Normative Comparison of Patient-Reported Outcomes in Patients With Noninfectious Uveitis

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Objective: To compare vision-related functioning and health-related quality of life of patients with noninfectious intermediate or posterior uveitis with those of the US general population and normal-vision reference groups.

Methods: Secondary analysis of health-related quality of life measures administered at baseline to patients with noninfectious intermediate or posterior uveitis participating in the HURON trial, a 26-week, multicenter, masked, randomized, sham-controlled trial of a dexamethasone intravitreal implant (n=224) was performed. Patient-reported outcome measures included the National Eye Institute Visual Function Questionnaire–25, the 36-Item Short-Form Health Survey, the Short Form–6 Dimensions, and the EuroQol-5D. The National Eye Institute Visual Function Questionnaire–25 scores from the HURON uveitis population were compared with published National Eye Institute Visual Function Questionnaire–25 scores from a normal-vision reference group (n=122). The 36-Item Short-Form Health Survey, Short Form–6 Dimensions, and EuroQol-5D scores were compared with the US general population using data from the National Health Measurement Study (n=3844) and the Medical Expenditure Panel Survey (n=955).

Results: Compared with a normal-vision population, the HURON uveitis population had clinically significant impairments across all National Eye Institute Visual Function Questionnaire–25 subscales and the composite score, with all subscale score differences exceeding 10 points (P<.001). The HURON uveitis population had significantly lower 36-Item Short-Form Health Survey mental component summary and Short Form–6 Dimensions scores compared with a US general population sample (P<.001). No significant differences were found for the 36-Item Short-Form Health Survey physical component summary and EuroQol-5D scores between the uveitis and US general population samples.

Conclusions: Compared with the US general population and normal-vision reference groups, noninfectious intermediate or posterior uveitis results in meaningful reductions in mental health outcomes, health-related quality of life, and vision-related functioning.

Trial Registration: clinicaltrials.gov Identifier: NCT00333814


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for all domains of vision-related functioning. In addition, these findings suggest that patient-reported outcome (PRO) measures capture unique aspects of visual functioning that are both relevant and important to patients.10,11

Previous studies have reported the impact of uveitis on patient-reported vision-related functioning through the use of established PRO instruments.12 However, to our knowledge, studies comparing vision-related functioning and health-related quality of life (HRQOL) of patients with uveitis relative to the US general population or normal-vision reference groups have not been documented. Comparisons such as these allow a more comprehensive view of the specific impact of disease and illness on the patient population.

It is also important to note that VA and HRQOL are mainly driven by a patient’s better-seeing eye (BSE).11,14 Treatment-related improvement in vision-related functioning may therefore be difficult to detect when the worse-seeing eye (WSE) is treated because of theordinate contribution of VA in the BSE to scores on PRO measures. There is a paucity of research specifically examining the contribution of VA in the BSE vs the WSE to scores on PRO measures.

This study reports PRO data from HURON, a phase 3 clinical trial designed to assess the safety and efficacy of a dexamethasone intravitreal implant (Ozurdex) compared with a sham treatment in patients with noninfectious intermediate or posterior uveitis.15 The primary objective of this analysis was to compare the vision-related functioning and HRQOL of patients with noninfectious intermediate or posterior uveitis vs those of the US general population and a normal-vision reference group. Additionally, because vision is a binocular condition, a secondary objective was to examine the relationship between the PROs and VA for the BSE vs WSE as the study eye.

**METHODS**

The primary data are from HURON, a phase 3, multicenter, masked, randomized, sham-controlled, parallel-group trial of 0.7-mg and 0.35-mg dexamethasone intravitreal implants compared with a sham treatment in patients with noninfectious intermediate or posterior uveitis compared with a sham treatment. Patients with noninfectious intermediate or posterior uveitis were followed up for 8 weeks with an 18-week masked extension, for a total of 26 weeks.13 The data in this article are from the baseline visit only.

The primary outcome measure in the HURON trial was based on the amount of vitreous haze that obscured visualization and the proportion of patients with a vitreous haze score of 0.0 at week 8. Vitreous haze was measured using a standardized photographic scale ranging from 0 to 4, with 0 indicating no inflammation; 0.5, trace inflammation (slight blurring of the optic disc margins and/or loss of the nerve fiber layer reflex); 1, mild blurring of the retinal vessels and optic nerve; 1.5, optic nerve head and posterior retina view obscuration greater than 1 but less than 2; 2, moderate blurring of the optic nerve head; 3, marked blurring of the optic nerve head; and 4, optic nerve head not visible. Additionally, best-corrected VA was measured using the Early Treatment Diabetic Retinopathy Study method.16 Best-corrected VAs were separately measured for the study eye and the nonstudy eye.

Patients were included in the study if they were at least 18 years of age and had a diagnosis of intermediate uveitis (with the vitreous as the primary site of inflammation) or posterior uveitis (with the retina or choroid as the primary site of inflammation). Patients were also required to have decreased VA attributable to uveitis, with a vitreous haze score of at least 1.5, and best-corrected VA between 10 and 75 letters (approximately 20/640 and 20/32 Snellen equivalent) in the study eye. In patients with both eyes eligible for the study, the right eye was used as the study eye. The study eye was identified at the baseline visit and remained the same throughout the entire study. Patients were excluded if they had any other active ocular disease or infection in the study eye that would prevent improvement in VA or any condition or treatment that would otherwise confound the results of the study. A total of 229 patients from 46 study sites in 18 countries were randomized to receive the 0.7-mg dexamethasone intravitreal implant (n = 77), the 0.35-mg dexamethasone intravitreal implant (n = 76), or the sham treatment (n = 76) between May 2006 and October 2008 and were followed up through April 2009.

**PRO MEASURES**

The PRO measures included the National Eye Institute Visual Function Questionnaire—25 (NEI VFQ-25), the 36-Item Short Form Health Survey (SF-36), the Short Form—6 Dimensions (SF-6D), and the EuroQol-5D (EQ-5D).

**NEI VFQ-25 Measure**

The NEI VFQ-25 includes 11 vision-related subscales (general vision, near vision, distance vision, driving, peripheral vision, color vision, ocular pain, vision-specific role difficulties, vision-specific dependency, vision-specific social functioning, and vision-specific mental health) and 1 general health item.17,18 Each domain is scored such that 0 represents the lowest visual functioning and 100 indicates the best possible visual functioning. An overall or composite score is also calculated. The NEI VFQ-25 was linguistically validated for administration in local languages to ensure accurate PRO assessments across multiple HURON clinical trial sites. The process used for linguistic validation was in accordance with the guidelines and standards for translation and cultural adaptation of PRO measures set forth by the International Society for Pharmacoeconomics and Outcomes Research.19 The eAppendix (http://www.jamaophth.com) includes a detailed description of the linguistic validation process and a list of the languages into which the NEI VFQ-25 was translated.

**SF-36 Measure**

The SF-36 consists of 8 subscales: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. Two overall summary scores, the physical component summary (PCS) and the mental component summary (MCS), can be also calculated.20,21 The SF-36 scores range from 0 to 100, with higher scores indicating better general health status. The summary scores are normalized to the US general population, with a mean (SD) of 50.0 (10.0).

**SF-6D Measure**

The SF-6D, a 6-dimensional health state classification, is estimated from selected SF-36 items (physical functioning, role limitations, social functioning, pain, mental health, and vitality).21 The SF-6D scores have a range of 0.29 (worst possible health) to 1.00 (full health).22,23
EQ-5D Measure

The EQ-5D is a preference-based measure of general health. It consists of items on 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a visual analog scale.24,25

COMPARISON DATA

Baseline pretreatment NEI VFQ-25 data from the HURON trial were compared with data from the normal-vision reference group in the NEI VFQ-25 development article.19 Baseline pretreatment SF-36, SF-6D, and EQ-5D scores were compared with the US general population using the National Health Measurement Study (NHMS) (n = 3844) and Medical Expenditure Panel Survey (MEPS) (n = 955) data.

Comparison of HURON Clinical Trial Population With Normal-Vision Population

Normal-vision population data on the NEI VFQ-25 were obtained from the reference group included in the original development of the NEI VFQ-25 instrument (n = 122).19 Participants in the reference group were specifically recruited to have no underlying eye disease except refractive error correctable to at least 20/25 in their WSE. Participants in this group could have subclinical morphological retinal or macular changes that did not meet criteria for age-related macular degeneration and early lens opacities that were less than Age-Related Eye Disease Study cortical or nuclear grade 2 or posterior subcapsular grade 1. The cohort was at least 50% female, and 30% of participants were from underrepresented minority groups.26,27

Comparison of HURON Clinical Trial Population With US General Population

For the US general population, normative data for the SF-36, SF-6D, and EQ-5D were obtained from 2 sources: the NHMS, a representative sample of the noninstitutionalized adult population aged 35 to 89 years in the United States (n = 3844),28 and the MEPS, a representative sample of the noninstitutionalized US civilian population (n = 955).29 To control for demographic characteristics in comparisons with the uveitis population in the HURON trial, age-, sex-, and race-matched cases were selected from each of these study samples.

STATISTICAL ANALYSIS

All subjects enrolled in the HURON clinical trial who completed the NEI VFQ-25, SF-36, and/or EQ-5D at baseline were included. Spearman product-moment rank correlations were used to examine the relationship between VA and the PRO measures. Correlations were assessed between VA of the WSE as the study eye, VA of the BSE as the study eye, and each of the PRO measures. Items or scales measuring similar concepts (ie, VA and the NEI VFQ-25) were expected to be substantially correlated (r ≥ 0.40).30 Conversely, items or scales measuring different concepts (ie, VA and the SF-36 or EQ-5D) were expected to have smaller correlations (r < 0.40). Two-sided independent-sample t tests were used to assess mean NEI VFQ-25 subscale and composite score differences between the HURON uveitis population and the normal-vision population and between mean SF-36, SF-6D, and EQ-5D score differences among the HURON uveitis population and the NHMS and MEPS US general population.

Table 1. Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n = 224)</th>
<th>Intermediate Uveitis (n = 180)</th>
<th>Posterior Uveitis (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>44.6 (14.3)</td>
<td>44.4 (14.2)</td>
<td>45.3 (15.1)</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>142 (63.4)</td>
<td>116 (64.4)</td>
<td>26 (59.1)</td>
</tr>
<tr>
<td>White, No. (%)</td>
<td>135 (60.3)</td>
<td>109 (60.6)</td>
<td>26 (59.1)</td>
</tr>
<tr>
<td>VA in study eye, median, ETDRS letters</td>
<td>62.5</td>
<td>63.0</td>
<td>61.5</td>
</tr>
<tr>
<td>Worse-seeing eye, No. (%)</td>
<td>189 (84.4)</td>
<td>154 (85.6)</td>
<td>35 (79.5)</td>
</tr>
</tbody>
</table>

Abbreviations: ETDRS, Early Treatment Diabetic Retinopathy Study; VA, visual acuity.

RESULTS

The analytical sample for this study included 224 patients with uveitis (80.4% with intermediate uveitis and 19.6% with posterior uveitis). Demographic and clinical characteristics by treatment group are summarized in Table 1. The mean age was 44.6 years, 63.4% were female, and a majority of the patients were white (60.3%). The median VA of the study eye was 62.5 letters (approximately 20/50 Snellen equivalent; range, 50.0-68.5 letters), while the median VAs of the BSE and WSE were 81.0 letters (approximately 20/25 Snellen equivalent; range, 72.0-88.0 letters) and 60.0 letters (approximately 20/63 Snellen equivalent; range, 50.0-68.5 letters), respectively.

RELATIONSHIP BETWEEN VA AND PRO MEASURES

Significant correlations of low to moderate magnitudes were observed between the VA of the BSE as the study eye and a majority of PRO composite and subscale scores (range, r = 0.37-0.59; all P < .05) (Table 2). Correlations between VA for the WSE as the study eye and the PROs were statistically significant for all PRO composite and subscale scores (range, r = 0.16-0.39; all P < .05) but lower in magnitude than correlations with the BSE as the study eye (range, r = 0.27-0.59).

HURON UVEITIS POPULATION VS NORMAL-VISION POPULATION

Comparisons based on the NEI VFQ-25 scores indicated that the HURON uveitis population had clinically significant impairments in vision-specific functioning compared with the normal-vision population (Figure). Significant differences between the HURON uveitis population and the normal-vision population were found across all 11 NEI VFQ-25 domain and composite scores and exceeded 10 points (all P < .001). Similar results were observed when the intermediate and posterior uveitis subgroups were compared with the normal-vision population (data not shown).
COMMENT

The results of our study indicate that VA, measures of vision-related functioning, and HRQOL are significantly correlated in patients with noninfectious intermediate or posterior uveitis. In previous research, the relationship between VA and PRO scores was observed to be driven mostly by VA in the BSE.11,14,31 We observed similar results, with significant low to moderate correlations between the VA of the BSE as the study eye and most PRO composite and subscale scores. Overall, correlations between the PRO scores and VA of the WSE were of a lesser magnitude than those for the VA of the BSE as the study eye. The significant but low to moderate magnitude of correlations between VA and PRO measures indicates that while VA and the included PROs are related, they also measure different and complementary aspects of visual functioning. The objective measure of VA is an important outcome in treating ocular conditions such as uveitis, but our results and...
the results of others highlight the importance of subjective assessments such as PRO measures as well.6-12

Based on the PRO measures included in the HURON trial, the results of our study indicate that patients with noninfectious intermediate or posterior uveitis had significant reductions in mental health outcomes, HRQOL, and vision-related functioning when compared with US general and normal-vision populations. Patients with uveitis in the HURON trial had statistically significantly worse general and normal-vision populations. A 5- to 10-point difference in NEI VFQ-25 scores has been established as being clinically meaningful in previous studies.32-34 Additionally, based on data reported in the NEI VFQ-25 development article, we observed that patients with uveitis in the HURON trial had lower scores on most NEI VFQ-25 subscales when compared with patients with diabetic retinopathy, age-related macular degeneration, glaucoma, cataract, and cytomegalovirus retinitis.13,18

When compared with US general population samples, patients with uveitis in the HURON clinical trial had significantly lower SF-36 MCS scores, but no differences were observed in PCS scores. The mean differences in MCS scores ranged from 3.5 to 5.7 points, which is a clinically significant difference.20,21 Patients with uveitis in the HURON trial also had significantly lower SF-36 role-physical, general health, vitality, role-emotional, and mental health scores and SF-6D scores when compared with US general population samples. Patients with uveitis in this study clearly are reporting impaired psychological well-being despite physical health status that is similar to the US general population. These differences are clinically significant and further confirm the impact of uveitis on psychological functioning.20,21

The results from this study also indicate that the NEI VFQ-25 provides a more clinically sensitive measure of patient functioning compared with the generic health status (SF-36) and preference-based health indices (EQ-5D and SF-6D). While the generic health status instruments showed some differences between the HURON uveitis population and the US general population, there were significant differences across all the NEI VFQ-25 subscales and overall scores, demonstrating greater and consistent impairments in the patients with uveitis. For clinical studies and clinical trials, the NEI VFQ-25 may be more likely to assess the impact of uveitis across a wide range of VA levels.

### Table 3. Comparison of Mean Patient-Reported Outcome Scores Between the HURON Uveitis Population and the US General Population From National Health Measurement Study Data

<table>
<thead>
<tr>
<th>PRO Measure</th>
<th>Uveitis Populationa (n = 137-138)</th>
<th>US General Populationb (n = 639-641)</th>
<th>P Valuec</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36 PCS</td>
<td>138</td>
<td>639</td>
<td>.27</td>
</tr>
<tr>
<td>Score, mean (SD)</td>
<td>47.7 (12.2)</td>
<td>48.9 (10.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No.</td>
<td>138</td>
<td>639</td>
<td>.10</td>
</tr>
<tr>
<td>Score, mean (SD)</td>
<td>47.6 (12.7)</td>
<td>53.3 (9.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Physical functioning No.</td>
<td>138</td>
<td>640</td>
<td>.99</td>
</tr>
<tr>
<td>Score, mean (SD)</td>
<td>79.7 (23.8)</td>
<td>83.6 (25.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Role-physical No.</td>
<td>138</td>
<td>641</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Score, mean (SD)</td>
<td>65.5 (40.7)</td>
<td>81.4 (25.0)</td>
<td></td>
</tr>
<tr>
<td>Bodily pain No.</td>
<td>138</td>
<td>641</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Score, mean (SD)</td>
<td>71.3 (23.3)</td>
<td>71.3 (24.5)</td>
<td>.01</td>
</tr>
<tr>
<td>General health No.</td>
<td>138</td>
<td>641</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Score, mean (SD)</td>
<td>64.7 (21.5)</td>
<td>70.1 (22.6)</td>
<td></td>
</tr>
<tr>
<td>Vitality No.</td>
<td>138</td>
<td>641</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Score, mean (SD)</td>
<td>57.8 (22.5)</td>
<td>65.0 (20.8)</td>
<td></td>
</tr>
<tr>
<td>Social functioning No.</td>
<td>138</td>
<td>640</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Score, mean (SD)</td>
<td>82.3 (25.3)</td>
<td>86.4 (22.6)</td>
<td></td>
</tr>
<tr>
<td>Role-emotional No.</td>
<td>137</td>
<td>640</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Score, mean (SD)</td>
<td>74.7 (39.5)</td>
<td>89.8 (19.8)</td>
<td></td>
</tr>
<tr>
<td>Mental health No.</td>
<td>138</td>
<td>641</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Score, mean (SD)</td>
<td>72.3 (19.0)</td>
<td>81.3 (17.2)</td>
<td></td>
</tr>
<tr>
<td>SF-6D No.</td>
<td>136</td>
<td>637</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Score, mean (SD)</td>
<td>0.84 (0.13)</td>
<td>0.85 (0.17)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: EQ-5D, EuroQol-5D; MCS, mental component summary; NHMS, National Health Measurement Study; PCS, physical component summary; PRO, patient-reported outcome; SF-6D, Short-Form–6 Dimensions; SF-36, 36-item Short-Form Health Survey.
aBaseline data.
bThe NHMS SF-36 values are matched for age (35-82 years), sex, and race.
cTwo-sided t test for independent groups.

### Table 4. Comparison of Mean Patient-Reported Outcome Scores Between the HURON Uveitis Population and the US General Population From Medical Expenditure Panel Survey Data

<table>
<thead>
<tr>
<th>PRO Measure</th>
<th>Uveitis Populationa (n = 105-221)</th>
<th>MEPS US General Populationb (n = 953-986)</th>
<th>P Valuec</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36 PCS</td>
<td>48.2 (11.4)</td>
<td>49.0 (10.9)</td>
<td>.34</td>
</tr>
<tr>
<td>MCS</td>
<td>46.9 (13.1)</td>
<td>50.4 (10.1)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
| SF-6D       | 0.67 (0.11) | 0.78 (0.15) | <.001  

Abbreviations: MCS, mental component summary; MEPS, Medical Expenditure Panel Survey; PCS, physical component summary; PRO, patient-reported outcome; SF-6D, Short Form–6 Dimensions; SF-36, 36-item Short-Form Health Survey.
aBaseline data.
bThe MEPS values are matched for age, sex, and race.
cTwo-sided t test for independent groups.
Several limitations should be considered when interpreting the findings from this study. First, given the inclusion and exclusion criteria for this clinical trial, the vision-related functioning results may not be generalizable to all patients with uveitis. Further, it should be noted that patients in the HURON trial were recruited from multiple regions (North America [n = 50], Brazil [n = 29], Europe [n = 79], Australia [n = 19], Israel [n = 7], India [n = 32], and South Africa [n = 10]). However, the primary effectiveness end point of the proportion of patients with a vitreous haze score of 0 at week 8 in each region was similar to that of the overall population, and there was no significant treatment-investigator interaction (P = .46 for the 0.7-mg dexamethasone intravitreal implant vs sham treatment and P = .83 for the 0.35-mg dexamethasone intravitreal implant vs sham treatment).15 Second, in addition to the impact of the disease, the general health status of patients with uveitis may also be related to the medications required to treat uveitis, particularly systemic steroids. Finally, the normal-vision reference group was taken from the study by Mangione et al18; it is the most relevant data set for normative comparison and has been shown to be comparable to more recent normal-vision populations.35-39 However, there may be differences in demographic characteristics, limiting the generalizability and interpretation of the findings.

In conclusion, this study demonstrates that compared with the US general population or normal-vision reference groups, monocular vision loss due to uveitis results in impairments in multiple domains of general health status and vision-related functioning. These impairments were seen despite the effects of better VA in the partner BSE in these clinical trial patients. The generic health status measures showed similar physical health in the patients with uveitis and the US general population but larger impairments in psychological functioning and well-being. These findings suggest that clinicians may need to consider interventions beyond ophthalmologic treatments to alleviate the psychological burden associated with vision loss.

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Conflict of Interest Disclosures: Dr Naik is an employee of Allergan Inc. Ms Rentz is an employee of United BioSource Corp, which received funding from Allergan Inc to conduct this research. Dr Whitcup is an employee of and has stock options in Allergan Inc. Dr Kowalski is an employee of and owns stock and stock options in Allergan Inc.

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Role of the Sponsor: Allergan Inc participated in the design of the study, data analysis, and interpretation of the data, supervised the preparation of the manuscript, and approved the final version.


Additional Contributions: Young Zhu, PhD, and Rebecca Liu, MS, provided support in conducting statistical analyses.

REFERENCES


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**Correction**

Error in Byline. In the Clinical Sciences article titled “Characterizing the Phenotype and Genotype of a Family With Occult Macular Dystrophy,” published in the December issue (2012;130[12]:1554-1559), the last author listed in the byline, Connie J. Chen, MD, should actually have been listed as the first author. Her name should also be listed first in the Author Affiliations.