Visual Function Response to Ocriplasmin for the Treatment of Vitreomacular Traction and Macular Hole: The OASIS Study

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PURPOSE. To assess the effect of ocriplasmin on visual function response (VFR) measured using visual acuity (VA) and vision-related quality of life, and to quantify the association between release of vitreomacular adhesion (VMA) at day 28 and VFR.

METHODS. Prespecified analysis of secondary endpoints from a randomized controlled trial. Of 220 participants with symptomatic VMA/vitreomacular traction (VMT), including VMT associated with a macular hole up to 400 μm, 146 received a single intravitreal injection of 125 μg ocriplasmin and 74 a sham injection. Based on principal components analysis results, a VFR was defined as either a VA improvement of ≥2 lines or an improvement exceeding the minimal clinically important difference (MCID) in the composite or the mental health subscale scores of the Visual Function Questionnaire (VFQ-25). The MCID was estimated using the standard error of measurement approach. The main outcome measure was the VFR at month 6, with further assessments at months 12 and 24.

RESULTS. The MCID was estimated at 3.71 points for the VFQ-25 composite score and 10.71 for the VFQ-25 mental health subscale score. A VFR occurred in 51.0% of ocriplasmin versus 23.3% of sham participants (P = 0.0001). The VFR was maintained through months 12 and 24: 53.1% and 50.3% in ocriplasmin versus 21.9% and 20.5% in sham participants, respectively (P < 0.0001). Resolution of VMA at day 28 significantly increased the odds of a VFR at each assessment period.

CONCLUSIONS. Treatment with ocriplasmin compared with sham resulted in a significant improvement in VFR. The 6-month treatment effect was sustained at months 12 and 24.

Keywords: macular hole, minimal clinically important difference, ocriplasmin, principal components analysis, patient-reported outcomes, sham, symptomatic vitreomacular adhesion/vitreomacular traction, VFQ-25
Visual Function Response to Ocriplasmin in OASIS Study

Benefit over placebo.17 Ocriplasmin produced a clinically meaningful visual function improvement in the composite score of the National Eye Institute Visual Function Questionnaire (VFQ-25) exceeding the minimal clinically important difference (MCID), estimated on a principal components analysis (PCA), a technique to reduce the dimensionality of multivariate data while preserving as much of the relevant information as possible.24 VFR was defined as either a VA improvement of ≥2 lines; an improvement in the composite score of the National Eye Institute Visual Function Questionnaire (VFQ-25) exceeding the minimal clinically important difference (MCID), estimated using the standard error of measurement approach; or an improvement in the VFQ-25 driving subscale score exceeding the MCID. Using this established methodology, we showed that ocriplasmin produced a clinically meaningful visual function benefit over placebo.17

The OASIS study presents the opportunity to repeat our previous analysis in a study group that is more generalizable to current care, as OASIS excluded eyes with ERM and there was a sham rather than placebo-injection control. The OASIS study also has longer follow-up than MIVI-TRUST. We aimed to test the hypothesis that ocriplasmin is more likely to produce a VFR than sham, and that short-term VMA release is associated with longer-term visual function benefit. We tested our hypotheses using a prespecified analysis of visual function data obtained during the OASIS study, looking specifically at VA and the VFQ-25.

METHODS

Participants

We analyzed data from the previously reported OASIS trial.12 Briefly, OASIS was a phase 3b, randomized, sham-controlled, double-masked, multicenter clinical trial designed to provide longer-term outcomes on the efficacy and safety profile of ocriplasmin, with refined case selection based on the MIVI-TRUST subgroup analyses.10,11 OASIS enrolled 220 participants (146 ocriplasmin, 74 sham) across 25 US sites. All participants were diagnosed with ERM by the central reading center at baseline or not.

Missing data for BCVA were imputed using the last observation carried forward (LOCF). LOCF is an often-used technique in clinical trials to enable the use of all evidence. It does not generate biases in the randomized comparison whenever we can assume that the missingness is random.

VFR-25 scores were computed on observed individual items as per its scoring algorithm.15 The effect of treatment on VFR (in the overall study population and in subgroups defined by main analyses).}

Assessment of Visual Function and VFR Definition

BCVA was measured at each study visit using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart.25 Because metamorphopsia, micropsia, and other symptoms of VMA are not quantifiable on ETDRS charts, another measure was needed to evaluate changes in vision-related function.3 Therefore, in addition to BCVA assessments, participants were examined using a functional assessment of visual ability, the VFR-25.12 The VFR-25 is a validated instrument designed to examine the influence of eye conditions and interventions on a patient’s day-to-day functioning and well-being. The 25-item survey measures the patient’s subjective assessments of visual function, and has been widely used in ophthalmologic research.20,21 In OASIS, the survey was administered at baseline and months 6, 12, and 24. The current VFR analysis was protocol prespecified and explored the change in BCVA and VFQ-25 scores from baseline to months 6, 12, and 24.

Following methods described in our previous analysis, we conducted a responder analysis that classified each participant as having a VFR, or not.17 First, PCA was used to determine the variables that summarize the VFR-25 responses best in two dimensions.24 A PCA can reduce a multidimensional response into a restricted set of responses, called Principal Components (PCs), in an objective way while preserving as much of the overall variability in the multidimensional response as possible (see Supplementary Materials for details on PCA and its [dis]advantages). Second, for each of these variables, a threshold for meaningful response reflecting the MCID was required.28 For BCVA, the MCID was defined as a 2-line or larger change, which is believed to be a clinically important change in people with better VA.29,30 In the absence of a suitable anchor, a distribution-based metric, the standard error of measurement, was used for the VFR-25 scores.31 These thresholds were determined by the best method available as recommended by the Food and Drug Administration Guidance on Patient-Reported Outcomes.32

Main Analyses

The primary analysis estimated the effect of treatment (ocriplasmin versus sham) on the VFR measures at month 6 and was performed on all randomized participants, per the intent-to-treat principle. Additional analyses explored the following: (1) the effect of treatment on VFR at months 12 and 24; (2) the association between anatomic response (VMA release versus persisting VMA defined as VMA resolution at day 28 versus no VMA resolution at day 28, respectively) and VFR at the different time points; (3) the effect of treatment in subgroups of participants with VMA release versus persisting VMA (release of VMA did not consider whether or not a macular hole was present); and (4) the effect of treatment on VFR in subgroups defined by whether the participants had a macular hole at baseline or not.

Statistical Methods

Missing data for BCVA were imputed using the last observation carried forward (LOCF). LOCF is an often-used technique in clinical trials to enable the use of all evidence. It does not generate biases in the randomized comparison whenever we can assume that the missingness is random.

VFR-25 scores were computed on observed individual items as per its scoring algorithm.15 The effect of treatment on VFR (in the overall study population and in subgroups defined by...
anatomic response), and the associations between anatomic response and VFR were estimated through logistic regression models. The latter provided insight into correlations between the anatomic response and the different VFR measures and identified whether participants without anatomic response still obtained a functional benefit. Odds ratios (ORs) reported the measure of association between exposure (active treatment; anatomic response) and outcome (VFR). The proportion of participants with VFR by exposure group was provided as a summary statistic. The likelihood ratio test was used to test whether the ORs differed from 1. All tests were considered significant if \( P < 0.05 \). All analyses were carried out using SAS version 6.5 (SAS Institute Inc., Cary, NC, USA).

RESULTS
Baseline Demographics
Demographics and baseline ocular characteristics were comparable between treatment groups. Differences in assessment between investigator and CRC for the presence or absence of VMA, macular hole (including diameter), and ERM led to the enrollment of participants meeting exclusion criteria. Of 145 participants in the ocriplasmin group, 33.0% (48/145) required a vitrectomy by month 24, versus 43.0% (32/73) in the sham group. Overall, 74.0% (108/146) and 68.9% (51/74) of participants randomized to ocriplasmin and sham, respectively, completed the 2 years of follow-up. In the ocriplasmin and sham groups, respectively, mean BCVA scores were 62.4 ETDRS letters, the VFQ-25 composite scores (VFQ-CS) were 78.0 and 80.7 (for scores per VFQ-25 subscale, see Supplementary Table S1).

VFR Definition
According to the PCA, the variables that best summarized the VFQ-25 questionnaire information in two dimensions corresponded to the VFQ-CS and the VFQ-25 mental health subscale score (VFQ-MHS). The BCVA score showed weak correlations with those two variables and was therefore considered to provide complementary information. For the BCVA score, the well-established threshold of an improvement of \( \geq 2 \) VA lines (10 letters) was used to distinguish response from nonresponse. The MCID values obtained were 3.7 points for the VFQ-CS, and 10.7 points for the VFQ-MHS. A PPV was considered a rescue therapy, so participants who required a PPV were classified as a visual function nonresponder. Overall VFR was defined as an improvement exceeding the MCID threshold in any of the three principal traits of visual function identified from the PCA: BCVA, the VFQ-CS, or the VFQ-MHS.

Assessment of Treatment Effect
At month 6, 51.0% of ocriplasmin-treated participants had a VFR, in that they improved in at least one of the three visual function scores (VFQ-CS, VFQ-MHS, or BCVA score) versus 23.3% of sham-treated participants (OR 3.43, \( P = 0.0001 \), \( \chi^2 \) test) (Table 1).

VFR results assessed at months 12 and 24 were similar to the month 6 analysis (Fig. 1). Treatment with ocriplasmin versus sham showed a significant effect on VFR for the individual visual function scores VFQ-CS, VFQ-MHS, and BCVA, as well as for the composite overall VFR score (Supplementary Table S2.1). Sensitivity analyses, in which participants who underwent vitrectomy were not automatically classified as visual function nonresponders, gave similar results to the primary analysis for the overall VFR (Supplementary Table S2.2).

Association Assessment
Participants who achieved a pharmacological VMA resolution at day 28 showed significantly higher odds of overall VFR at each time point (Fig. 2). Details per individual visual function score over time are provided in Supplementary Table S3.

Subgroup Analyses
In the subgroup of participants with VMA release, no significant differences were observed between ocriplasmin and sham participants for any of the individual VFR scores, or the combined, overall VFR (Fig. 3). In the persisting VMA subgroup, a significantly higher proportion of responders was observed in the ocriplasmin compared with the sham participants for the overall VFR, VFQ-CS, and VFQ-MHS, but not BCVA score (details are provided in Supplementary Table S4).

In the subgroup of participants with no macular hole at baseline, a significant treatment effect on the overall VFR was found at month 6 (\( P < 0.0001 \)), but not for the subgroup with macular hole at baseline (\( P = 0.297 \)). Participants with no macular hole at baseline seem to benefit more from the active treatment. The overall treatment effect (across the total population) mainly comes from the subgroup with no macular hole (larger OR), and less from the subgroup with macular hole at baseline (Table 2).

DISCUSSION
The VFR analysis demonstrated that half of the ocriplasmin-treated participants had a VFR, compared with just under a quarter of those receiving sham (51.0% vs. 23.3%; OR 3.43; \( P = 0.0001 \)). This treatment effect was maintained up to month 24.
In addition, pharmacological VMA resolution at day 28 was significantly associated with higher VFR, out to 24 months. Finally, the treatment effect at month 6 was significant in the subgroup with no macular hole at baseline but not in the subgroup with macular hole at baseline.

These results are in line with those we obtained using similar methodology on the MIVI-TRUST dataset, although OASIS found a greater magnitude of difference between the ocriplasmin and control groups. For example, there was a 35.5% and 16.5% greater anatomic response compared with the control group, for OASIS and MIVI-TRUST, respectively.\(^9,12\) This is most likely due to the patient eligibility criteria and the absence of a volume effect from saline placebo injection used in MIVI-TRUST (OASIS used a sham injection). Similarly, a larger difference in VFR response was found in the current OASIS analysis (27.7% difference favoring ocriplasmin over sham) compared with the MIVI-TRUST study (20.9% difference favoring ocriplasmin over placebo).\(^1^7\)

From the output of the current PCA, the VFQ-25 mental health subscale was retained as the second trait of visual function. This contrasts with our MIVI-TRUST VFR report, whereby the driving subscale of the VFQ-25 was identified as important and complementary information of visual function in symptomatic VMA/VMT patients.\(^1^7\) This is not totally unexpected, because the OASIS study population differs somewhat from the MIVI-TRUST population in terms of eligible vision (BCVA of 20/32 or worse in study eye), exclusion criteria (e.g., presence of ERM), or the study setting (United States only). In addition, the proportion of participants with a
It could be expected that vitrectomy leads to VFR in some participants. This was explored in our sensitivity analysis in which participants who required a vitrectomy were not automatically classified as a failure in terms of their VFR. This sensitivity analysis confirmed higher VFR rates in both treatment groups (Supplementary Table S2.2). However, as the incidence of vitrectomy was higher for sham-treated compared with ocriplasmin-treated participants, the additional increase in VFR was larger in the sham group.

This analysis has several strengths. The randomized, double-masked design of the OASIS trial suggests that the observed differences may be causal and unbiased, the visual and functional outcomes were collected rigorously within a clinical trial, and the total sample size was sufficiently large to detect meaningful clinical differences for most measures. All SD-OCT assessments were determined by a masked CRC. Further, the analysis was protocol prespecified, and used a scientifically accepted method. The MCID for the VFQ-25 scores were established using a data-driven technique and were in line with published evidence.

Limitations of the analysis include the fact that subgroup analyses based on posttreatment variables, such as VMA resolution at day 28 postinjection, are descriptive, as each subgroup represents a selection of participants that may deviate from the randomized population, and may no longer be equally represented across the two arms of the trial. Also, in some subgroups, particularly those with released VMA, there were few sham-injected participants, so results must be interpreted cautiously.

This study focuses on the beneficial effects of ocriplasmin and observes VFR in the OASIS treatment arms as a whole. It does not consider the impact of any safety events on individuals. The decision to use ocriplasmin is based on a benefit-risk consideration, taking also the potential safety risks into account. Adverse events observed in the trial are detailed in the main OASIS report,12 and summarized in Supplementary Table S5. The three most commonly reported adverse events in the ocriplasmin group (study eye) were vitreous floaters, photopsia, and vision blurred. Retinal breaks (defined as retinal detachment and retinal tear) were more common in the...
control arm, most likely due to a higher rate of vitrectomy. Serious adverse events (study eye) were comparable between treatment groups; the most common serious adverse events were macular hole and retinal detachment. Other adverse events are reported in the OASIS study, and other reports in the literature, including outer photoreceptor dysfunction, enlargement of the basal diameter of macular holes, and electrophysiology changes.\textsuperscript{12,34,35} Our study considers adverse events only insofar as they influence the overall VFR.

PCA is a data reduction technique that simplifies complex datasets. It aims to reveal the internal structure of a high-dimensional dataspace in a way that best explains the variance (or information) in the data. The advantage of our PCA was that the PCs were determined using baseline data, in the form of the VFQ-25 values. As such, the key dimension or internal structure of visual functioning was established independent of treatment. A possible disadvantage of PCA is that its typical outputs (PCs) are rather abstract concepts and difficult to associate with a clinical reality. In the PCA of the OASIS dataset, we could replace the PCs by highly correlated original variables ("response measures") that are easier to understand from a clinical point of view. The alternative approach would entail an analysis of each of the questionnaire items separately, correctly adjusted for multiple comparisons.

In conclusion, this prespecified analysis suggests that ocriplasmin and VMA release are associated with visual benefit, and that a data-driven, composite patient-reported outcome may provide additional insight into the therapeutic effects of ocriplasmin.

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References


