is the most common juvenile macular dystrophy with a prevalence of 10-12.5 per 100,000 persons\(^1\), and is inherited as an autosomal-recessive trait associated with mutations in the \(ABCA4\) gene\(^2\). 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 macular atrophic lesions. Patients with STGD1 are known to experience impairment of visual acuity progressively and at various ages. Currently there is no approved treatment for the disease. Understanding the natural history of STGD1 and determining the rate of disease progression using multiple functional or structural methods is of great interest for determining appropriate outcome measures in clinical trials of potential treatments\(^3^–^8\).

Prior studies reporting the rate of change of visual acuity (VA) in STGD1\(^9^–^15\) were all based on retrospective review of medical records. In this study, we used data from the prospective international multi-center study of the natural history of the Progression of Atrophy Secondary to Stargardt Disease (ProgStar), to assess the rate of VA change and identify participants’ demographic, clinical and behavioral characteristics associated with VA loss over one year.

Participants and Methods

Data for this analysis are from the prospective ProgStar study which was approved by the Western Institutional Review Board, the local institutional review boards, and the Human Research Protection Office of the United States Army Medical Research and Materiel Command. The study was registered at www.clinicaltrials.gov (identifier, NCT01977846).
Details of the prospective ProgStar study have been described in detail elsewhere. In brief, from September of 2014 to March 2015, eligible STGD1 patients were enrolled into the ProgStar study at nine participating sites from the USA, United Kingdom, France and Germany. Eligibility of participants included: age ≥ 6 years; willingness to undergo ocular examinations every 6 months for up to 24 months; having two pathogenic mutations in the ABCA4 gene, or, having one pathogenic mutation in the ABCA4 gene together with a typical Stargardt phenotype such as flecks at the level of the RPE (further inclusion and exclusion criteria are described in ProgStar Report #1). The particularly relevant inclusion criteria for analysis herein are that study eyes had to have a best corrected visual acuity (BCVA) ≥ 20 ETDRS letters (i.e. 20/400 Snellen equivalent or better); have at least one well-demarcated area of atrophy on fundus autofluorescence imaging with a diameter ≥ 300 microns and the sum of all lesions ≤ 12 mm²; and have clear ocular media and adequate pupillary dilation per site investigators’ assessment. All participants gave written informed consent prior to enrollment in the study.

Participants were followed every six months. At each visit, participants underwent detailed ophthalmic examinations; refraction and best corrected visual acuity (BCVA) was obtained following the ETDRS (Early Treatment of Diabetic Retinopathy Study) protocol at all sites. For data collection, a standardized demographic form and clinical report form (CRF) was used at all sites to record age, sex, race, age of symptom onset and clinical information on BCVA, results from the biomicroscopy of the anterior segments and dilated fundus examination, and behavioral characteristics (use of vitamin supplementation, smoking history) at each study visit. All data were double entered by study coordinators into the REDCap (Research Electronic Data Capture) system and transferred to Data Coordinating Center for data quality control and management.
**Statistical analysis**

Data from the baseline, 6 month and 12 month visits were used in this analysis. Participant demographic and clinical characteristics at baseline visit were first summarized. Baseline BCVA was also categorized in referencing the World Health Organization's International Classification of Diseases, 10th revision and as (1) VA $\geq$20/25 (i.e logarithm of the minimum angle of resolution [logMAR] $\leq$0.1 or ETDRS letters $\geq$80) (i.e., no visual impairment [VI]); (2) worse than 20/25 to 20/70 (logMAR 0.1 – 0.54, i.e. ETDRS letters 58-80) (i.e., mild VI); (3) worse than 20/70 to 20/200 (logMAR 0.54 – 1.0, i.e. ETDRS letters 35-58) (i.e., moderate VI); (4) worse than 20/200 to 20/400 (logMAR 1.0–1.3, i.e. ETDRS letters 20-35) (i.e., severe VI); and (5) worse than 20/400 (logMAR >1.3, i.e. ETDRS letters <20) (i.e., blindness).

For all analyses, ETDRS letter scores were converted to the logMAR scale. Baseline data of participants and study eyes were used to explore the cross-sectional association of BCVA with participant demographic and behavioral characteristics including age (categorized as $\leq$18, >18-50, 50+ years), sex, race (white vs. non-white), smoking status and vitamin A use, and with clinical characteristics including age at symptom onset (categorized into $\leq$14, 15-20, 21-30, 30+ years upon considering data distribution and prior publications) and duration since symptom onset at baseline (categorized as 0-2, >2-6, >6-11.5 and >11.5-53 years upon considering data distribution and prior publications). Age, age of symptom onset, and duration since onset were also modeled as continuous variables in separate models. Eye-level clinical characteristics included observations from biomicroscopy of the anterior segments and dilated fundus examination. 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 associations adjusting for variables associated with BCVA in univariate analyses with p<0.1.

To estimate the longitudinal change of BCVA, a linear mixed effects model (LMM) was used to estimate the yearly change rate: the mean of participants’ BCVA was modeled as a linear function of time since baseline visit, with the intercept and slope parameters assumed to be normally distributed random effects. Additionally, BCVA change from baseline to year 1 was further dichotomized as whether or not there was a loss of one or more lines (i.e. loss of 5 or more ETDRS letters), and the proportion of such loss was estimated. Univariate log-binomial models with GEE were used to estimate the risk ratios of baseline variables (for the behavioral variable of vitamin A use, the report at year 1 visit was considered) in association with the risk of one or more lines of BCVA loss during the year. Multivariate log-binomial models with GEE were used to estimate the adjusted risk ratios for variables associated with risk of BCVA loss of one or more lines in univariate analysis with p≤0.10 and for variables associated with baseline BCVA with p≤0.10.

All analyses were conducted in SAS 9.3, and two-sided p-values from Wald-tests were reported. For analyses using GEE models, model fit was assessed using aggregated residuals, and for the longitudinal analysis using LMMs, model fit was inspected visually and based on plots of scaled residuals.

**Results**

There were 259 participants with 489 study eyes enrolled in the prospective ProgStar study. Follow-up rate was 92% at Month 6 and 93% at Month 12 (Figure 1). Table 1 summarizes characteristics of participants and their study eyes. The median age at baseline was 31
(interquartile range [IQR] 21-44) years, and 54% (N=141) were female. Most participants
were white (N=222, 86%), 7.7% were black (N=20), and 4% were Asian (N=10). The median
age of self-reported age of symptom onset was 19 (IQR 12-29) years, and the median duration
since symptom onset at the baseline visit was 9 (IQR 5-15) years. Vitamin A use was reported
by 37 (14%) participants (a summary of dosage and frequency is presented in Supplemental
Table 1). Current smoking was reported in 29 (11%) participants, and 35 (14%) were former
smokers.

At baseline, the median BCVA of the study eyes was 41 (IQR 35-52, range 20-88) ETDRS
letters (i.e. median LogMAR=0.88), and 21% eyes had no or mild visual impairment (VI),
55% were moderately impaired, and 25% were severely impaired. Lens change or
abnormalities of the anterior segment were rare. Clinical exam data showed that 9.5% eyes
had nerve pallor, 93% eyes had RPE atrophy, and 67% eyes had RPE pigmentary abnormality
(i.e. hypo- and/or hyper-pigmentations at the level of the RPE). Most eyes (92%) had flecks
present within the arcades, and 46% eyes had flecks outside the arcades (Table 1).

Cross-sectional associations of participant characteristics with baseline BCVA

Table 2 presents the baseline BCVA in subgroups by participant characteristics, and the
difference of BCVA between subgroups. Compared to participants with age ≤18 years, the
BCVA of those aged 18-50 years and those aged >50 years was better by 4.5 and 10.5
ETDRS letters (i.e ~0.09 and 0.21 LogMAR difference) respectively. Such differences
however were not significant in adjusted analysis. When age was modeled as a continuous
variable, older age was associated with better BCVA in univariate analysis (p=.007). But in
multivariate analysis controlling for age of symptom onset, older age was associated with
worse BCVA (adjusted p=0.02). There was no significant difference in BCVA by sex or by
race. Older age of symptom onset was significantly associated with better BCVA (p<.001):
for example, compared to participants with onset age ≤14 years, the BCVA of those with
onset age>30 years was 11.5 ETDRS letters better (i.e. adjusted logMAR difference -0.23).
Such an association was also significant when age of onset was modeled as a continuous
variable (adjusted p<.001). Longer duration of symptoms was significantly associated with
worse BCVA (p<.001): e.g. compared to participants with symptoms ≤2 years, the BCVA of
those with symptoms for >11.5 years was 13 ETDRS letters worse (i.e. adjusted LogMAR
difference 0.26). The association was also significant when duration was modeled as a
continuous variable (adjusted p<0.001). For behavioral variables, vitamin A use was not
associated with BCVA (p=0.34). The BCVA of current smokers was 5 ETDRS letters (i.e
logMAR difference 0.1) worse than never smokers, but this difference was not statistically
significant (p=0.26)

For eye-level clinical characteristics, having nerve pallor and flecks within the arcades was
not associated with worse BCVA. BCVA of eyes with RPE pigmented abnormalities was 5
ETDRS letters (i.e. LogMAR difference 0.1, adjusted p=.003) worse than eyes without this
abnormality; BCVA of eyes with flecks outside the arcades was 6 ETDRS letters (i.e.
LogMAR difference 0.12, adjusted p<.001) worse than eyes without flecks outside the
arcades. Associations of BCVA with other fundus examination variables were not assessed
due to the small sample sizes in certain subgroups.

**Longitudinal analysis of the yearly change of BCVA**

Overall there was no statistically or clinically significant change of mean BCVA over 12
months (Figure 2): the rate of change was -0.36 ETDRS letters (0.007 LogMAR)/year (95%
CI: (-1.18, 0.46) ETDRS letters; p=0.38). However, the change was statistically significantly
different by baseline BCVA level (p<.001) (Table 3 and Figure 3): eyes with no VI at
baseline (N=17) had a non-significant BCVA change of -2.8 ETDRS letters (0.056
LogMAR/year (95% CI: -6.01, 0.49 ETDRS letters); eyes with mild VI (N=83) showed a significant BCVA change of -2.3 ETDRS letters (0.047 LogMAR)/year (95% CI: -3.86, -0.83 ETDRS letters); eyes with moderate VI (N=267) showed a non-significant BCVA change of -0.8 ETDRS letters (0.015 LogMAR)/year (95% CI: -1.59, 0.09 ETDRS letters); and eyes with severe VI (N=122) had a statistically significant gain of 2.3 ETDRS letters (-0.045 LogMAR)/year (95% CI: 1.00, 3.52 ETDRS letters). These change rates (Table 3) suggested a dose-response relationship between baseline BCVA level and the rate of BCVA change. We therefore modeled baseline BCVA as continuous in the linear mixed effects model which confirmed that the better the baseline BCVA, the larger the BCVA decline over one year (p<.001).

Longitudinal analysis of the factors associated with risk of loss of one or more lines from baseline to 12 month visit

Among the 456 study eyes observed at baseline and month 12, the proportion losing one or more lines was 12.9% (59/456). The risk of such loss was significantly different by baseline BCVA level (adjusted p=0.02): it was 11.8%, 25%, 12.7% and 5.5%, respectively, in eyes without VI, with mild, moderate, or severe VI at baseline (Table 4). The risk of BCVA loss was also significantly different by age of symptom onset (adjusted p=0.03): in particular, compared to participants with symptom onset age ≤14 years, the risk of BCVA loss was 66% lower in participants with symptom onset age between 15 and 20 years (adjusted risk ratio [RR]=0.34, 95%CI: 0.14-0.82). BCVA loss of one or more lines at one year was not associated with duration of symptoms at baseline, vitamin A use (at year 1), smoking status, and having nerve pallor, RPE pigmentary abnormalities, or flecks within the arcades. Having flecks outside arcades was associated with lower risk of BCVA loss in univariate analysis, but the association was not significant in adjusted analysis.
Discussion

We reported the demographic and clinical characteristics and change of BCVA during one year for STGD1 patients enrolled in the multi-center ProgStar prospective study. Our longitudinal analysis found that the rate of BCVA change was significantly different by baseline BCVA level, but overall there was no significant change over one year of follow-up (estimated rate=0.007 LogMAR/year). This finding differs from our ProgStar retrospective cohort where BCVA declined at a small but statistically significant rate of 0.03 LogMAR/year. The difference between these two findings may be due in part to the differences in the length of follow-up between our two cohorts: the current analysis on the prospective cohort focused on data during one year of follow-up, whereas the retrospective study had variable but longer follow-up, with a median of 3.6 years. The difference in the two findings may also be due to the fact that the retrospective cohort had better baseline VA than the prospective cohort, especially considering that both studies found that the rate of VA change was significantly different by baseline VA, with better baseline VA associated with a greater yearly rate of decline. These findings suggest that VA loss in STGD1 is not a linear process, where loss is greatest at an early stage when a degree of foveal vision is still present despite accompanying parafoveal degeneration\textsuperscript{21-23}, then BCVA loss slows after foveal vision is lost and fixation becomes eccentric.

For eyes without any visual impairment at baseline, there was a loss of VA over one year but it was not statistically significant. This may be due to the small sample size in the group. The estimated rates of change in eyes without impairment (0.056 LogMAR/year) and eyes with mild impairment (0.047 LogMAR/year) were smaller than the estimates in the ProgStar retrospective cohort (0.096 and 0.094 LogMAR/year, respectively)\textsuperscript{20}. This difference again is most likely due to the difference in length of follow-up and due to the non-linear process of BCVA loss in STGD1. The rates of change in eyes with moderate or severe impairment at...
baseline were similar to those estimated in the retrospective study (~0.02 loss and 0.05 gain LogMAR/year, respectively), suggesting that VA change may be relatively constant at these stages.

In particular, similar to our findings in the ProgStar retrospective study and in our analysis with ProgStar participants with recent onset of symptoms\textsuperscript{11-20}, we found that eyes with severe impairment (VA worse than 20/200) at baseline showed a small (~0.5 lines/year) but statistically significant improvement in VA over time. The improvement may be due to regression to the mean, where patients with poor vision tested poorly at baseline, and tested slightly better at subsequent visits reflecting normal variation. Additionally, VA is known to vary to a greater extent in patients with more severe visual impairment. However, it is also plausible for VA to improve as a result of change of the location of the preferred retinal locus (PRL), as has been observed in participants with geographic atrophy and inherited macular dystrophies\textsuperscript{24-27}. Also, fixation stability may improve over time\textsuperscript{28}. In the case of STGD1, it is possible for the PRL to move from a superior retinal locus to the parapapillary region as the central scotoma expands with disease progression.\textsuperscript{29} This hypothesis will be tested in conjunction with the microperimetry data from the ProgStar prospective study.

In clinical trials, loss of 15 ETDRS letters (equivalent to three Snellen lines) or more are considered clinically significant\textsuperscript{30}. However, such loss was rare in our cohort during the 12 months: 12 eyes lost three or more lines from baseline to year 1, i.e. a risk of 2.6%.

Clinically, loss of one or more lines may be concerning for patients and their physicians, and such loss was not rare in our cohort, occurring in 59 (12.9%) eyes. Consistent with the findings regarding the yearly rates of BCVA change, baseline BCVA level was the strongest predictor for BCVA loss of one or more lines, with eyes with severe impairment at baseline having the lowest risk of such loss. For the variable of age of symptom onset, results from the
multivariable model were similar to those from our retrospective ProgStar study: older age of symptom onset was associated with lower risk of BCVA loss of one or more lines during the year. However, in this prospective cohort, the risk of BCVA loss of one or more lines in the oldest onset age group of (>30 years) was not significantly lower than the youngest onset age group (≤14 years). This discrepancy could be due to the difference in outcomes in the two studies: the current analysis considered the dichotomized outcome of BCVA loss of one more lines during one year (which was of clinical relevance), whereas the retrospective study was assessing the yearly change rate which used the actual BCVA values (rather than dichotomized) and which was based on data of variable follow-up lengths among participants.

Similar to the retrospective study, duration of symptoms, presence of RPE pigmentary changes, flecks within the arcades and flecks outside the arcades were not associated with the one-year risk of BCVA loss of one or more lines. We are not aware of prior studies that assessed the effects of smoking and vitamin A use in STGD1 patients. Our longitudinal analysis did not find a higher risk of loss of BCVA during the year associated with smoking and vitamin A use. Since few people used vitamin A (14%) or smoked (11%) in this cohort, it is possible that the study was underpowered to detect small effects.

Examination of the brand names of the supplement showed that the supplementation was often through multivitamin use. The cross-section analysis at baseline showed that baseline BCVA was not significantly different by smoking or vitamin A use. Other results from the baseline cross-sectional analysis are similar to prior published studies and to our earlier findings in the retrospective ProgStar cohort\textsuperscript{11, 13, 14, 31}: a younger age of symptom onset and a longer duration since symptom onset was associated with worse VA; and older age was associated with worse VA, which is compatible with the finding that the longer the duration since symptom onset the poorer is VA.
The ProgStar prospective study is a large-scale and the first study of STGD1 with prospective data collection under a pre-designed standardized study protocol involving multiple sites from both the US and Europe, greatly increasing generalizability. One limitation of the study herein is that we inferred that the VA loss trajectory was non-linear in STGD1. However, this inference was not based on directly observing the VA trajectory over many years from the same individuals; rather, it was based on data from multiple participants with different current VA levels and who showed different rates of VA change during one year. Nonetheless, considering the small rate of change per year, it is reasonable to use linear models to describe the BCVA change during one year.

STGD1 patients may present with distinct phenotypes, such as macular atrophy surrounded by flecks, patchy/mottled foveal changes, bull’s eye maculopathy, foveal sparing, and others\(^8\). These phenotypes may be associated with different genetic variants and may have different VA progression patterns\(^33\)\(^-\)\(^35\), for example, the foveal sparing phenotype is known to be on the milder end of the spectrum of the disease, and VA of patients with such phenotype may be maintained longer\(^34\),\(^36\),\(^37\). However, since our clinical data did not record specific phenotype information, we were unable to assess VA change associated with each phenotype in our cohort. Nevertheless, utilizing information from fundus autofluorescence image grading, we will evaluate VA in patients with no foveal involvement at baseline in a subsequent ProgStar report. Another limitation of this report is that at baseline, the study only tested participants BCVA once using ETDRS protocol, and thus did not control for any potential learning effect associated with the ETDRS chart. However, at least 56% of participants had received ETDRS VA testing during their routine clinical visits before this study enrollment, and thus learning effect should be minimal in these participants.
BCVA is an important visual function outcome directly related to participants daily activities, and is the most common outcome measure for efficacy studies of retinal diseases. However, our data suggest that the change of BCVA in STGD1 was small and not statistically significant during one year. Since it will be difficult for trials aiming to prevent or slow VA loss to show a difference over a one year period, VA is not sensitive enough to serve as a primary outcome. Nevertheless, we found that the change of BCVA depended on the starting level of BCVA, and faster progression was observed in patients with baseline BCVA better than 20/70. This information may inform planning of future trials that target on patients who are most likely to show VA loss in 12 months.

In summary, we found that there was no significant change of BCVA during one year, but baseline BCVA level was associated with different rates of subsequent BCVA change. We found that patients with poor vision at baseline showed a small, but statistically significant gain in visual acuity. Smoking and vitamin A use was not associated with worse BCVA at baseline, nor associated with higher risk of BCVA loss during the one year follow-up. BCVA appears to be relatively insensitive to detect changes in a reasonable time period. Therefore, it is important to explore other potentially more sensitive outcome measures derived from functional or morphological analysis, such as microperimetry, optical coherence tomography, adaptive optics, or fundus autofluorescence imaging.

List of Figure Legends:

Figure 1. Flowchart of enrollment and follow-up of the prospective ProgStar study.

Figure 2. Spaghetti plot showing visual acuity of the participants during their one year follow-up. Each gray line is data for one eye. The blue line represents the estimated average VA change: -0.36, 95% CI: (-1.18, 0.46) letters (i.e. 0.007 LogMAR) per year.

Figure 3. Spaghetti plots showing visual acuity change during one year follow-up by baseline VA level. Each gray line is data for one eye. The blue line represents the estimated average VA change. (VI: visual impairment.)
3A. Visual acuity change in eyes with no visual impairment (i.e. Snellen VA 20/25 or better) at baseline. Rate of change: -2.77 (95% CI -6.02, 0.49) letters/year (i.e. 0.056 LogMAR/year).

3B. Visual acuity change in eyes with mild visual impairment (Snellen VA between 20/25 and 20/70) at baseline. Rate of change -2.35 (95% CI -3.96, -0.83) letters/year (i.e. 0.047 LogMAR/year).

3C. Visual acuity change in eyes with moderate visual impairment (Snellen VA between 20/70 and 20/200) at baseline. Rate of change -0.75, (95% CI -1.59, 0.09) letters/year (i.e. 0.015 LogMAR/year).

3D. Visual acuity change in eyes with severe visual impairment (Snellen VA worse than 20/200) at baseline. Rate of change 2.26 (95% CI 1.00, 3.52) (i.e. -0.045 LogMAR/year).
References:


