Interocular Difference and Duration for Doubling of the Minimal Angle of Visual Resolution in Patients with Stargardt Disease

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PURPOSE. To determine the extent of interocular difference in visual acuity (VA) and the time to at least double the minimal angle of resolution (MAR) in a cohort of patients with Stargardt disease.

METHODS. One hundred fifty patients with Stargardt disease who were examined at least four times over a minimum period of 3 years were identified and their VA and age at each visit recorded. The maximum interocular difference of VA was determined by whether the MAR between the two eyes differed by less than a factor of 2 or by a factor of 2 or greater. Differences in maximum VA between the two eyes were also examined according to a Bland-Altman–type approach. One hundred thirty-one eyes from 76 patients were subjected to survival analysis to determine whether the time to at least double the MAR was dependent on age at baseline or starting VA.

RESULTS. Of the 150 patients, 48% had interocular MAR that differed maximally by a factor of less than 2. Thirty-five percent showed a maximum interocular difference in their Snellen VA of less than one line. The Bland-Altman–type analysis showed that maximum interocular acuity difference was dependent on the mean acuity of the two eyes. The hazard for at least doubling the MAR was related to baseline vision and patient age.

CONCLUSIONS. This information has clinical significance for patient counseling and for monitoring possible benefits and patient selection in future treatment trials. (Invest Ophthalmol Vis Sci. 2009;50:3574–3577) DOI:10.1167/iovs.08-2775

S targardt disease is the most common form of juvenile-onset macular dystrophy. It is predominantly an autosomal recessive disease caused by a mutation in the \textit{ABCA4} gene. It is characterized by a loss of central vision and fundus changes that include the presence of yellowish-white fundus flecks and often an atrophic-appearing macular lesion that results in a central or a perifoveal scotoma.

Visual acuity (VA) in Stargardt disease was studied by, among several other investigators, Klien and Krill, Fishman et al., Aaberg, Stone et al., and Oh et al. Most agree that a level of 20/200 to 20/400 in VA is often ultimately reached. It was found that the probability of maintaining a VA better than 20/40 decreases with age and that once VA drops to 20/40 or less, it often decreases more rapidly and stabilizes at, most frequently, 20/200. However, it was found that the younger the patients at the initial visit, the more rapidly they will reach 20/200 vision or worse. Rotenstreich et al. reported that the median number of years it took for the VA to decrease from 20/40 or better at baseline to 20/200 was dependent on patient age at the initial visit. In those who were first seen at age 20 or younger, the median time to reach a VA level of 20/200 or worse was 7 years. In contrast, it took 22 and 29 years for those who were initially seen at ages 21 to 40 and 41 to 60, respectively.

To our knowledge, the interocular difference of VA in patients with Stargardt disease has not been reported previously except in a publication by Aaberg, who found 26% (15 of 56) of patients had a difference in VA between fellow eyes of two or more lines on a Snellen distance acuity chart on initial presentation. As the patients were monitored over 3 or more years, VA became more symmetrical between the two eyes.

It will be important to determine the rate of VA loss and the interocular difference in VA to design future treatment trials in this disease. These data may also be of value in counseling patients on the natural history of VA loss. Therefore, in this report, we determined the extent of interocular difference in VA between eyes in patients with Stargardt disease. Additionally, we analyzed factors associated with at least a doubling in the minimal angle of resolution (MAR) in a cohort of patients with Stargardt disease.

METHODS

We reviewed the medical records of all patients with Stargardt disease seen and diagnosed by one of the authors (GAF). From 518 charts, we ascertained patients who had had at least four visits with full eye examinations over a minimum period of 3 years. We excluded all those who had corneal or lens opacities, vitreous hemorrhage, diabetic retinopathy, uveitis, glaucomatous optic nerve changes, or any other ocular or systemic disease that could have caused VA changes. No patients with autosomal dominant Stargardt disease were included.

The diagnosis of Stargardt disease was based on the clinical findings of an atrophic-appearing macular lesion surrounded by a ring of a garland of yellow-white, round, or fishtail-shaped flecks within the posterior pole. Patients had various degrees of decreased central vision and a central scotoma with a relatively normal peripheral visual field. Some of these patients underwent electroretinogram (ERG) testing to determine the extent of their functional impairment. A number of patients had a dark choroid on fluorescein angiography, and several had a positive family history of Stargardt disease to confirm the diagnosis.

One hundred fifty patients with Stargardt disease, between 4 and 60 years of age at their initial visit, were included in this study. For each patient, we recorded monocular best-corrected Snellen VA and age at each visit, number of visits, and total number of years the patient was
followed up. We calculated the MAR and the log value (logMAR) for every VA recorded for each patient by the conventional procedure of dividing the denominator by the numerator of the Snellen acuity value. We then calculated the maximum and minimum interocular differences for the logMAR values by subtracting these values between the two eyes. Differences in VA between the two eyes were also examined using a Bland-Altman–type approach. First, the absolute value of the interocular logMAR acuity difference was determined for each patient. These values were plotted as a function of the mean logMAR acuity of the two eyes for each patient.

Additionally, of the 150 patients, we found 76 patients whom we had monitored for years and on whom we could determine a baseline visit when they initially reached a certain level of VA, within an average of 1 year, from the previous visit (range, 1–18 months). In 40 of the 76 patients, MAR had at least doubled in at least one eye. We used a survival analysis, which adjusted results for the inherent clustering of patients, MAR had at least doubled in at least one eye. We used a survival analysis, which adjusted results for the inherent clustering of patients, and we found 76 patients whom we had initially seen in their third or fourth decade (46%), and 69 patients were initially seen in their second decade (41%), 69 patients were initially seen in their fifth or sixth decade (13%). The number of visits for this project was conducted in the Department of Ophthalmology at the University of Illinois at Chicago; it was approved by an institutional review board and was performed in accordance with tenets of the Declaration of Helsinki.

**RESULTS**

The average age of patients at presentation was 25 years (range, 4–60 years). There were 92 females (61%) and 58 males (39%). Among these, there were 108 Caucasians (72%), 30 African Americans (20%), 8 Hispanics (5%), and 4 Asians (3%). Sixty-one patients were initially seen in their first or second decade (41%), 69 patients were initially seen in their third or fourth decade (46%), and 20 patients were initially seen in their fifth or sixth decade (13%). The number of visits for all patients ranged between 4 and 21 (average, 7.1 visits), and the number of years of follow-up ranged from 3 to 42 years (average, 14.8 years). The range of the VA for the 150 patients using the MAR was 0.75 to 20 minutes of arc (average, 8.5 ± 6.6), which corresponds to 20/15 to 20/400 on a Snellen acuity chart.

We found that 53 of our 150 patients (35%) had less than one line maximum interocular difference on a distance Snellen acuity chart. In 72 of our 150 patients (48%), the maximum interocular difference between their MAR differed by a factor of less than 2 (logMAR < 0.3). In the remaining 78 patients, it differed by a factor of 2 or more. A factor of 2 would be apparent as a difference of between 20/20 and 20/40, 20/40 and 20/80, or 20/200 and 20/400 on a Snellen acuity chart. Table 1 provides summary information of the ages at the maximum interocular difference, the number of years of follow-up, and the number of visits for patients with a maximum interocular difference of less than a factor of 2 and those with a factor of 2 or more. Student’s two-sample t-test was used to compare the means of these variables. No statistical difference was detected in the two groups between the mean initial age (P = 0.41), the mean age at maximum interocular difference (P = 0.94), or the mean number of years of follow-up (P = 0.49). The mean number of visits was statistically significantly different between the two groups (P = 0.003). However, the actual mean difference was only 1.6 years.

We analyzed our VA data for the maximum interocular difference by a Bland-Altman–type plot, as shown in Figure 1. The absolute value of the interocular logMAR acuity difference is plotted as a function of mean interocular logMAR acuity. For reference, equivalent Snellen acuity values are given on the upper x-axis. Each open circle represents a patient, and the symbols were jittered slightly along the x-axis to avoid overlap (Fig. 1). Data points for patients with the same acuity in each eye, or zero interocular acuity difference, fall on the x-axis. The negatively sloped parallel lines passing through the data points show how interocular acuity differences could vary across different levels of acuity. The lines intersect the x-axis in increments of Snellen acuity (e.g., 20/400, 20/200, 20/100). The extent of the line indicates the maximum possible interocular acuity difference for a fixed acuity value in one eye. For

### Table 1. Patients with Maximum Interocular Difference Less Than a Factor of 2 and Equal to or Greater Than a Factor of 2

<table>
<thead>
<tr>
<th>Interocular Difference</th>
<th>No. Patients</th>
<th>Age at Baseline (y)</th>
<th>No. Years Follow-up</th>
<th>No. Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than factor of 2</td>
<td>72</td>
<td>Min: 6 Max: 60 Mean: 26.1 SD: 13.7</td>
<td>Min: 3 Max: 42 Mean: 14.3 SD: 8.1</td>
<td>Min: 4 Max: 16 Mean: 6.3 SD: 2.7</td>
</tr>
<tr>
<td>Factor of 2 or greater</td>
<td>78</td>
<td>Min: 4 Max: 59 Mean: 24.4 SD: 12.0</td>
<td>Min: 3 Max: 40 Mean: 15.2 SD: 8.8</td>
<td>Min: 4 Max: 21 Mean: 7.9 SD: 3.8</td>
</tr>
</tbody>
</table>

![Figure 1](image-url)
example, the right-most line represents all possible combinations of acuities for both eyes of patients in whom one or both eyes had acuities of 20/400. The intersection of this line and the x-axis represents patients with acuities of 20/400 in each eye who, thus, have no difference in interocular acuity. Moving upward along this line, increasingly smaller values of logMAR acuity are found in the better eye. The intersection of this line and the positively sloped line indicates the maximum possible interocular difference for a patient with 20/400 acuity in the worse eye and 20/15 acuity in the better eye. The positively sloped line represents acuity values of approximately 1.0 logMAR (20/15) in the better eyes, a value that was not obtained from any patient in the sample. Thus, the triangular space defines all possible interocular acuity differences for all possible mean interocular acuity values, as measured with the Snellen chart.

This figure shows that the interocular acuity difference was dependent on the mean acuity of the two eyes. Specifically, for patients with a mean acuity better than approximately 0.3 logMAR (20/40 Snellen) or a mean acuity worse than approximately 1.0 logMAR (20/200 Snellen), the interocular acuity difference was always equal to a factor of 2 or less, as indicated by the horizontal dashed line. The data for these patients fall in the shaded boxes in Figure 1. However, for patients with a mean interocular acuity between approximately 0.3 and 1.0 logMAR, a wide range of interocular acuity differences was observed. Across this range of mean acuity values, some patients had the same acuity in each eye, whereas the eyes of other patients differed by more than 1 log unit.

Each of 145 of the 150 patients had at least one visit during which VA was the same in both eyes; for the other five patients, the minimum interocular difference was less than one line.

In the second part of this project, we analyzed the data for 131 eyes from 76 patients. We could demonstrate when each patient reached a VA that could be considered a starting point to determine the effect of baseline VA or age on the hazard for at least doubling the MAR. In 40 of the 76 patients, this event occurred in at least one eye. In 13 of those 40 patients, the MAR angle in at least one eye doubled more than once from baseline. (Second and third doublings were not used in the present analysis.)

Analysis of all 131 eyes eligible for at least doubling of the MAR was performed with the use of survival analysis (available with PROC PHREG, SAS version 9.1.3; SAS Institute, Cary, NC), which accounts for the inherent clustering of eyes within a subject; 68 eyes at least doubled. Univariate models used either the (natural) log of the starting MAR or the age at the start of the observation in the eligible time period. A hazard ratio of 1 indicated no change between younger or older patients or between those with higher or lower levels of starting MAR values. The hazard ratio for at least doubling the MAR was 0.831 ($P = 0.0002$) for any doubling of the starting MAR and 0.864 ($P = 0.025$) for any 5-year increase in starting age. That is, the hazard for at least doubling the MAR decreases with increasing age. For example, with a 5-year increase in age, the hazard of at least doubling the MAR is reduced by a factor of 0.864. Additionally, the hazard for at least doubling the MAR becomes smaller as vision worsens. If the starting (baseline) MAR doubles (i.e., worsening of VA), the hazard of eventually doubling the MAR is reduced by a factor of 0.831. When both variables were included in a multivariate model, the corresponding hazard ratios were 0.730 ($P < 0.0001$) for any doubling of the starting MAR and 0.739 ($P = 0.0001$) for a 5-year difference in starting age.

**DISCUSSION**

In studying the maximum interocular difference in VA based on a difference by a factor of less than 2 or a factor of 2 or greater in the MAR, we found the extent of interocular difference to be independent of the patient’s age at the initial visit or at the visit with the maximum interocular difference. In addition, it was independent of the number of years of follow-up. We expressed maximum interocular difference in reference to the logMAR because this measure is less dependent on the baseline level of VA, and a factor of 2 computes to a difference of 0.3 log units, which is a three-line difference on an ETDRS chart, independent of the baseline level of VA.

The decrease in the interocular acuity difference for patients with high mean acuity values is largely a result of range restriction. For example, if the mean interocular acuity is approximately 1.18 logMAR (equivalent to 20/300), then the difference between the eyes must be 0.3 logMAR because of the increments of the Snellen chart (i.e., 20/200 in one eye and 20/400 in the other). Similarly, for patients with 20/40 acuity or better in at least one eye, the relatively minimal differences in acuity (a factor of 2 or less) between the two eyes is primarily attributed to a floor effect. For example, if VA in the worse eye is 20/40, then VA in the better eye is limited to values of 20/30, 20/25, 20/20, and 20/15. Consequently, only a value of 20/15 in the better eye would yield an interocular acuity difference greater than a factor of 2. No patients in the present sample had a VA value better than 20/20.

Our data show that at least one-third of our cohort of patients with Stargardt disease had less than one line of maximum interocular difference; hence, VA in the eyes of these patients remained symmetrical over at least four visits. However, because we only studied VA at the visit that showed the maximum interocular difference, we could have underestimated the number of patients with less than one line difference between eyes. We chose to express an analysis of the maximum interocular difference because this measure would more directly provide insight into the cohort of patients with Stargardt disease who might not be qualified to participate in treatment trials that use monocular therapy and VA as outcome measures.

We used a Snellen acuity chart to test the VA of most of our patients as part of their clinical management. However, if VA had been determined with the Early Treatment Diabetic Retinopathy Study (ETDRS) charts introduced by Ferris et al. in 1982, the analysis would have been facilitated because these charts have a geometric progression of lines that is lacking in a Snellen chart. An ETDRS chart was not used primarily because none was available at the time VA was initially measured in a number of patients or because of its subsequent lack of application. Thus, we evaluated our data in an alternative manner using the MAR and its log equivalent as a criterion to assess VA.

We found that the hazard for at least an eventual doubling of the MAR was related to the starting VA and age of the patients. This finding is consistent with a previous report that showed loss of VA in patients with Stargardt disease was dependent on the initial age of the patient. This finding was similar to the observation of Sunness et al. who described the VA loss in 148 patients with geographic atrophy associated with age-related macular degeneration. They found that patients whose VA was better than 20/50 were at greater risk to lose three lines on an ETDRS chart than those with worse VA.

Oh et al. reported that the VA loss in patients with Stargardt disease is dependent on the extent of fundus flecks in the posterior pole, whereas those with midperipheral flecks were less likely to maintain 20/200 or better VA compared with those whose disease was confined to the macula. In our retro-
spective study, we examined the maximum interocular difference and the factors associated with at least doubling of the MAR without considering the variability in fundus findings as a factor.

Our findings have clinical significance for providing additional understanding of the factors related to VA loss in patients with Stargardt disease and further significance for patient selection in future treatment trials.

References