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Assessment of Aflibercept Treatment Outcomes in Diabetic Macular Edema Using the Quick Contrast Sensitivity Function

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Josep Callizo [1], Marco Cattaneo [2], Petra Rossouw [1], Chrysoula Gabranni [1], Philipp Anders [3], Hanna Zuche [4], Nicolas Feltgen [1]

1. Department of Ophthalmology, Universitätsspital Basel, Basel, CHE 2. Department of Biostatistics, Institute of Molecular and Clinical Ophthalmology Basel, Basel, CHE 3. Department of Ophthalmology, Vista Klinik, Binningen, CHE 4. Department of Ophthalmology, AugenCentrum Zytglogge, Bern, CHE

Corresponding author: Josep Callizo, jo.callizo@googlemail.com

Abstract

Background: Diabetic macular edema (DME) is a leading cause of visual impairment among patients with diabetes. Aflibercept, a high-affinity vascular endothelial growth factor (VEGF) inhibitor, reduces macular edema and improves visual acuity. Best-corrected visual acuity (BCVA) primarily assesses high-contrast visual resolution, provides limited information about vision at lower contrast levels, and may therefore miss subtle functional changes in certain conditions. Contrast sensitivity, however, is crucial for daily tasks. The quick contrast sensitivity function (qCSF; Adaptive Sensory Technology, San Diego, CA, USA), a computer-based clinical tool, provides a more comprehensive evaluation of visual function and may therefore capture additional functional information. This exploratory pilot study investigated longitudinal changes in qCSF outcomes, compared with conventional visual acuity testing, during intravitreal aflibercept treatment in patients with DME.

Materials and methods: This prospective, observational, non-randomized longitudinal study included 21 eyes from 15 patients with clinically significant DME. With a median of 18 prior anti-VEGF injections, participants received further aflibercept (Eylea®, 2 mg) injections and were followed for 26 weeks (visits at baseline and at four, 12, and 26 weeks). Visual function was assessed using BCVA with Early Treatment Diabetic Retinopathy Study charts, quick visual acuity (qVA), and qCSF, with the area under the logarithmic contrast sensitivity function (AULCSF) as the primary outcome and CSF acuity as a secondary outcome. Central subfield thickness (CST) on optical coherence tomography and National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) scores were also recorded. Statistical analyses were exploratory and used linear mixed-effects models accounting for repeated measurements and inter-eye correlation.

Results: Median BCVA improved from 80 to 82 letters (+0.74 letters per injection, 95% CI 0.03 to 1.45, $p = 0.045$). The qVA threshold showed no significant change. Median AULCSF increased by 0.12 log units after the first injection, but this was not statistically significant ($p = 0.12$), and no significant change was detected at 26 weeks. The reduction in CST correlated significantly with improvements in BCVA ($p = 0.002$), qVA threshold ($p = 0.011$), and AULCSF ($p = 0.001$). NEI-VFQ-25 scores were associated with functional outcomes (BCVA: $p = 0.006$; CSF acuity: $p = 0.027$).

Conclusions: In this small exploratory pilot study, qCSF showed a numerically larger early change than BCVA after aflibercept injection; however, this difference was not statistically significant, was not formally compared, and was not sustained at 26 weeks. The findings are hypothesis-generating and do not establish that qCSF is more sensitive than BCVA; qCSF appears promising as a complementary functional measure, but larger controlled studies are needed.

Categories: Ophthalmology
Keywords: aflibercept, best-corrected visual acuity, contrast sensitivity, diabetic macular edema, qcsf, quick contrast sensitivity function

Introduction

In 2019, 463 million people had diabetes mellitus, a number projected to exceed 700 million by 2045 [1]. Similarly, the estimated global prevalence of diabetic retinopathy (DR) was 103.12 million and that of diabetic macular edema (DME) was 18.83 million, projected to rise to 160.50 million and 28.61 million, respectively, by 2045 [2]. DME represents the most common vision-threatening complication in patients with diabetes, significantly contributing to the growing burden on healthcare systems worldwide [3].

Anti-vascular endothelial growth factor (VEGF) drugs, which are first-line treatments for DME, improve vision and slow DR progression [4]. Unlike other drugs, aflibercept binds VEGF-A, VEGF-B, and placental growth factor (PlGF) [5]. In the VISTA trial, aflibercept increased vision by +12.5 Early Treatment Diabetic

Retinopathy Study (ETDRS) letters at 52 weeks, compared to +0.2 with focal laser [6]. The study also highlighted the efficacy of aflibercept in patients previously treated with anti-VEGF agents, and demonstrated that an eight-week injection interval after five monthly doses was as effective as monthly injections.

Visual acuity (VA), commonly measured with ETDRS logMAR charts, is widely used in routine clinical practice and often serves as a primary endpoint in DME trials [7]. However, best-corrected VA (BCVA) mainly evaluates high-contrast spatial resolution. It provides limited insight into lower-contrast image perception and may therefore fail to capture visual changes associated with certain conditions [8,9].

Optical coherence tomography (OCT) retinal thickness measurements offer anatomical data but are not recognized by the US Food and Drug Administration as a surrogate endpoint because they lack a direct correlation with visual function. In a post hoc analysis of Protocol T, changes in central subfield thickness (CST) accounted for only a small part of BCVA variation, suggesting that CST is not a reliable surrogate for BCVA in trials or routine patient care [10].

Therefore, there is a clear need for improved metrics to assess visual performance. Contrast sensitivity (CS), which measures the ability to perceive outlines of small objects, is more comprehensive than BCVA because it reflects both spatial resolution and contrast perception [11]. CS is crucial for everyday tasks such as driving in dim light and recognizing faces [12]. Unlike BCVA, which captures a single point at the highest spatial frequency and contrast, the contrast sensitivity function (CSF) covers a range of spatial frequencies [13]. Although CSF better characterizes visual performance than BCVA, its clinical use is limited because accurate measurement is time-consuming and can take up to 60 minutes [14]. Consequently, CSF is rarely assessed in routine clinical practice.

The quick CSF (qCSF; Adaptive Sensory Technology, San Diego, CA, USA), introduced by Lesmes et al. in 2010, is a precise and time-efficient clinical tool [15]. This computer-based method employs active learning and Bayesian inference to determine VA. The system yields accurate results within 4 to 10 minutes, typically over 20-25 test rounds. qCSF may therefore offer a faster and more comprehensive assessment of contrast sensitivity than conventional methods. Studies indicate that qCSF can detect early DR when BCVA does not, underscoring its value as a sensitive indicator of visual performance [16].

This exploratory pilot study aimed to describe longitudinal changes in visual function, measured with qCSF and conventional VA tests, during intravitreal aflibercept treatment in patients with significant DME. It was not designed to establish treatment efficacy or to formally test whether qCSF is superior to BCVA. The primary objective was to describe the change in the area under the logarithmic CSF (AULCSF) from baseline to week 4 (after the first injection) and to week 26. Secondary objectives were to describe the changes in CSF acuity, BCVA, and quick VA (qVA) threshold at weeks 4, 12, and 26, to explore their relationship with CST, and to explore their relationship with patient-reported visual function, assessed with the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) [17]. We hypothesized, as an exploratory proposition, that qCSF might detect early treatment-related functional changes that are not reflected by BCVA. Because most eyes had already received extensive anti-VEGF treatment, a clinically relevant further improvement in function was not expected; the aim was therefore to explore whether qCSF could capture subtle functional changes in such eyes, not to prove functional improvement.

Materials And Methods

This prospective, observational, non-randomized longitudinal study was conducted in the Department of Ophthalmology, University Hospital Basel, Switzerland. Patients were enrolled between December 2021 and October 2023, and the last follow-up visit took place in April 2024. Eligible patients were recruited consecutively from the medical retina outpatient clinic. The cohort included 21 eyes from 15 individuals (both eyes were included in six patients when both eyes met the eligibility criteria) with clinically significant DME on OCT. The study was designed as exploratory, and no formal sample size calculation was performed. All participants had type 1 or 2 diabetes. The study followed the Declaration of Helsinki, Good Clinical Practice, the Human Research Act, and the Human Research Ordinance, and was approved by the Northwest Switzerland Ethics Committee (approval number: 2021-01691).

Inclusion criteria were age >18 years, type 1 or 2 diabetes, vision loss due to DME involving the central 1 mm (no minimum CST was required for inclusion), BCVA 0.8 to 0.063 decimal (0.1-1.2 logMAR) in the study eye, and either treatment-naïve status or no anti-VEGF therapy for eight weeks before entry. Exclusion criteria included vision loss unrelated to DME, recent use of intraocular or periocular corticosteroids, refractive error >±6 diopters, active proliferative DR, recent intraocular surgery, retinal laser photocoagulation, history of glaucoma surgery or corneal transplant, recent or planned major surgery, age-related macular degeneration, retinal vein occlusion, inability to consent or complete tests, other neurologic or systemic diseases, and pregnancy or lactation.

The primary outcome was the change in AULCSF from baseline (visit 1) to week 4 (visit 2) and to week 26 (visit 4). Secondary outcomes were the changes in CSF acuity, BCVA, qVA threshold, and CST at weeks 4, 12,

and 26 (visits 2, 3, and 4) and the association of these measures with the NEI-VFQ-25 score.

After baseline, all enrolled patients received a single intravitreal aflibercept (Eylea®, 2 mg) injection in the study eye(s). Reinjection decisions and injection intervals were individualized by the treating physician based on DME activity, as assessed by OCT findings (for example, intraretinal or subretinal fluid and CST). qCSF results were not used for treatment decisions. Treatment after the first injection was therefore individualized and not standardized. Examiners and treating physicians were not masked, and there was no control group. The number of injections was defined as the cumulative number of aflibercept injections received from study initiation to the respective visit (0 at baseline). Patients were examined at four, 12, and 26 weeks regardless of the injection frequency. Each visit included BCVA with ETDRS charts, qVA, qCSF, spectral-domain OCT (SD-OCT; SPECTRALIS®, Heidelberg Engineering, Heidelberg, Germany) of the macula, slit-lamp biomicroscopy, and dilated fundus examination. Participants also completed the NEI-VFQ-25 at the first and last visit.

Demographic data collected from all participants at baseline included age, gender, ethnicity, and the number of previous anti-VEGF injections; the latter was not included as a covariate in the models because of the small sample size. BCVA was determined using conventional ETDRS logMAR charts from 4 meters with best-corrected refraction. qVA was tested as previously reported [18]. A computerized method (Adaptive Sensory Technology, San Diego, CA, USA) using an active learning algorithm determined the qVA threshold. Testing was monocular with Sloan letters at 3 m on a monitor with 95.4 cd/m² luminance. The qVA threshold was defined as the letter size correctly recognized in two of three presentations, equating to a 67% detection rate. Adaptive Bayesian inference incorporated information from each round into the next. The qCSF method (Adaptive Sensory Technology, San Diego, CA, USA), which employs an algorithm that adjusts letter size and contrast to determine optimal contrast-spatial frequency combinations, was used to assess contrast sensitivity [15]. The qCSF measures the AULCSF, representing all visible contrast-threshold-spatial frequency combinations. The CSF acuity value indicates the smallest visible full-contrast stimulus at the x-axis intersection with the CSF. All qVA and qCSF measurements were performed monocularly with best-corrected refraction by trained examiners according to the manufacturer's instructions, using the same device and testing room at every visit. Each test was performed once per visit; test-retest repeatability was not assessed in this study. CST was measured in micrometers (µm) using SD-OCT. CST was defined as the thickness of a 1 mm circular area centered on the fovea, as measured by the OCT software.

Statistical analysis

Categorical data are shown as absolute and relative frequencies. Numerical variables are described using the median and interquartile range (IQR; 25th to 75th percentile). Vision improvement from aflibercept injections, assessed by qVA and qCSF, is summarized with descriptive statistics. Linear mixed-effects models with random intercepts for patient and for eye nested within patient were used to account for the correlations arising from repeated measurements and from the inclusion of both eyes of the same patient. Each predictor was analyzed in a separate univariable model (outcome ~ fixed effect + random intercepts for patient and eye within patient); no covariates were included because of the small sample size. For the effect of aflibercept injections on visual metrics, the fixed effect was the cumulative number of injections across all four visits. To assess the effect of a single injection, the fixed effect was the first injection (visit 2 vs. visit 1). For correlations between anatomical (CST) and functional measures and patient-reported outcomes (NEI-VFQ-25), the respective anatomical or functional measure was the fixed effect. NEI-VFQ-25 scores were available only at baseline and week 26. The p-values were obtained from t-tests of the fixed effect using Satterthwaite's approximation for the degrees of freedom, and 95% confidence intervals (CIs) were calculated using the profile likelihood method. Standardized effect estimates were obtained from models fitted to standardized variables and are expressed as percentages (standardized regression coefficient × 100). Comparisons between treatment-naïve and previously treated eyes were purely descriptive. Analyses were performed in R using the lme4 and lmerTest packages (R Core Team, Vienna, Austria). Missing data were handled using available-case analysis; outcome data were available for 15 to 16 eyes at visit 2 and for 17 to 18 eyes at visit 3, compared with 20 to 21 eyes at visits 1 and 4. All analyses were exploratory, and p-values should be interpreted as hypothesis-generating. No adjustment for multiple testing was applied; for transparency, a conservative Bonferroni threshold for the 14 p-values reported would be $p < 0.0036$.

Results

A total of 21 eyes from 15 participants were included in the study; the median age was 62 years. Of these, 66.7% (n = 10) were male, and 93.3% (n = 14) were of Caucasian descent. Of the 15 participants, 5 had type 1 and 10 had type 2 diabetes. Slit-lamp biomicroscopy was unremarkable in most examinations. Fifteen eyes (71.4%) were pseudophakic. Isolated findings were an iris defect in one eye, mild posterior capsule opacification in four pseudophakic eyes, and a peripheral corneal opacification in one eye at visit 2 that was no longer present at visit 4. All eyes presented with non-proliferative DR. Baseline characteristics and follow-up data are summarized in Tables *1*-*2*, and the course of AULCSF, BCVA, and qVA threshold by number of injections is shown in Figure *1*. Except for two treatment-naïve eyes, all others had undergone a median of 18 anti-VEGF injections (IQR: 8, 28) before enrollment in the study. At baseline, the median BCVA was 80 letters, and the median CST was 285 µm.

Characteristic	Value
Age, years (median)	62
Sex (male)	66.70%
Number of eyes	21
Right eyes	52.40%
Pseudophakic eyes	71.40%
Anti-VEGF injections before study start (median, IQR)	18 (8-28)

TABLE 1: Baseline characteristics

Descriptive statistics only; no statistical tests were applied. IQR is reported as the 25th-75th percentiles.

VEGF: vascular endothelial growth factor, IQR: interquartile range

Metric (unit)	Visit 1 (baseline)	Visit 2 (4 weeks)	Visit 3 (12 weeks)	Visit 4 (26 weeks)
BCVA (letters)	80 (79 to 84)	82.5 (77.5 to 84.25)	82 (80 to 86.75)	82 (78 to 85)
qVA threshold (logMAR)	0.10 (0.04 to 0.23)	0.07 (-0.16 to 0.14)	0.01 (-0.30 to 0.11)	0.09 (-0.15 to 0.26)
VA range (lines)	3.65 (2.58 to 4.62)	5.90 (2.70 to 7.70)	3.90 (3.10 to 6.30)	4.50 (3.30 to 6.40)
CSF acuity (cpd)	15.6 (11.1 to 17.2)	18.7 (16.3 to 20.2)	18.5 (14.1 to 23.6)	16.0 (12.7 to 20.8)
AULCSF (log units)	0.84 (0.68 to 1.10)	0.96 (0.80 to 1.19)	1.04 (0.75 to 1.23)	0.86 (0.68 to 1.01)
CS at 1 cpd	1.12 (0.81 to 1.32)	1.05 (0.77 to 1.26)	1.29 (1.19 to 1.41)	1.16 (1.04 to 1.31)
CS at 1.5 cpd	1.14 (0.86 to 1.37)	1.17 (0.89 to 1.40)	1.29 (1.22 to 1.40)	1.18 (1.09 to 1.38)
CS at 3 cpd	1.12 (0.88 to 1.36)	1.18 (0.89 to 1.44)	1.33 (1.05 to 1.41)	1.17 (0.95 to 1.27)
CS at 6 cpd	0.87 (0.76 to 1.14)	0.98 (0.81 to 1.25)	1.06 (0.69 to 1.25)	0.90 (0.66 to 1.04)
CS at 12 cpd	0.33 (0.00 to 0.51)	0.47 (0.32 to 0.68)	0.59 (0.21 to 0.74)	0.25 (0.09 to 0.54)
CS at 18 cpd	0.00 (0.00 to 0.00)	0.04 (0.00 to 0.16)	0.04 (0.00 to 0.32)	0.00 (0.00 to 0.11)

TABLE 2: Functional median values per visit (BCVA, qVA, and qCSF)

Values are median (IQR, 25th to 75th percentile); descriptive statistics only; no statistical tests were applied.

BCVA: best-corrected visual acuity, qVA: quick visual acuity, AULCSF: area under the logarithmic contrast sensitivity function, CSF: contrast sensitivity function, CS: contrast sensitivity, cpd: cycles per degree, IQR: interquartile range

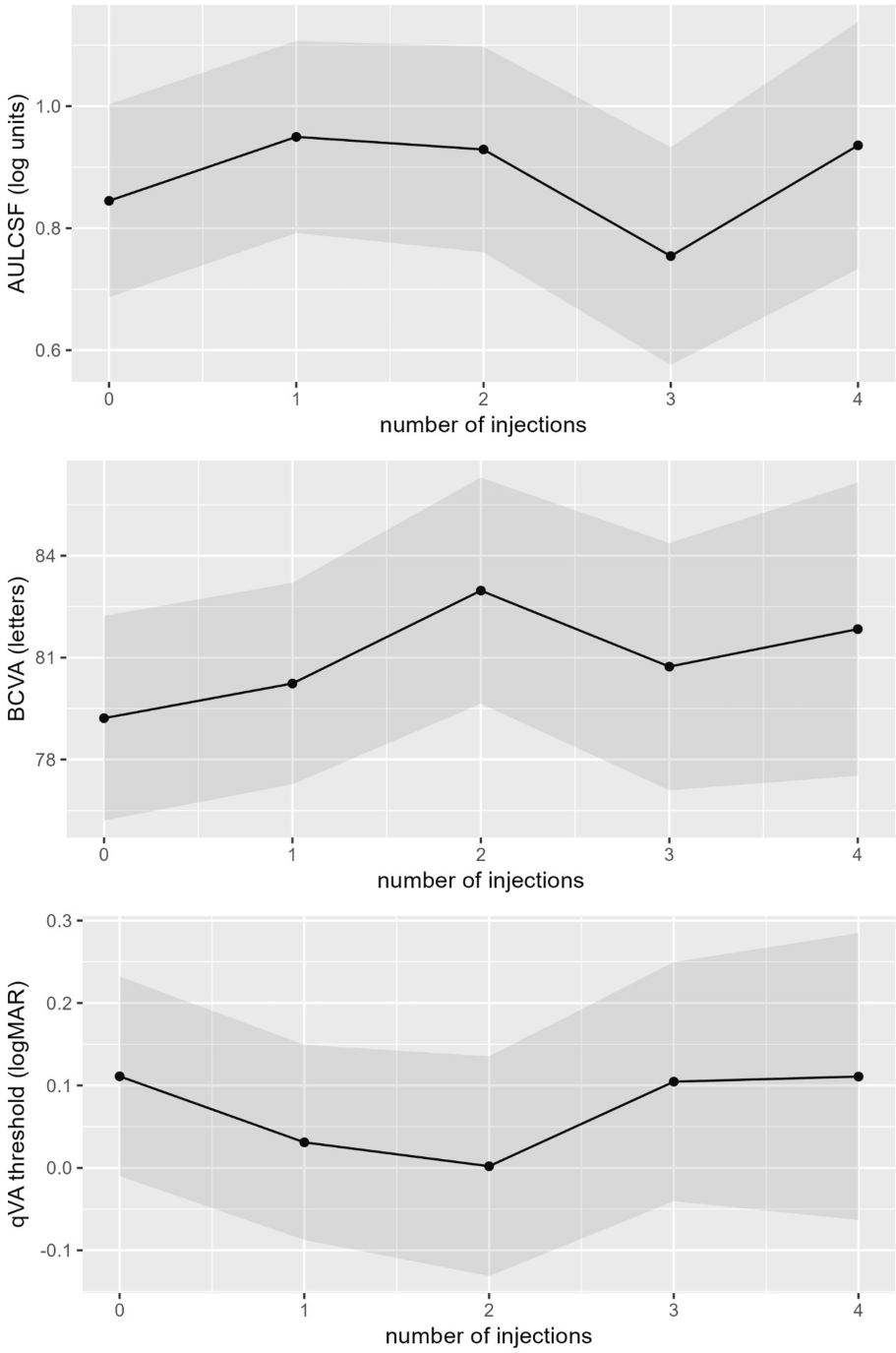


FIGURE 1: Evolution of measurements vs. number of injections during the study

Over the course of the study, 29% (n = 6) of eyes received one injection, 10% (n = 2) received two injections, 38% (n = 8) received three injections, and 24% (n = 5) received four injections.

Median BCVA improved from 80 to 82 letters during the study period. Although a linear mixed-effects model estimated +0.74 letters per injection (95% CI 0.03 to 1.45; p = 0.045), examination of the trajectory suggested a nonlinear improvement with an early rise and subsequent plateau, making a constant per-injection effect potentially misleading (Table *3*). The median qVA threshold decreased slightly (-0.01 logMAR), which was not statistically significant.

Metric	Change per injection	Test statistic (t-value)	p-value
BCVA (letters)	+0.74 (0.03 to 1.45)	2.05	0.045
AULCSF (log units)	+0.0004 (-0.0307 to 0.0318)	0.02	0.98
qVA threshold (logMAR)	-0.0045 (-0.0343 to 0.0251)	-0.30	0.77

TABLE 3: Effect of aflibercept injections on visual metrics

Summary of results from the univariable linear mixed-effects model analysis for the full 26-week study period.

BCVA: best-corrected visual acuity, AULCSF: area under the logarithmic contrast sensitivity function, qVA: quick visual acuity

Median CSF acuity increased by +3.1 cycles per degree (cpd), and median AULCSF increased by +0.12 log units after a single injection. However, this early change in AULCSF was not statistically significant (standardized estimate +11.9%, 95% CI -2.6% to +26.5%; p = 0.12), and no statistically significant improvement in AULCSF was detected by week 26. Following the first injection, the standardized effect estimate was numerically larger for AULCSF (11.9%) than for BCVA (3.6%) (Table *4*); the two estimates were not formally compared, and their CIs overlapped widely. When the two treatment-naïve eyes are compared with the previously treated eyes, the standardized effect estimate for visit 4 vs. visit 1 in AULCSF shows a marked difference between the groups (58.4% vs. 0.5%); this comparison is purely descriptive and based on two eyes.

Metric (fixed variable)	Standardized effect estimate	Test statistic (t-value)	p-value
AULCSF	+11.9% (-2.6% to + 26.5%)	1.65	0.12
qVA threshold	-10.6% (-33.0% to +11.3%)	-0.96	0.35
BCVA	+3.6% (-11.9% to +19.7%)	0.46	0.65

TABLE 4: Effect of a single aflibercept injection (visit 1 vs. visit 2)

Univariable linear mixed-effects models. Although AULCSF shows a larger effect, none of these values are statistically significant because of the small sample size.

AULCSF: area under the logarithmic contrast sensitivity function, qVA: quick visual acuity, BCVA: best-corrected visual acuity

In the univariable linear mixed-effects analysis, only BCVA showed a significant increase, with +0.74 letters per injection (95% CI 0.03 to 1.45; p = 0.045). AULCSF showed an increase of 0.0004 log units per injection that was not statistically significant (95% CI -0.0307 to 0.0318; p = 0.98).

The CST remained largely stable throughout the four visits, with a median of 285 µm at baseline (IQR: 253-308) and 269 µm at visit 4 (IQR: 248-293), corresponding to a median decrease of 16 µm over the six-month period. The overall effect of aflibercept on CST was not statistically significant (p = 0.43). However, reductions in CST were significantly correlated with improvements in BCVA (p = 0.002), qVA threshold (p = 0.011), and AULCSF (p = 0.001).

The median NEI-VFQ-25 score improved slightly, from 86.7 to 89.2. Moderate associations were observed with the qVA threshold (-0.44, p = 0.032) and BCVA (+0.44, p = 0.006) and a weaker association with CSF acuity (+0.39, p = 0.027). Higher CST was associated with lower NEI-VFQ-25 scores (-0.31, p = 0.0004) (Table *5*).

Predictor	Standardized effect estimate (95% CI)	Test statistic (t-value)	p-value
BCVA (letters)	0.44 (0.14 to 0.72)	3	0.006
qVA threshold (logMAR)	-0.44 (-0.82 to -0.05)	-2.28	0.032
CSF acuity (cpd)	0.39 (0.07 to 0.72)	2.35	0.027
CST (µm)	-0.31 (-0.45 to -0.17)	-4.33	0.0004

TABLE 5: Correlation between anatomical (CST) and functional measures with patient-reported outcomes (NEI-VFQ-25)

Univariable linear mixed-effects models. Standardized effect estimates of various measures on the NEI-VFQ-25 score.

BCVA: best-corrected visual acuity, qVA: quick visual acuity, CSF: contrast sensitivity function, cpd: cycles per degree, CST: central subfield thickness, CI: confidence interval, NEI-VFQ-25: National Eye Institute Visual Function Questionnaire-25

Discussion

This exploratory prospective observational study examined longitudinal changes in qCSF outcomes and conventional VA measures during aflibercept treatment in patients with DME. Our main results were as follows: (1) After the initial injection, the standardized effect estimate was numerically larger for AULCSF (11.9%) than for BCVA (3.6%), but neither was statistically significant, and the estimates were not formally compared; (2) The early numerical AULCSF gain was not maintained, and no significant AULCSF change was detected by week 26, whereas BCVA showed a small gain per injection (+0.74 letters, $p = 0.045$) that did not remain significant after conservative correction for multiple testing; (3) Changes in both BCVA and qCSF were significantly associated with anatomical improvement, as reflected by CST reduction, although the strength of these correlations was moderate; (4) NEI-VFQ-25 scores were associated with both BCVA and CSF acuity. Overall, these exploratory results are hypothesis-generating and do not allow the conclusion that qCSF is more sensitive than BCVA. The study evaluated longitudinal functional changes during aflibercept treatment and was not designed to establish treatment efficacy.

The modest BCVA improvement observed in our study (+2 letters over 26 weeks, +0.74 letters per injection) can be attributed to the cohort consisting mainly of previously treated eyes (median 18 prior injections) with relatively good baseline vision (median 80 letters). This reflects a population with chronic DME that may have already achieved near-maximal benefit from prior anti-VEGF therapy, leaving limited potential for further improvement.

Our results add to a growing body of work investigating qCSF in retinal disease and support its feasibility. Anders et al. [19] reported that qCSF identified functional impairments between early and intermediate stages of age-related macular degeneration that were not captured by Pelli-Robson testing [20] or conventional VA measures. Likewise, Joltikov et al. [16] found that qCSF could reveal early DR even when BCVA remained normal, underscoring its sensitivity to subclinical retinal dysfunction. Nonetheless, most prior studies have examined qCSF either cross-sectionally or in treatment-naïve cohorts. To our knowledge, longitudinal qCSF data during anti-VEGF treatment of DME are scarce; a previous longitudinal study using Pelli-Robson charts in eyes switched from ranibizumab to aflibercept reported small contrast sensitivity gains that accompanied anatomical improvement [21]. Our study adds longitudinal qCSF data in a DME population consisting predominantly of previously treated eyes, in which persistent changes were difficult to detect. In our cohort, only two eyes were treatment-naïve, and the increase in contrast sensitivity at the end of the study was substantially greater in these eyes than in the previously treated eyes (effect estimate 58.4% vs. 0.5%); this descriptive observation is based on two eyes only and is purely hypothesis-generating.

The moderate correlations between reductions in CST and improvements in both BCVA and qCSF are consistent with previous evidence that anatomical and functional outcomes in DME are related but not strongly linked. In a post hoc analysis of Protocol T, changes in CST accounted for only a small fraction of the variability in BCVA, leading to the conclusion that CST is an unreliable surrogate endpoint [10]. Our data extend these findings to qCSF, demonstrating that contrast sensitivity changes are also incompletely explained by anatomical changes, underscoring the importance of measuring visual function directly rather than relying on anatomical surrogates.

Our findings may have implications for the design of DME clinical trials. The numerically larger early effect estimate for AULCSF (11.9%) compared with BCVA (3.6%) is not conclusive, but the effect estimates reported here may help inform sample size calculations for future studies in which qCSF could be evaluated as an exploratory endpoint.

In routine clinical practice, one potential application may be monitoring patients with good BCVA, in whom ceiling effects limit the utility of acuity testing. In such patients, qCSF could detect subclinical functional deterioration warranting intensified monitoring or therapy, although this potential application remains to be demonstrated. Because contrast sensitivity is rarely assessed in clinics, qCSF may serve as a practical complementary test to BCVA, as it is faster and more comprehensive than conventional contrast sensitivity charts.

If confirmed in larger studies, differences in qCSF and BCVA sensitivity to early treatment may reflect distinct neurobiological mechanisms, though this remains speculative. BCVA primarily measures the foveal cone pathway and is relatively insensitive to mild retinal dysfunction. In contrast, contrast sensitivity is influenced by multiple retinal cell types, spatial summation, and lateral inhibition. DME disrupts retinal structure via fluid accumulation, photoreceptor displacement, and inflammatory mediators. Aflibercept blocks VEGF-A, VEGF-B, and PlGF, reducing vascular permeability and fluid, and it may rapidly restore retinal function. Early improvement of qCSF may therefore reflect quick intraretinal fluid resolution that improves contrast processing even when foveal cone function remains largely intact. Subsequent loss of these gains may result from recurrent fluid between injections, irreversible photoreceptor damage, or neural remodeling that impairs contrast sensitivity despite apparent anatomical improvement. Correlating longitudinal qCSF changes with OCT biomarkers such as ellipsoid zone integrity and disorganization of retinal inner layers may help clarify these mechanisms.

Strengths of this study are its prospective design with a predefined follow-up protocol, the use of a clinically feasible functional measure, and the combination of objective functional, anatomical, and patient-reported outcomes. This study should be interpreted in light of several important limitations. First, the sample size was small (21 eyes from 15 patients) and not based on a formal sample size calculation, resulting in limited statistical power and precision, as reflected by wide CIs; the study is best regarded as a pilot study. Second, the study population consisted predominantly of previously treated patients (only two treatment-naïve eyes), which may have introduced selection bias; these patients had good baseline VA, which may have limited the potential for detectable improvement and may not reflect treatment-naïve DME patients or those with poorer initial vision. Third, the observational nature of the study and the absence of a control group, combined with individualized injection intervals, resulted in heterogeneous treatment exposure, making longitudinal interpretation more challenging; because reinjections were administered at the treating physician's discretion, the treatment protocol was not standardized, the results are difficult to reproduce, and examiners were not masked. Changes over time may partly reflect natural fluctuation, regression to the mean, or learning effects with repeated testing rather than a treatment effect, and the per-injection estimates assume a linear effect although the trajectory appeared nonlinear. Fourth, the models were univariable; therefore, potential confounders such as age, diabetes duration, glycemic control, lens status, and the number and timing of previous injections could not be adjusted for. Although random effects accounted for inter-eye correlation, both eyes were included in six patients, and the number of independent clusters was small. Fifth, multiple outcomes were analyzed without adjustment for multiple testing, which increases the risk of false-positive findings; only the associations of CST with BCVA, AULCSF, and NEI-VFQ-25 remained significant under a conservative Bonferroni correction, and the other significant findings should be regarded as exploratory. Sixth, outcome data were incomplete at visits 2 and 3, and the test-retest repeatability of qCSF and qVA was not assessed in our cohort. Finally, the single-center setting may restrict the generalizability of the findings.

Conclusions

In this small, exploratory observational pilot study, qCSF showed a numerically larger early change than BCVA after aflibercept injection in DME. This difference was not statistically significant, was not formally compared, and was not sustained over the study period; the findings are therefore hypothesis-generating and do not establish that qCSF is more sensitive than BCVA. Both qCSF and BCVA were moderately associated with anatomical findings and patient-reported visual function, suggesting that they capture overlapping but not identical dimensions of visual function.

Larger controlled studies with prespecified endpoints, assessment of test-retest repeatability, and adjustment for confounders are needed. Until then, qCSF may be considered a complementary exploratory measure in DME research, particularly for early treatment effects and for patients with good baseline acuity, but it does not replace BCVA as the primary functional endpoint; the present data do not support replacing BCVA with qCSF.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Acquisition, analysis, or interpretation of data: Josep Callizo, Petra Rossouw, Marco Cattaneo, Chrysoula Gabranni, Philipp Anders, Hanna Zuche, Nicolas Feltgen

Drafting of the manuscript: Josep Callizo, Petra Rossouw, Nicolas Feltgen

Critical review of the manuscript for important intellectual content: Josep Callizo, Petra Rossouw, Marco Cattaneo, Chrysoula Gabranni, Philipp Anders, Hanna Zuche, Nicolas Feltgen

Concept and design: Petra Rossouw, Chrysoula Gabranni, Philipp Anders, Hanna Zuche

Disclosures

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