Vision-Related Quality of Life Outcomes in the BEVORDEX Study: A Clinical Trial Comparing Ozurdex Sustained Release Dexamethasone Intravitreal Implant and Bevacizumab Treatment for Diabetic Macular Edema

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PURPOSE. To determine the patient-centered effectiveness of treatment with the slow-release dexamethasone intravitreal implant (DEX implant) and intravitreal bevacizumab using the Impact of Vision Impairment Questionnaire (IVI), a vision-related quality of life (VRQoL) measure, in patients with visual impairment secondary to center-involving diabetic macular edema (DME).

METHODS. Patients with DME were enrolled in a phase 2, prospective, multicenter, randomized, single-masked clinical trial and received either DEX implant 4 monthly or bevacizumab monthly, both pro re nata. Vision-related quality of life was measured at baseline and 24 months, using the IVI’s three component scales, namely reading, mobility, and emotional well-being. Rasch analysis was used to generate interval-level estimates of VRQoL, which were then analyzed using t-tests to assess changes over time.

RESULTS. Forty-eight patients completed the main study; 43 (90%) answered the IVI at the baseline and 24-month (final efficacy) visits. Vision-related quality of life improved significantly, with average increases of 1.44, 0.99, and 1.49 logits, for the reading, mobility, and emotional well-being scales respectively, from baseline to 24 months, (𝑃 < 0.001). There was no significant between-group difference in improvement in VRQoL in the DEX implant only compared with the bevacizumab-only group, in any of the three scales listed above (with 1.41, 1.08, and 2.11 logits improvement, in reading, mobility, and emotional well-being, respectively, for DEX implant group, compared with 1.48, 1.06, and 2.11 for bevacizumab; 𝑃 values > 0.1).

CONCLUSIONS. We found that both DEX implant and bevacizumab treatment result in significant and similar improvements in VRQoL in patients with DME over a 24-month period. (Clinicaltrials.gov identifier NCT01298076)

Keywords: diabetic macular edema, therapeutics, quality of life

Diabetic macular edema (DME) is the major cause of visual loss in patients with diabetes. A breakdown of the retinal–blood barrier results in the leakage of plasma and lipids into interstitial layers of the macula, causing the thickening of the fovea and severely compromising central vision.1,2 The impact of DME on patients’ quality of life is considerable,3,4 and comparable to that of AMD.5

Both bevacizumab6–7 and slow-release dexamethasone intravitreal implant (DEX implant)8–9 have been shown to be effective in reducing swelling due to DME and improving visual acuity. However, few studies have reported the effects of these treatments from the patient’s perspective. Okamoto and colleagues10 found short-term VRQoL improvements (using the 25 item version of National Eye Institute Vision Functioning Questionnaire [NEI VFQ-25]), following a single injection of bevacizumab for persistent post vitrectomy DME, and Ramu and associates11 similar vision and VRQoL outcomes for both fixed or pro re nata (PRN) treatment schedules for DEX implant in refractory DME.

However, both studies were only conducted over a short time-period (3 and 12 months, respectively) so the longer-term treatment effect of either bevacizumab or DEX implant on VRQoL is unknown. Moreover, most studies reporting VRQoL after treatment for DME12–13 have used traditional summary scoring methods, which have inherent limitations.14,15 Importantly, recent studies using Rasch analysis, a form of item response theory, have found the NEI VFQ-25 to be multidimensional, suggesting its measurement precision may be compromised.16–18

In contrast to the NEI VFQ-25, the Impact of Vision Impairment Questionnaire (IVI) is a VRQoL instrument, which has been shown to be reliable and responsive to interven-
Vision-Related Quality of Life in the BEVORDEX Study

Methods

The BEVORDEX study was a 2-year clinical trial that directly compared sustained release intravitreal DEX implant (Ozurdex; Allergan, Inc., Irvine, CA, USA) versus intravitreal injections of bevacizumab (Avastin; Genentech, South San Francisco, CA, USA) for center-involving DME. As previously described,28 the study was conducted in accordance with the Declaration of Helsinki and was approved by relevant Health Research Ethics Committees. Safety data were reviewed by an independent safety monitoring committee. Patients gave written informed consent before being randomized to receive study treatment. Both eyes of patients were enrolled if inclusion criteria were met; the right eye received the randomized treatment and the left eye the other treatment.

Protocol Synopsis

The eligibility requirements for patients and eyes, clinical evaluation, clinical data collection methods, and study schedules have been detailed elsewhere.28,29 Briefly, baseline measurements included best-corrected logMAR and best-corrected visual acuity (BCVA) with Early Treatment of Diabetic Retinopathy Study (ETDRS) charts measured using standardized procedures by certified staff. Central macular thickness (CMT) was measured from the central 1-mm subfield from spectral-domain ocular coherence tomography (OCT; Cirrus; Carl Zeiss, Meditec, Jena, Germany). Bevacizumab 1.25 mg (Avastin) or DEX implant 0.7 mg (Ozurdex) was injected into the vitreous under sterile conditions as an outpatient procedure. All eyes were considered for retreatment at appropriate intervals (4 weekly for bevacizumab or 16 weekly for DEX implant); treatment was either administered or withheld in accordance with prospectively defined criteria.

Patients with both eyes enrolled had each eye treated at separate visits.

The Impact of Vision Impairment Questionnaire

The IVI was either self- or interviewer-administered at baseline and 24 months. The IVI was developed as a measure of patients’ perception of vision-related restriction on their activity and quality of life, particularly in the context of low vision rehabilitation.30 The questionnaire was revised using Rasch analysis to improve measurement characteristics.5-24 The revised version used in the current study has 28 items, with three to four response options for each item. Patients can rate their perceived impact of vision limitation from “not at all,” “a little,” “a fair amount,” to “a lot,” which are allocated number scores from 0 to 3. There is an additional response, “I don’t do this for other reasons” for 15 of the items, which was categorized as “missing.” In this paper, Rasch analysis supported the use of the three IVI scales; reading and accessing information, mobility and independence, and emotional well-being.23-24

Psychometric Assessment of the Impact of Vision Impairment Questionnaire

The psychometric properties of the IVI questionnaire were assessed using Rasch analysis in Winsteps (version 3.91.0; Beaverton, OR, USA) with the Andrich rating scale model,52 with different rating scale structures to allow for the two out of 28 items having three response choices rather than four. Rasch analysis has been described in detail previously; in brief, we assessed whether category thresholds were ordered, scale precision and targeting were adequate, measurement was unidimensional and that items ‘fit’ the underlying trait of VRQoL (Supplementary Table S1). Baseline and 24 month IVI data were “stacked” and item measures anchored to pretreatment values in order to keep pre- and post-measurement in the same frame of reference. This involves entering the two sets of IVI responses for each patient as separate “cases,” which were then analyzed simultaneously as one data file.53 The resulting scores are “person measures,” expressed in logits (log of the odds units), and in this study ranged from −4.95 to +4.90. Higher scores indicate better VRQoL. In brief, the IVI had good psychometric properties with ordered thresholds (demonstrating appropriate use of the range of questionnaire response categories) and excellent precision, as demonstrated in person reliability and separation values. However, principal components analysis revealed evidence of multidimensionality with an eigenvalue of four and three misfitting items. Therefore, based on the standardized residual loadings for items, the IVI was split into three scales for analysis, namely reading and accessing information or “reading” (9 items), mobility and independence or “mobility,” (11 items) and emotional well-being (8 items). The reading and emotional well-being scales had no misfitting items and good precision. However, the mobility scale was not well targeted for this sample, as the participants were on average, above the average level of item difficulty (difference of 1.54 logits between person and item mean score). Similarly, the person separation index was 1.71, which suggests this scale had less than adequate precision. In addition, one item (13), displayed borderline misfit (infit MnSq 1.36), but was retained for the analysis.

In this paper, we use ‘VRQoL’ to describe the overarching construct of QoL, and reading, mobility, and emotional to describe the three subtraits of VRQoL measured by the IVI.

Statistical Analysis

The Statistical Package for the Social Sciences (v. 22.0; SPSS, Inc., Chicago, IL, USA) was used to analyse the data. Descriptive statistical analysis of demographic, clinical, and IVI data was performed using Student’s t-tests. The IVI person measures in logits were analyzed using paired t-tests to assess change over time. Pearson’s correlation coefficient r was used to explore the relationship between VRQoL and BCVA. Change in BCVA was assessed for the study eye or, in patients with both eyes enrolled, the most improved study eye. The most-improved study eye was either the better or equal seeing eye54 at the 24-month visit in 21/24 patients with both eyes enrolled. Of 43 eyes whose BCVA was used, 19 were treated with DEX implant and 24 with bevacizumab.

Due to the wide range of BCVA changes in a relatively small sample, the patients were divided into two groups according to BCVA gain (one with vision gain of ≤15 letters, and the other >15 letters) to compare VRQoL changes. Fifteen letters is equivalent to approximately three lines and is likely to be associated with VRQoL improvements.55,56 The subgroup of
patients with single eye enrolment was used to evaluate whether there was any difference in VRQoL between the bevacizumab and DEX implant treatments, using t-tests.

## Results

### Demographic and Clinical Characteristics of Patients

A total of 48 patients completed the 24 months of the study and 43/48 (90%) answered the IVI questionnaire at both time points. The mean age of these 43 patients (n = 17, 40% male) was 62 (SD 10.80) years at study entry, ranging from 36 to 86 years. A total of 24/43 (56%) patients had both eyes enrolled (subsequently, 3/24 of patients with both eyes enrolled had one eye withdrawn by the Principal Investigator), while 19/43 (44%) received treatment to only one eye. The mean BCVA of the 64 study eyes of the above 43 patients increased from 57 (SD 10.80) years at study entry, ranging from 36 to 86 years. There was a significant decrease in the study eye, the vision in the better seeing eye has been found to correspond to binocular vision when both have been measured.36

When we stratified the 43 patients according to number of letters gained, patients gaining greater than 15 letters had 2.2-logits increase in reading scores at 24 months compared with 1.0 logits in those than those who gained less than or equal to 15 letters; however, the P value was 0.050, which indicated that the difference was of borderline significance. The gain in mobility and emotional well-being scales was similar for both stratified groups (Table 2).

### Comparison of IVI Scores Between the Bevacizumab and DEX Implant Treatment Groups

Patients (24/43) who had both eyes enrolled were used to explore the relationship of improved vision and VRQoL, we used the vision gain in the study eye in patients with a single eye enrolled, and in the group of 24/43 patients who both eyes treated the vision gain in the most improved study eye. The vision in the better seeing eye has been found to correspond to binocular vision when both have been measured.36

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<tr>
<th>IVI (Logits)</th>
<th>Baseline</th>
<th>24 mo</th>
<th>Change</th>
<th>P Value of Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reading (n = 45)</td>
<td>0.14 (SD 1.95)</td>
<td>1.58 (SD 2.06)</td>
<td>1.44 (SD 1.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mobility (n = 45)</td>
<td>1.05 (SD 1.77)</td>
<td>2.04 (SD 1.78)</td>
<td>0.99 (SD 1.51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Emotional (n = 42)</td>
<td>0.34 (SD 2.13)</td>
<td>1.82 (SD 2.18)</td>
<td>1.49 (SD 2.49)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Significant P values in bold.

### IVI Scores for 43 Patients at Baseline and 24 Months

<table>
<thead>
<tr>
<th>IVI baseline (logits)</th>
<th>Baseline</th>
<th>24 mo</th>
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</tbody>
</table>

Significant P values in bold.

### IVI and BCVA Results in Patients Stratified for Vision Gain

<table>
<thead>
<tr>
<th>BEVORDEX Patients Stratified for BCVA</th>
<th>&gt;15 Letters Gain, n = 15/43</th>
<th>≤15 Letters Gain, n = 29/43</th>
<th>P Value of Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVI baseline (logits)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reading</td>
<td>−0.16 (SD 1.73)</td>
<td>0.30 (SD 2.03)</td>
<td>0.47</td>
</tr>
<tr>
<td>Mobility</td>
<td>1.27 (SD 1.99)</td>
<td>0.93 (SD 1.67)</td>
<td>0.55</td>
</tr>
<tr>
<td>Emotional</td>
<td>0.17 (SD 2.08)</td>
<td>0.45 (SD 2.18)</td>
<td>0.70</td>
</tr>
<tr>
<td>IVI, Mean change baseline to 24 mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reading</td>
<td>2.21 (SD 2.07)</td>
<td>1.03 (SD 1.71)</td>
<td>0.050</td>
</tr>
<tr>
<td>Mobility</td>
<td>1.20 (SD 1.85)</td>
<td>0.87 (SD 1.32)</td>
<td>0.501</td>
</tr>
<tr>
<td>Emotional</td>
<td>2.07 (SD 2.90)</td>
<td>1.35 (SD 2.06)</td>
<td>0.357</td>
</tr>
<tr>
<td>BCVA, mean change (logMAR letters)</td>
<td>23 (SD 7.8)</td>
<td>6 (SD 10.4)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>BCVA baseline</td>
<td>48 (SD 15)</td>
<td>60 (SD 9)</td>
<td>0.01</td>
</tr>
<tr>
<td>BCVA 24 mo</td>
<td>71 (SD 15)</td>
<td>66 (SD 14)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Significant P values in bold.
correlation was only observed in the group who gained greater than 15 letters. This, together with findings of Okamoto and colleagues, suggests that changes in other aspects of visual function such as contrast sensitivity, reading speed, or central visual fields could be driving the VRQoL improvements seen in patients in our study who gained less than or equal to 15 letters, and future studies assessing the impact of VRQoL in DME patients should include these relevant clinical measurements, in addition to BCVA.

Our finding that VRQoL improvements were similar for both bevacizumab and DEX implant treatment was surprising considering the differing treatment regimen and side-effect profiles of the two treatments. Although the frequency of bevacizumab treatments given during the study decreased from an average of nine injections over the first 12 months to four during the second 12 months, substantially fewer DEX implant treatments were required overall (an average of 2–3 and 2 injections in first and second years, respectively). This suggests that number of injections may not be a contributing factor to patients’ VRQoL or, alternatively, that our IVI instrument did not have the sensitivity to detect treatment-related burden such as inconvenience, and so on. Our sample size comparing these two groups was very small and we may not have had the power to detect a difference between the two treatment groups. Future studies in larger sample sizes with additional patient-reported outcome measures are required to answer this question definitively.

There was also a trend for worse VA results for all phakic eyes in the main study treated with DEX implants, most likely related to the known side effect of development and progression of cataract. However, no significant difference in improvement in VRQoL was found between treatments in our subgroup (n = 13) of phakic eyes, although comparison was problematic due to the small sample size. Both these results, if replicated in future larger samples, may suggest that DEX implant should be a second, rather than a first line treatment for DME in patients with phakic eyes.

Our study is the first to report on VRQoL changes in patients with DME treated with DEX implant and/or bevacizumab over a 24-month randomized clinical trial. Previous studies in either of these treatments used in DME, and reporting VRQoL, have been of 3 or 12 months duration only. A major strength of our study is the use of the Rasch-validated IVI questionnaire and the fact that we conducted Rasch analysis anew on our study sample. The use of interval level person measures in our parametric testing is likely to have increased measurement precision, thus increasing the likelihood of detecting a change over time. Another strength is that the scale did not have the sensitivity to detect treatment-related burden such as inconvenience, and so on. Our sample size comparing these two groups was very small and we may not have had the power to detect a difference between the two treatment groups. Future studies in larger sample sizes with additional patient-reported outcome measures are required to answer this question definitively.

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Limitations include the small sample size, precluding subgroup, and multivariate regression analysis, which could have revealed confounding factors influencing our results. Also, the mobility scale had some psychometric issues including suboptimal precision and targeting of items to our patient group. Lack of precision is problematic because it suggests that the scale did not have discriminatory ability and therefore the results on mobility must be interpreted with some caution. Another limitation of our study is that we did not include the commonly used NEI-VFQ questionnaire, which makes our results difficult to compare with other, similar studies. However, given that the NEI-VFQ has been found to function best with just two subscales, socioemotional and visual functioning, it would still be difficult compare such results with studies reporting all 12 subscales.

### Table 3. Change in IVI Scores in Patients With Single Eye Enrolled (n = 19)

<table>
<thead>
<tr>
<th>IVI Mean Change</th>
<th>DEX Implant</th>
<th>Bevacizumab</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline to 24 mo</td>
<td>n = 9/19</td>
<td>n = 10/19</td>
<td></td>
</tr>
<tr>
<td>Reading</td>
<td>1.41 (SD 2.09)</td>
<td>1.48 (SD 1.72)</td>
<td>0.96</td>
</tr>
<tr>
<td>Mobility</td>
<td>1.18 (SD 1.88)</td>
<td>1.06 (SD 0.95)</td>
<td>0.87</td>
</tr>
<tr>
<td>Emotional</td>
<td>2.11 (SD 2.55)</td>
<td>0.95 (SD 2.77)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

* Difference in baseline IVI and IVI change between treatment groups.

was no significant difference between average VA changes in the study eye in this small patient subgroup between the two treatments, namely a 2.4 letter gain (SD 21.67) in the DEX implant group, and a 9.3 (SD 7.06) gain in the bevacizumab group, respectively (P = 0.36). The VRQoL improvement was similar in both treatment groups (Table 3).

We also compared IVI scores of patients in the single eye enrolled group whose eyes were phakic (i.e., eyes with natural lens) at baseline (13/19). Of the 13 eyes, 5 were treated with DEX implant, and 8 with bevacizumab. We found no significant difference in reading or emotional well-being scores between the two treatments. However, there was a trend for greater mobility improvement in bevacizumab-treated patients, compared with DEX implant patients (0.96 and 0.02 logits, respectively, P = 0.072; Table 4).

### DISCUSSION

Using Rasch-transformed data from the IVI questionnaire, our findings suggest that treatment of DME with both bevacizumab and DEX implants results in substantial and similar improvements in VRQoL.

The study by Ramu and colleagues, who compared fixed versus PRN dosing schedule for DEX implant in refractory DME, reported similar increase in the NEI-VFQ-25 composite score, as well the two other questionnaires used in the study corresponding to similar VA outcomes for both regiments. Okamoto and colleagues found that patients in an observational study, who received a single bevacizumab injection for persistent post vitrectomy DME, had a transient, but significant increase of 13% in the mental health domain of the 25-item NEI-VQI, and this correlated with improved letter contrast sensitivity, rather than BCVA which did not improve.

Previous large clinical trials have reported improved VRQoL in patients following other anti-VEGF treatment (such as ranibizumab) compared with laser or sham in DME. However, in these studies improvements were not consistent across all NEI-VFQ subscales and were predominantly related to visual functioning. This contrasts with our study, where we found significant improvements across all three VRQoL domains, including emotional well-being.

In our study, the relationship between change in BCVA and change in VRQoL was not linear, as a strong positive

### Table 4. Change in IVI Scores in Patients With Single Eye Enrolled and Phakic at Baseline (n = 13)

<table>
<thead>
<tr>
<th>IVI Mean Change</th>
<th>DEX Implant</th>
<th>Bevacizumab</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline to 24 mo</td>
<td>n = 5/13</td>
<td>n = 8/13</td>
<td></td>
</tr>
<tr>
<td>Reading</td>
<td>0.53 (SD 1.07)</td>
<td>1.08 (SD 1.73)</td>
<td>0.54</td>
</tr>
<tr>
<td>Mobility</td>
<td>0.02 (SD 0.57)</td>
<td>0.96 (SD 0.94)</td>
<td>0.072</td>
</tr>
<tr>
<td>Emotional</td>
<td>1.13 (SD 1.59)</td>
<td>0.81 (SD 3.02)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

P value, difference in baseline IVI and IVI change between treatment groups.
**Conclusions**

We have shown that both DEX implant and bevacizumab treatment result in significant and similar improvements in VRQoL in patients with DME over a 24-month period.

**Acknowledgments**

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**References**


