Association Between Visual Function Response and Reduction of Inflammation in Noninfectious Uveitis of the Posterior Segment

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PURPOSE. To examine the association between visual function response (VFR) and inflammation reduction in active noninfectious uveitis of the posterior segment (NIU-PS).

METHODS. Phase 3 SAKURA Study 1 randomized 347 subjects in a double-masked fashion to receive injections of intravitreal sirolimus 44 µg (n = 117); 440 µg (n = 114); or 880 µg (n = 116) every other month. Vitreous haze (VH) response, a measure of inflammation reduction, was defined as a VH score of 0 or 0.5+ at month 5 based on the modified Standardized Uveitis Nomenclature Scale. Visual function was assessed with best-corrected visual acuity (BCVA) and the National Eye Institute (NEI) Visual Function Questionnaire-25 (VFQ-25). In this post-hoc analysis, principal component analysis was used to reduce the information in the multidimensional visual function outcome to a restricted number of independently relevant VFR measures. Minimal clinically important differences (MCID) for the VFQ-25–derived components were based on the standard error of measurements. Overall VFR was defined as either a BCVA improvement of ≥2 lines, or an improvement exceeding the MCID in the VFQ-25 based visual function measures.

RESULTS. The VFQ-25 composite score (VFQCS) and mental health subscale score (VFQMHS) were retained as relevant VFRs, with MCIDs of 4.3 and 11.7 points, respectively. A vitreous haze response was significantly associated with each VFR measure: VFQCS (odds ratio [OR] = 2.23; P = 0.0004); VFQMHS (OR = 2.84; P = 0.0001); BCVA (OR = 2.60; P = 0.0009), and overall VFR (OR = 2.65; P < 0.0001).

CONCLUSIONS. Inflammation reduction to a VH score of 0 or 0.5+ was significantly associated with improved visual function. Achieving a VH response of 0 or 0.5+ is a patient-relevant outcome.

Keywords: minimal clinically important difference, non-infectious uveitis, patient reported outcomes, posterior segment, principal components analysis, VFQ-25, visual acuity, visual function response

Uveitis is a potentially blinding inflammatory ocular condition that predominantly affects young adults in their active years of life.1-4 Chronic uveitis with longstanding ocular inflammation can cause complications with secondary visual impairment including cystoid macular edema, glaucoma and cataract.5-9 In addition to vision loss, patients with non-infectious uveitis (NIU) report markedly decreased vision-and health-related quality of life (QoL).10-15 A comprehensive assessment of visual functioning is therefore paramount in studies of NIU; but the best method to quantify this outcome is not well-defined.14,15 Although distance visual acuity (VA) is the standard measure of visual function in most ophthalmologic studies, it is an imperfect indicator of day-to-day visual functioning, as it fails to capture the full impact of ophthalmic disease on a patient’s life.16,17 Best-corrected VA (BCVA) does not assess other patient-related factors such as general health, mood, and compliance.18,19 Also, BCVA is considered a poor marker of drug efficacy in inflammatory eye diseases as the impact of uveitis on VA depends on both the disease activity as well as the damage caused by the disease.19 Since NIU is a heterogeneous collection of uveitic conditions characterized by intraocular inflammation and presents with a wide range of clinical manifestations, it is clear that no single measure can comprehensively capture the impact of disease or treatment benefit.17,20 To complement clinical parameters such as vitreous haze (VH) and BCVA, patient reported outcome
(PRO) measures are increasingly used to represent the impact of NIU disease or benefit of treatment experienced by the patient.13,16,21–23 As a consequence, several outcomes are now collected to assess the full impact of new treatments. These measures are often related to each other to some degree, making interpretation challenging. However, robust exploratory methods exist to organize and summarize multiple interrelated variables to reveal new meaningful information.24

We present a new measure for assessing visual functioning i.e., Visual Function Response (VFR), which combines BCVA and PRO measures, and investigate the clinical relevance of this combined endpoint. Using a post hoc analysis of data obtained from the SAKURA Study 1,25 a phase III clinical trial in subjects with NIU of the posterior segment (PS) of the eye, we first define a restricted set of clinically meaningful VFR components, and secondly describe the associations between different definitions of ocular inflammation and the newly constructed VFR measures.

METHODS

SAKURA Trial Participants

This study of visual function outcomes is based on the SAKURA Trial, which has been presented elsewhere.25 The SAKURA Study 1, a phase 3, randomized, multicenter, double-masked, multinational trial (ClinicalTrials.gov number, NCT01358266) was conducted to evaluate the safety and efficacy of intravitreal (IVT) injections of three doses of sirolimus for the treatment of chronic NIU-PS of the eye. Participants were randomized 1:1:1 to receive IVT sirolimus 440 µg, 880 µg, or an active control dose of 44 µg every alternate month for 5 months. A total of 347 participants with active posterior, intermediate or panuveitis, and decreased BCVA attributable to uveitis were randomized at 103 centers in 15 countries. The SAKURA trial was conducted in accordance with the tenets of the Declaration of Helsinki and informed consent was obtained for all randomized participants. The primary endpoint was defined as having a VH score of 0 at month 5 using the Standardized Uveitis Nomenclature (SUN) photographic scale. Additional predetermined secondary endpoints assessed at month 5 included a VH response of 0 or 0.5, VH response of 0 or 2 units, use of rescue therapy, and change from baseline in BCVA or in the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) composite score. Rescue therapy was considered any treatment with a therapeutic effect on NIU in the PS, other than IVT sirolimus.25

Measures of Visual Function

At enrollment in the SAKURA Study 1, the visual function (VF) outcomes were measured using BCVA (based on the Early Treatment of Diabetic Retinopathy Study (ETDRS) protocol), and vision-related function using the NEI VFQ-25.26,27 The NEI VFQ-25 is a survey used across a wide range of eye diseases to assess how ocular conditions and their therapy affect a patient’s daily-to-day functioning and well-being.15,28–30 The VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs or subscales, plus an additional single-item general health-rating question. An overall VFQ-25 composite score (VFQCS) is calculated as the unweighted average from the vision-targeted scores, excluding the general health item.27 Scores for each subscale and the composite score range from 0 (worst vision functioning) to 100 (best vision functioning or minimal subjective impairment). The VFQ was self-administered in the participant’s native language. Across all non-US sites, the VFQ version including 25 items was used. Whereas US participants used the expanded 39-item questionnaire, we only analyzed those questions included in the VFQ-25.31

Statistical Analyses

Clinical and VFQ-25 Database. All analyses were performed using the intent-to-treat principle (including all randomized participants). Missing data were imputed using the last observation carried forward (LOCF) method. The composite and subscale VFQ-25 scores were computed as per the VFQ-25 scoring algorithm of Mangione et al.27

Identifying VFR Measures Through Principal Components. The VFQ-25 is a PRO measure comprising multiple items that assess various facets of ophthalmologic disease.27 If all items of a PRO instrument are well correlated and can be summarized in a single composite score, the instrument is said to be unidimensional, meaning it measures a single latent trait or common underlying concept.24–32 A principal component analysis (PCA) is an established approach to empirically test the unidimensionality of a PRO and was applied to examine the unidimensionality of the VFQ-25 in the SAKURA NIU population. A PCA works by reducing the multidimensionality of a large number of interrelated scores, while retaining as much as possible the variation present in the dataset. The outcome of a PCA is a new set of variables, the principal components (PCs), that are linear combinations of the original responses, constructed in such a way that the first PC captures as much variation as possible of the complete set of responses, whereas the second PC is independent of the first one and captures as much as possible of the remaining variation and so forth.33 If the first PC captures over 60% of the variability, the PRO dataset is said to be unidimensional and well captured by the first PC.34–35 If the first PC captures a smaller proportion of the variability, more than one PC is required to represent the dataset. In this analysis phase, the multidimensional visual function outcome is reduced to a restricted number of relevant VFR measures that capture as much of the variation as possible.

Defining a VFR. For each of the VFR measures identified from the PCA, the minimal clinically important difference (MCID) is determined. The MCID is the smallest change or difference in an outcome measure that is perceived as beneficial and that would lead to a change in the patient’s medical management.30 For our analysis, a distribution-based approach, the Standard Error of Measurement (SEM) of the VFQ-25 baseline values, was used to establish the threshold for a meaningful improvement from baseline to month 5 in the VFQ-25 scores.37 The SEM-based MCID was estimated as the standard deviation of the measure multiplied by the square root of one minus the reliability of the measure. Cronbach’s α (a measure of how closely the items are related in the specific multi-item domain) was used as the measure of reliability.38,39 For measures of VFR with a well-established clinical criterion of response (e.g., BCVA), the existing threshold of an improvement of ≥2 lines of letters was used to distinguish response from nonresponse.13,40 An overall VFR based on these three individual measures was also generated. Participants who required rescue therapy were systematically categorized as VFR nonresponders.

Measuring the Associations Between VFR and VH. Associations between the different definitions of ocular inflammation and the binary measures of VFR (responder versus nonresponder) were estimated through logistic regression, incorporating the treatment factor (dose of sirolimus) as a fixed effect. The definitions of VH used in this post hoc analysis were consistent with the primary endpoint of the SAKURA Trial (a VH score of 0 at month 5) and with the key secondary VH endpoints (i.e., a VH score of 0 or 0.5+ at month 5; a VH
score of 0 or a decrease of at least 2 units from baseline in VH score at month 5). Analyses were carried out using statistical software (SAS version 6.3; SAS Institute, Cary, NC, USA) and a significance level of 0.05 was considered significant.

RESULTS

Clinical and VFQ-25 Database
The characteristics of SAKURA participants have been published elsewhere. Briefly, the participants were predominantly white (47.3%) and female (59.9%), with a mean age of 46.5 years (±14.5). A majority (68%) of participants had intermediate or posterior uveitis while 66.6% had bilateral uveitis, and 77.8% had no systemic disease associated with their uveitis diagnosis. The median (range) time from initial uveitis diagnosis to enrollment was 26.2 (0.1–411.7) months. The mean visual acuity in the study eye was 65.3 (±15.9) ETDRS letters (20/50 Snellen equivalent). The mean VFQCS score at baseline was 65.8 (±19.3) points, and mean subscale scores ranged from 54.6 (vision-specific mental health) to 85.2 (color vision; Fig. 1).

Identifying VFR Measures Through Principal Components
The output of the PCA showed that the first PC (PC1) captured a substantial but insufficient proportion (50.9%) of the variation to consider the VFQ-25 dataset unidimensional. Principal components 2 and 3 explained an additional 6.8% and 5.6% of the variation, respectively (Supplementary Fig. S1). The PC1 correlated highly with the VFQCS (ρ = 0.99), while its correlation with BCVA was low (ρ = 0.34; Supplementary Fig. S2). The items of VFQ-25 best describing the variation in PC2 and PC3, based on their loadings (i.e., the weight given to each question in constructing the PC), were mainly those included in the mental health subscale (Supplementary Figs. S3A, S3B). Hence, the key VFR measures retained from the PCA were the VFQCS, as a surrogate for PC1, the BCVA score providing information that is complementary to PC1, and the VFQ-25 mental health subscale score (VFQMHS). The thresholds of MCID for a clinically meaningful response were ≥4.3 units for the VFQCS (Cronbach’s α = 0.95) and ≥11.7 units for the VFQMHS (Cronbach’s α = 0.77). The threshold of MCID for the BCVA score was set at ≥2 VA lines (10 ETDRS letters). Patients with a value above the MCID are considered responders.

Treatment Effect on Visual Function Response
Treatment with sirolimus 440 μg did not result in a significantly higher proportion of responders as compared to the active control for the BCVA score (21.1% vs. 18.8%, OR: 1.15, P = 0.67); the VFQCS (40.7% vs. 35.9%, OR: 1.23, P = 0.45); the VFQMHS (29.2% vs. 26.5%, OR: 1.14, P = 0.65); and the overall VFR (51.3% vs. 43.6%, OR: 1.36, P = 0.24). Similarly, results for sirolimus 880 μg vs. 44 μg were comparable. Treatment with sirolimus 880 μg did not result in a significantly higher proportion of responders as compared to the active control for the BCVA score (20.7% vs. 18.8%, OR: 1.13, P = 0.72); the VFQCS (41.4% vs. 35.9%, OR: 1.26, P = 0.39); the VFQMHS (32.8% vs. 26.5%, OR: 1.35, P = 0.30) or the overall VFR (50.9% vs. 43.6%, OR: 1.34, P = 0.27).

Measuring the Associations Between VFR and VH
Achieving a VH score of 0 was not significantly associated with the VFQCS response (OR = 1.51, P = 0.124), and VFQMHS response (OR = 1.72, P = 0.051). However, achieving a VH score of 0 was significantly associated with a BCVA ≥2 lines improvement (OR = 2.28, P = 0.006) and the overall VFR (OR = 1.77, P < 0.0001; Fig. 2A).

There was a statistically significant association between reaching a VH score of 0 or 0.5+ and each of the VFR measures (i.e., VFQCS response (OR = 2.23, P = 0.0004); VFQMHS response (OR = 2.84, P < 0.0001); BCVA response (OR = 2.60, P = 0.0099); and overall VFR response (OR = 2.65, P < 0.0001; Fig. 2B).

Considering an endpoint of reaching a VH score of 0 or a 2-unit decrease, a significant association was observed only with respect to BCVA response (OR = 1.40, P = 0.0281; Fig. 2C).
The corresponding proportion of responders for the individual VFR measures and the overall VFR are presented according to the different VH response definitions in the Table.

**DISCUSSION**

Vitreous haze is the current standard for assessing posterior segment inflammation and is accepted as a valid surrogate endpoint for disease activity.\(^{15,17,19,41-43}\) Endpoints such as improvement in BCVA are also considered for assessing efficacy in clinical trials of uveitis as it reflects a clinical endpoint of significance to the patient.\(^{41}\) Although there is limited evidence on the significance of VH as a clinical marker for assessing therapeutic benefit in NIU-PS, the analysis results of SAKURA Study 1 data reported here demonstrates the patient relevance of ocular inflammation control measured through the intermediate endpoint of VH.\(^{45-45}\) Achieving a VH score of 0 or 0.5\(^{+}\) at month 5 following treatment was significantly associated with clinically meaningful improvements in patient visual functioning. Also, we observed a significant association between inflammation control and meaningful improvement in BCVA, regardless of the definition used for VH control. To the best of our knowledge, this is the first study to report the association between VFR and VH response for NIU-PS.

Principal component analysis is a data-driven procedure frequently used in exploratory data analysis, including PRO research. In ophthalmology, it is a recognized method to validate new questionnaires, or to endorse established questionnaires applied to new conditions.\(^{24,34,46}\) The VFQ-25 generates a multidimensional dataset and like many PRO instruments with multiple domains, its multiple scores are combined to calculate a general score creating a composite endpoint, the VFQCS.\(^{47}\) Composite endpoints have advantages such as reducing multiplicity problems; however, the use of an aggregate PRO score has limitations and its validity has been critiqued as it may not capture all clinically important variation in the set of multiple items of the instrument.\(^{16,47}\) If all items of a PRO instrument are well related and can be summarized in an aggregate score, the instrument is said to be unidimensional. Typically, it is expected that the first PC captures a minimum of 60% of the variation to label an instrument as unidimensional.\(^{34,35}\) Our PCA showed that the first PC captured 50.9% of the relevant information suggesting that the VFQ-25 responses from the SAKURA Study 1 population cannot be considered as unidimensional. Hence, it is preferable to represent the VFQ-25 dataset through more than one single measure. Further exploration of the PCA suggested VFQMHS as an additional dimension of visual functioning. Our observations regarding multidimensionality are in line with those made by other researchers. Marella et al.\(^{35}\) studied the psychometric validity of the VFQ-25 in a low vision population and concluded that the VFQ-25 is a better-performing instrument when split into a visual functioning and socioemotional scale. Similarly, other researchers\(^{34}\) found multidimensionality with near vision items loading onto the second PC. Nevertheless, the VFQCS demonstrated good internal consistency, a Cronbach’s \(\alpha\) of 0.95, consistent with psychometric evaluation results in other NIU studies.\(^{29}\)

The thresholds of MCID for the VFQCS and VFQMHS were estimated using a distribution-based approach. In the absence of a strong correlation between BCVA and the VFQCS (\(\rho = 0.34\)), the use of a distribution-based over an anchor-based approach is justified. While the MCID assessed using SEM by Naik et al.\(^{29}\) found a 3.86-point change in VFQCS and 8.92-point change in VFQMHS to be clinically meaningful, the

![Figure 2](http://arvojournals.org/)
Visual Function Responders for Each VFR Measure According to the Different Definitions of VH Response

<table>
<thead>
<tr>
<th>VFR Measure</th>
<th>VH 0*</th>
<th>VH 0.5+</th>
<th>VH 0 or 2-Unit Change*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 72</td>
<td>N = 275</td>
<td>N = 250</td>
</tr>
<tr>
<td>VFQCS†</td>
<td>34 (47.2)</td>
<td>102 (37.2)</td>
<td>42 (43.3)</td>
</tr>
<tr>
<td>BCVA ≥ 2 lines‡</td>
<td>23 (31.9)</td>
<td>47 (17.1)</td>
<td>27 (27.8)</td>
</tr>
<tr>
<td>VFQMHS‡</td>
<td>28 (38.9)</td>
<td>74 (27.0)</td>
<td>32 (33.0)</td>
</tr>
<tr>
<td>Overall VFR‡</td>
<td>43 (59.7)</td>
<td>125 (45.6)</td>
<td>53 (54.6)</td>
</tr>
</tbody>
</table>

* Vitreous haze response definitions follow the primary and secondary endpoints of VH response in the SAKURA Study 1: the primary VH endpoint defined as having a VH score of 0 at month 5; the secondary VH endpoint defined as having a VH score of 0 or 0.5+ at month 5; the additional secondary VH endpoint defined as having a score of VH 0 or a ≥2-unit change. For each VH response definition, N represents the number of participants achieving a VH response (versus nonresponse); n represents the number of participants with a visual function response (%) for the respective VFR measure.
† For the VFQCS, VFQMHS and overall VFR, the denominator was 274, 166, and 249 in the VH 0, VH 0.5+, and VH 0 or 2-unit change groups, respectively, due to one patient for which no VFQ-25 assessment was available at month 5.
‡ A VFQCS responder is a participant with aVFQCS change from baseline to month 5 of ≥4.3 points. A BCVA ≥2 lines responder is a participant with a BCVA change from baseline to month 5 of ≥2 lines of VA. A VFQMHS responder is a participant with aVFQMHS change from baseline to month 5 of ≥11.7 points. An overall VFR responder is a participant with a response based on the VFQCS or the BCVA score or the VFQMHS change from baseline to month 5.

SAKURA Study 1 data identified a threshold of 4.3 and 11.7 units for VFQCS and VFQMHS similar to other studies.46,49

Previous research demonstrated that the NEI VFQ-25 is a reliable, valid and responsive instrument to assess vision-related functioning in NIU-PS.29 Our research did not aim to test the psychometric performance of the VFQ-25 in the SAKURA Study 1 population. Rather, we investigated the association between different definitions of VH response and patient-reported outcomes. Our VFQ-25 findings showed significant associations between control of ocular inflammation, when defined as VH score of 0 or 0.5+, and meaningful improvements in the VFQCS or VFQMHS scores. This suggests that from a patient perspective, the standard threshold for the NEI photographic VH scoring equal to 0 may be too strict. Clinical trials in NIU typically the NEI technique to grade the severity of VH whereby the clinical examination of the posterior pole is compared against a standard set of photographs. This photographic assessment technique comes with limitations (subjective, poorly discriminatory at lower levels of VH, limited sensitivity in trial context), which may contribute to nonsignificant correlation between markers of disease activity (VH) and measures of visual function (VF).12,45,50 Nevertheless, our BCVA has been used in all clinical trials that included measures of visual function performance. A combined endpoint based on BCVA and PRO measures has not yet been reported in NIU-PS, even though the burden of NIU is known to comprise reductions in vision-related functioning in addition to vision loss. Exploring new measures of visual functioning for inflammatory eye diseases is supported in the literature.10,12,13,17,19,22 As reported in this study, the value of PRO measures of vision-related functioning consists of complementing clinical measures such as VH and VA, and providing the patient’s perspective on disease burden and outcomes of treatment, hence capturing a more complete response to disease control.60

While NIU may present many potential insults to visual functioning, it is notable that mental health appears the most impaired vision-related domain (lowest subscale score) across several NIU populations including the SAKURA Study 1.15,22,61 Although results for all VFQ-25 items differ significantly from the normal-vision population, it is likely that not all items are equally relevant to uveitis or that NIU-PS patients may have specific items impacting their QoL more than others.12,17 A significant decline of psychological well-being, despite an unequivocal physical health status similar to the normal-vision population, is often reported by patients with uveitis.12 This is not surprising given that activities of daily life are impacted with vision impairment, which in turn affects the psychological status of the patient. Qian et al.61 reported depression to be a prevalent comorbidity in patients with ocular inflammatory disease, with VFQ-25 scores (composite and subscales) in the same range as those found in other studied uveitis populations. Our results in the SAKURA Study 1 found a low correlation between BCVA and the VFQCS (ρ = 0.34), indicating that VA and PRO measure different and complementary aspects of visual functioning. The apparent absence of correlation between BCVA and VFQ-25 responses may be due to unmeasured symptoms such as depression, known to affect visual functioning. Depression may impact a patient’s visual experience without a proportional change in VA and hence a combined VFR endpoint.
may be more sensitive to detect dysfunctional vision compared to VA testing alone.

Several limitations should be considered when interpreting the findings from this study. First, given the inclusion and exclusion criteria of the SAKURA study 1, the BCVA and vision-related functioning may not be generalizable to all patients with NIU-PS. Additional analyses (data not shown) indeed demonstrated that achieving an overall VFR was significantly associated with lower baseline values for the BCVA, VFQCS, or VFQMHS compared with non-responders. However, for the association analyses we considered an endpoint of overall VFR that allowed participants to be classified as a responder if they experienced a meaningful improvement in any of the 3 individual VFR measures. Thus, a participant with a relatively high baseline BCVA score could still be a VFR responder based on improvement shown in other dimensions of visual functioning (e.g., VFQMHS). Second, our threshold for meaningful VFR for the VFQ-25 outcomes was based on a distribution-based criterion (SEM) only, in absence of patient or physician criteria. Nevertheless, the MCIDs observed in the SAKURA Study 1 were in the range of those observed in other NIU populations. Finally, the SAKURA Study 1 was a multicountry study including mainly Caucasian and Asian populations. As the functional impact of treatment was based on patient self-reporting and regional/cultural differences in reporting may exist, this can be considered a limitation of the study. Nonetheless, the analysis of composite data has the advantage that it avoids an arbitrary choice between several important outcomes associated with a patient’s disease status (visual acuity, daily functioning, mental health, etc.) independent of regional or geographic differences. Further research to investigate the role of regional/cultural differences in predicting visual function response may be warranted.

In conclusion, our results showed that improvement in intraocular inflammation is significantly associated with improvement in visual functioning defined by BCVA, the VFQCS or the VFQMHS. The VFQ-25 complements clinical measures of disease activity (i.e., VH) and provides a patient perspective on burden of disease. A clinically measurable VH response of 0 or 0.5+ indicates an improvement in visual functioning as perceived by the patient. New measures for VFR may be more sensitive and meaningful outcomes to the patient than the classical VA and vision-related functioning measures. In addition, health care practitioners, payer decision-makers, and health technology assessment authorities may perceive this combined endpoint as more patient relevant than endpoints of disease activity.

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