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Ellipsoid zone mapping and outer retinal characterization following intravitreal ocriplasmin

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Abstract

Purpose—To assess outer retinal architectural alterations following intravitreal ocriplasmin with a novel automated EZ mapping algorithm.

Methods—A single center retrospective consecutive case series of image analysis was performed. Quantitative assessment of EZ status imaged with spectral domain optical coherence tomography (SDOCT) was performed prior to and following single intravitreal injection of 0.125 mg ocriplasmin (Jetrea, Thrombogenics, Leuven, Belgium). A novel EZ mapping algorithm was utilized to assess the EZ-RPE central area, EZ-RPE macular volume, and *en face* EZ integrity based on percentage of sampling areas with 20 microns or greater EZ-RPE thickness. Longitudinal assessment of these changes with custom OCT reading software was completed. Clinical characteristics and outcomes were compared to these retinal changes.

Results—Nineteen eyes were included in this study. The retinal volume between EZ and retinal pigment epithelium was significantly reduced at 1 week following ocriplasmin ($P = 0.0036$). Seven of 19 (36.8%) patients complained of color abnormalities or brightness reduction after injection. All of these 7 cases had increased SRF following ocriplasmin and EZ attenuation. The EZ-RPE volume was reduced at 1 week ($P = 0.0036$), 1 month ($P = 0.015$) following ocriplasmin and restored by 3 months. The area with EZ-RPE thickness below 20 microns was increased at 1 week ($P = 0.046$) following ocriplasmin and recovered with time.

Conclusions—EZ mapping is feasible to assess EZ-RPE volume as well as overall EZ integrity with *en face* thickness mapping. EZ alterations occur in a significant proportion of eyes following ocriplasmin therapy. The EZ-RPE volume and the EZ-RPE central foveal area typically recover to baseline by 3 months. This effect appears to be panretinal and associated with subjective symptoms.

Keywords

ocriplasmin; spectral-domain optical coherence tomography; vitreomacular traction syndrome; ellipsoid zone change; ellipsoid zone mapping

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Introduction

Ocriplasmin (Jetrea, Thrombogenics, Leuven, Belgium) is the first FDA-approved pharmacologic alternative to surgical treatment for vitreomacular traction (VMT). The phase 3 pivotal clinical trials determined that a single intravitreal ocriplasmin 125 µg was superior to placebo for vitreomacular adhesion (VMA) release.¹ Additionally, the phase 3 trials found a similar safety profile of ocriplasmin and placebo after the first post-injection week.¹ Anti-VEGF intravitreal therapy has become the gold standard for conditions, such as neovascular age-related macular degeneration and diabetic macular edema.^{2,3} In general, the risks of major complications from intravitreal injections, such as endophthalmitis and retinal detachment, are considered to be lower than vitrectomy.

Various factors have been associated with increased efficacy for the use of ocriplasmin, including VMT adhesion length, presence of epiretinal membrane (ERM), presence of a macular hole, age, and lens status.^{1,4} In the phase 3 trials, several symptoms including photopsia, transient visual acuity (VA) loss, and dyschromatopsia were reported at higher rates during the first week after injection in the ocriplasmin group.¹ Recently, reports have surfaced that OCT-based alterations were identified in a substantial number of eyes (17–56% of the cases) following ocriplasmin therapy.^{5–8} These transient changes are particularly prominent in the ellipsoid zone (EZ). In addition, the accumulation of subretinal fluid (SRF) has also been described and appears to be closely linked to the changes in the ellipsoid zone.^{5,9} The phase 3 trials utilized time domain OCT, making detection of these changes difficult.

EZ integrity has been identified as an important factor for visual acuity in multiple vitreoretinal conditions. Several reports have described utilizing qualitative and/or quantitative retinal anatomical assessment by using single cross-sectional spectral domain OCT (SDOCT) images.^{10–13}

Panmacular assessment of these alterations remains challenging. Linear measurements of the EZ-retinal pigment epithelium (RPE) height have been described, but these focal measurements may not be an optimal representation of the retinal alterations, particularly in a diffuse process.⁹

The purpose of this study was to characterize and evaluate the outer retinal alterations that may occur following ocriplasmin utilizing a novel analysis tool for EZ mapping, volumetric EZ-RPE assessment and *en face* visualization.

Patients and Methods

This retrospective consecutive case series was approved by the Institutional Review Board of the Cleveland Clinic. Inclusion criteria included patients who received an ocriplasmin injection and SDOCT imaging immediately prior to injection and at least 1 week following intravitreal injection. Exclusion criteria included inability to perform SDOCT EZ mapping analysis due to poor quality and active concurrent macular disease (e.g., diabetic retinopathy, neovascular age-related macular degeneration) that could affect VA and retinal layer integrity.

All eyes received intravitreal injection ocriplasmin (125 µg in a 0.1 mL volume) as per manufacturer guidelines. Clinical variables collected included age, gender, stage of full thickness macular hole (if present), symptom duration, Snellen VA, and incidence of any ocular adverse events. The SDOCT examinations were performed with a Cirrus HD-OCT (Cirrus V.6.1 software, Carl Zeiss Meditec, Dublin, CA) and performed at baseline and at various post-injection time points (e.g., 1 week, 1 month, 3 months).

Automated EZ-RPE Analysis with EZ Mapping

For area and volumetric analysis, a custom software analysis program was developed for EZ-RPE mapping, macular hole, and SRF segmentation, as previously described.^{14, 15} Utilizing the macular cube, frame-by-frame B-scans were processed using automated segmentation and EZ mapping. Each scan was manually reviewed and corrected as needed for segmentation errors. Subretinal fluid was similarly identified and segmented using the automated algorithm.¹⁴ A three-dimensional surface representation of the SRF was generated and the SRF volume and area was calculated by the software. Numerous parameters were assessed with the EZ mapping tools, including the EZ-RPE volume and central EZ-RPE horizontal area. The EZ-RPE volume was defined as the volume between the EZ and RPE in the entire macular cube. The central EZ-RPE horizontal area was defined as the EZ-RPE on the central foveal B-scan. Additionally, utilizing the *en face* EZ map representative areas of normal (> 20 micron EZ-RPE thickness), attenuated (< 20 microns EZ-RPE thickness), and total EZ absence were calculated across the macular scan *en face* area.

To compare two groups, Mann-Whitney U tests were used with nonparametric distribution data. Spearman's rank correlation test was used to determine the correlation between the SRF accumulation and subjective symptoms, and EZ-RPE volume and subjective symptoms. The data were analyzed with Statcel software (3rd edition OMS, Tokyo, Japan). A p-value less than 0.05 was considered statistically significant.

Results

Clinical Overview

Nineteen eyes in 19 patients met the inclusion/exclusion criteria for the study. VMA release was noted in 9 of 19 eyes following intravitreal ocriplasmin.¹⁶ Representative case examples prior to and following intravitreal ocriplasmin are shown in Figure 1. The mean central subfield thickness prior to injection was 361.4 microns (range 144 - 988.5 microns) in those eyes without full-thickness macular hole. The mean central subfield thickness after the injection was 299.1 microns at 1 week, 271.5 microns at 1 month, and 180.5 microns at 3 months ($p = 0.048$ at 1 week, 0.030 at 1 month, 0.00041 at 3 months after injection compared to baseline).

EZ Mapping Volumetric and Area Analysis

Utilizing the EZ-mapping, analysis was performed in all eyes (Figure 2). The mean EZ-RPE volume before treatment was $1.21 \pm 0.15 \text{ mm}^3$ and the mean EZ-RPE central foveal area was $0.18 \pm 0.04 \text{ mm}^2$ (Figure 3A, 3B, respectively). One week and one month following

ocriplasmin, EZ-RPE volume was significantly reduced ($0.98 \pm 0.29 \text{ mm}^3$, $1.06 \pm 0.18 \text{ mm}^3$, $p = 0.0036$, $p = 0.015$, respectively). There was a trend towards decreased EZ-RPE central foveal area at one week and one month following ocriplasmin therapy ($0.14 \pm 0.059 \text{ mm}^2$, $0.16 \pm 0.042 \text{ mm}^2$, $p = 0.062$, 0.068 , respectively). Both EZ-RPE volume and EZ-RPE central foveal area recovered by 3 months after injection ($p = 0.29$, $p = 0.78$, respectively).

Comparative analysis was performed between those eyes with and without VMT release (Figure 3C, 3D). The EZ-RPE volume prior to ocriplasmin injection was similar in eyes that showed VMT release ($1.17 \pm 0.13 \text{ mm}^3$) and in eyes that did not experience VMT release ($1.24 \pm 0.16 \text{ mm}^3$, $p = 0.21$). The EZ-RPE volume at 1 week ($0.78 \pm 0.20 \text{ mm}^3$) and 1 month ($0.94 \pm 0.14 \text{ mm}^3$) was significantly decreased in eyes with VMT release compared to eyes that did not undergo VMT release ($1.14 \pm 0.23 \text{ mm}^3$, $P = 0.001$ at 1 week, $1.17 \pm 0.17 \text{ mm}^3$, $P = 0.025$ at 1 month, respectively). EZ-RPE volume was similar between both groups at 3 months (1.08 ± 0.14 , 1.03 ± 0.55 , respectively, $P = 0.65$) following ocriplasmin. The EZ-RPE central foveal area prior to ocriplasmin injection was $0.18 \pm 0.031 \text{ mm}^2$ in eyes that showed VMT release after injection and $0.18 \pm 0.044 \text{ mm}^2$ in eyes that did not experience VMT release ($P = 0.27$). The EZ-RPE central foveal area cases which showed VMT release was decreased significantly at 1 week following ocriplasmin compared to baseline ($0.11 \pm 0.043 \text{ mm}^2$, $P = 0.0087$) and trended towards a significant reduction when compared to the cases without VMT release ($0.17 \pm 0.058 \text{ mm}^2$, $P = 0.076$). The decrease of EZ-RPE central foveal area recovered at 1 month following ocriplasmin ($0.15 \pm 0.031 \text{ mm}^2$, $0.16 \pm 0.050 \text{ mm}^2$, respectively, $P = 0.95$).

The EZ-RPE volume and EZ-RPE central foveal area were also analyzed in the context of SRF accumulation (Figure 3E, 3F). Of the cases with SRF accumulation, both the EZ-RPE volume and the EZ-RPE central foveal area were significantly decreased at 1 week ($0.76 \pm 0.17 \text{ mm}^3$, $0.10 \pm 0.030 \text{ mm}^2$, $P = 0.0013$, 0.0031 , respectively) following ocriplasmin when compared to cases without SRF accumulation ($1.19 \pm 0.20 \text{ mm}^3$, $0.19 \pm 0.049 \text{ mm}^2$). At 1 month after ocriplasmin, the EZ-RPE volume was significantly decreased in eyes with SRF compared to cases without SRF accumulation ($P = 0.025$) but the EZ-RPE central foveal area was not ($P = 0.14$). Both the EZ-RPE volume and the EZ-RPE central foveal area recovered to baseline at 3 months.

EZ Mapping En Face Analysis

The *en face* area of which EZ-RPE thickness of < 20 microns before ocriplasmin was in $10.4 \pm 9.4 \%$ of sampled size. This significantly increased 1 week ($33.0 \pm 27.0 \%$) after ocriplasmin (Figure 4, $P = 0.0038$). This improved over time ($13.9 \pm 10.0 \%$ at 1 month, $13.7 \pm 9.1 \%$ at 3 months, respectively). Comparative analysis was performed between those eyes with and without VMT release. Prior to ocriplasmin injection, the percent sampled area of EZ-RPE thickness that was < 20 microns $9.5 \pm 7.9 \%$ in sampled size in eyes that showed VMT release after injection and 11.0 ± 10.4 in eyes that did not experience VMT release ($p = 0.79$). One week following injection, the percentage of area of EZ-RPE thickness of < 20 microns was significantly increased in eyes that underwent VMT release ($50.0 \pm 28.8 \%$) compared to cases with did not show VMT release (19.4 ± 10.4 , $P = 0.041$). By one month there was no difference between the 2 groups.

The area of EZ-RPE thickness of < 20 microns in sampled area was also analyzed in the context of SRF accumulation. Of the cases with SRF accumulation, the area EZ-RPE thickness of < 20 microns in sampled area significantly increased at 1 week and 1 month ($52.8 \pm 23.8\%$, $20.0 \pm 6.7\%$ $P = 0.0012$, 0.025 , respectively) following ocriplasmin when compared to cases without SRF accumulation ($13.2 \pm 10.7\%$, $7.8 \pm 9.0\%$). At baseline and 3-month after ocriplasmin, the EZ-RPE thickness of < 20 micron was not significantly different when compared to the cases without SRF accumulation ($P = 0.63$, $P = 0.99$, respectively).

Visual function recovery and OCT features

Decreased VA at 1 week after the injection was significantly associated with the increased volume of SRF ($p = 0.015$, F value = 7.4) but not at 1 month ($p = 0.74$, F value = 0.12). The correlation between self-reported ocular adverse events following ocriplasmin injection and occurrence of increased SRF was analyzed. The major self-reported ocular adverse events were color abnormalities or reduction of brightness ($n = 7$), photopsia ($n = 6$) and subjective visual acuity decrease or blurred vision ($n = 12$). All 7 cases had subjective symptoms of color abnormalities or reduction of brightness after intravitreal ocriplasmin injection had increased SRF following intravitreal ocriplasmin. There were no reports of these symptoms in patients without SRF accumulation. The occurrence of SRF accumulation correlated to subjective color abnormalities and/or brightness reduction ($p = 0.0024$, Fisher's exact test).

The correlation between EZ volume or EZ central foveal area and incidence of these adverse events was evaluated. Low EZ volume and small EZ central foveal area at 1 week following ocriplasmin was significantly correlated with photopsias ($r = 0.59$, $P = 0.016$, $r = 0.63$, $p = 0.009$, respectively), color abnormalities, and reduction in perceived brightness ($r = 0.52$, $P = 0.031$, $r = 0.33$, $P = 0.011$, respectively).

Discussion

Ocriplasmin represents a novel therapeutic for pharmacologic vitreolysis in eyes with symptomatic vitreomacular traction. Early reports suggest that careful patient selection may result in higher rates of clinical efficacy than reported in the phase III studies.¹ Alterations in vision and changes in retinal structure (e.g., photoreceptor layer, SRF accumulation) have been reported following ocriplasmin injection. Freund et al first reported a case of VMT treated with intravitreal ocriplasmin injection with subsequent marked loss of the EZ with resolution of the VMT.⁶ These changes were also transient and showed a marked improvement in the integrity of EZ four weeks after the injection.

In this report, we utilized a novel EZ mapping tool to evaluate the volumetric and area alterations to the EZ-RPE relationship in eyes undergoing ocriplasmin injection. Eyes that exhibited VMT release and SRF accumulation showed dramatic EZ-RPE area and volume reduction that recovered with time. Our group has previously reported that the disruption of the EZ after ocriplasmin injection appears to be linked to therapeutic response.⁵ Linear evaluation of outer retinal thickness, especially EZ-RPE height after intravitreal ocriplasmin has been reported. Similar to this study, the reduction of EZ-RPE height was particularly prominent 1 week after the injection and recovered with time.⁹

Animal model studies have identified transient reductions in the a- and b-waves of the electroretinogram (ERG) after ocriplasmin injection to rabbit eyes.¹⁷ Amplitudes of a- and b-wave were decreased 2 days after ocriplasmin injection in eyes receiving 25, 125 and 250 µg of and the amplitudes recovered in the eyes receiving 25 and 125 µg at 14 days after injection. Animals that received 250 µg exhibited persistent ERG changes even 90 days after injection. In early human studies, de Smet et al reported that ERG changes appeared transient following ocriplasmin injection.¹⁸ These changes were consistent with random variations and no clinically significant abnormalities were noted 1-month following the injection. However, subsequent publications have described persistent ERG changes lasting from 4–15 months.^{19, 20}

Ocriplasmin is an enzyme with activity against fibronectin and laminin, two major constituents of the vitreoretinal interface. However, both fibronectin and laminin are panretinal proteins that are present at the RPE, photoreceptor, and Bruch's membrane layers.²¹ In animal models, laminin and fibronectin degradation has been identified in the photoreceptor layer. The quantitative assessment and decrease in EZ-RPE height suggests potential significant loss of the outer segment discs and that these discs slowly regenerate the baseline length of the outer segment over 1–3 months. The strong link between EZ loss and SRF suggests that potentially the dissolution of the outer segments could be the etiology of the SRF.

In our case series, EZ mapping showed the significant changes after ocriplasmin injection. Both of EZ-RPE central foveal area and EZ-RPE volume were significantly decreased after ocriplasmin in eyes with therapeutic response and gradually recovered with time. In addition, the EZ-RPE central foveal area significantly correlated to visual acuity before and 1 week after ocriplasmin.

As with any retrospective analysis, the limitations of this study must be considered. Although to our knowledge, this represents the first volumetric and *en face* assessment of the retinal alterations associated with ocriplasmin therapy, the study is small and the results should be considered preliminary. Further assessment and research is needed to better understand the underlying pathophysiology of these retinal changes and the potential implications for ocriplasmin therapy and ocular safety. The follow-up in this study is also relatively short-term and this study did not include electrophysiologic assessment. Although retinal alterations appeared to normalize at 3 months, the long-term implications are unclear. Long-term follow-up and assessment of retinal architecture changes are needed to better understand whether this normalization at 3 months is enduring or whether potential future degradation occurs. Finally, the cause of the outer retinal changes remains unknown and further animal studies and prospective human studies are required to determine the true nature of these changes.

In conclusion, transient attenuation of EZ-RPE retinal area/volume, and subretinal fluid accumulation following intravitreal ocriplasmin injection appear to be common findings. These changes appeared to be associated with VMT release, subretinal fluid accumulation, and post-injection visual symptoms. The structural impact of these changes appear to be transient, but the long-term consequences of these changes remain unclear. Further

investigation with longer prospective follow-up and larger sample numbers are needed to better delineate these effects and to assess the long-term functional and anatomic impact of these changes. Overall, the EZ mapping tool provided a unique and novel approach to evaluating outer retinal integrity and longitudinal alterations throughout the macula. This tool may be useful for evaluating additional retinal conditions, as well as providing a quantitative link between assessing visual function and status of the EZ in retinal pathologies.

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Summary statement

Transient ellipsoid zone alterations have been described following intravitreal ocriplasmin. Quantifying these alterations remains challenging. In this study, a novel technique of ellipsoid mapping demonstrates significant transient alterations in the ellipsoid zone that can be followed longitudinally and demonstrates that the process appears to be panmacular.

Figure 1. Case Examples Following Intravitreal Ocriplasmin

Case example 1 (A, B, C) demonstrates vitreomacular traction (VMT) release (arrow highlights posterior hyaloid) with accompanying significant attenuation of the ellipsoid zone (EZ, arrowhead) and concurrent accumulation of subretinal fluid (asterisk). Case example 2 (D, E, F) reveals persistent VMT (arrow) and no appreciable architectural alterations, including in the stability of the EZ and subretinal space.

Figure 2. Case Examples of Ellipsoid Zone Mapping Following Intravitreal Ocriplasmin
 Ellipsoid zone (EZ) mapping prior to (top) and 1-week following ocriplasmin (bottom) with
 EZ segmentation (A,B), 3D reconstruction (C,D), and *En face* mapping (E,F). *En face*
 mapping shows the subretinal fluid area enlargement (arrow) and mosaic-like thinning of the
 EZ.

Figure 3. Longitudinal Quantitative Comparison of Ellipsoid Zone Volume and Central Foveal Area with Comparison of Eyes with and without Vitreomacular Adhesion Release
 Quantitative comparison of ellipsoid zone -retinal pigment epithelium (EZ-RPE) volume (A, C, E) and EZ-RPE central foveal area (B, D, F). (A) Bar graph showing the reduction of the EZ-RPE volume at 1 week ($P = 0.0036$) and 1 month ($P = 0.015$) following ocriplasmin. (B) Bar graph showing the slight reduction of the EZ-RPE central foveal area at 1 week and 1 month following ocriplasmin. (C, D) Alterations in the EZ-RPE volume and central foveal area based on vitreomacular adhesion (VMA) status following ocriplasmin. VMA release group (dark gray) and VMA non-release group (light gray) are shown. (E, F) Alterations in the EZ-RPE volume and central foveal area based on presence of subretinal fluid following ocriplasmin. Subretinal fluid group (dark gray) and lack of subretinal fluid group (light gray)

are shown. * $P < 0.05$ versus baseline and # $P < 0.05$ comparing between each group at same period (Mann-Whitney U test). Error bars indicates the standard deviation.

Figure 4. Longitudinal Ellipsoid Zone Mapping

Longitudinal *en face* mapping of ellipsoid zone (EZ) following intravitreal ocriplasmin injection in a representative case which demonstrated vitreomacular traction (VMT) release (A, B, C, D) and a representative case which did not show VMT release (E, F, G, H). In the eye that experienced VMT release, a significant EZ change was noted at 1 week following ocriplasmin (B). The EZ change recovered with time (C, D). The case without VMT release does not show marked EZ change from baseline to 3 months after ocriplasmin (E, F, G, H).