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Retinal Layers Changes in Patients with Diabetic Macular Edema Treated with Intravitreal Anti-VEGF Agents: Long-Term Outcomes of a Spectral-Domain OCT Study

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Keywords
Diabetic macular edema · Anti-vascular endothelial growth factor · Optical coherence tomography · Retinal layers · Predictive factors · Visual outcome · HbA1c · Treatment response

Abstract
Purpose: The purpose of this study was to investigate retinal layers' changes in patients with diabetic macular edema (DME) treated with anti-vascular endothelial growth factor (anti-VEGF) agents and to evaluate if these changes may affect treatment response. ***Methods:*** Participants in this prospective study were 110 treatment-naïve patients with center involved DME, who were treated with anti-VEGF agents and followed up for at least 12 months. A qualitative and quantitative analysis of retinal layers that can affect visual acuity was performed. Patients with persistent DME were defined, and factors which could affect this outcome were determined. ***Results:*** Visual acuity was significantly improved, while there was also a statistically significant reduction in central retinal thickness and in all separate retinal layers' thickness at month 12 compared to baseline ($p < 0.001$). Visual acuity was associated with central retinal thickness and outer retinal layers' thickness;51.8% of the patients presented with persistent DME at month 12, which was found to be significantly associated with baseline visual acuity and HbA1C levels. ***Conclusions:*** Anti-VEGF treatment is effective in reducing retinal thickness as a whole and in all separate retinal layers at 12-month follow-up in patients with DME. Changes in central retinal thickness and in outer retinal layers were found to affect visual acuity. HbA1c was the most significant factor to determine persistence of DME at month 12.

Introduction

Diabetes mellitus (DM) is a global growing epidemic, affecting more than 400 million people worldwide, a number which is estimated to reach around 642 million by 2040 [1, 2]. Chronic complications of DM include macrovascular and microvascular complications, with diabetic retinopathy (DR) to be one of the most common of the latter [3]. Diabetic macular edema (DME) may occur at any stage of DR, affecting about 20% of patients with type 1 DM and 25% of those with type 2 DM during

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a 10-year follow-up [4, 5]. It is the main cause of vision loss in patients with DR, occurring as a result of blood-retinal-barrier breakdown due to chronic hyperglycemia, while vascular endothelial growth factor (VEGF) seems to play an essential role in the pathogenesis of DME [6]. Therefore, anti-VEGF agents have been considered the gold standard in the treatment of DME with large randomized clinical trials to show their efficacy and safety [7–9].

However, recent studies showed that a considerable proportion of patients do not respond satisfactorily to anti-VEGF agents, even with intensive treatment over the first year, and present with chronic DME [10, 11]. Specifically, a post hoc analysis of the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol I and Protocol T revealed that approximately 40% of patients with DME had persistent edema after 6 monthly ranibizumab injections, leading commonly to decreased visual acuity [11, 12]. As a result, early identification and characterization of specific patterns in patients with DME is crucial to predict treatment response and consider switching to other treatment alternatives, such as intravitreal steroids [13–17], providing individualized treatment.

Spectral-domain optical coherence tomography (SD-OCT) allows the detailed visualization of retinal layers [18]. Several OCT biomarkers have been described in previous studies to predict treatment response in patients with DME treated with either intravitreal anti-VEGF agents or intravitreal dexamethasone implant, such as ellipsoid zone (EZ) condition, disorganization of inner retinal layer (DRIL), hyperreflective foci (HF), subretinal fluid, or cysts [19–23]. Nevertheless, it should be mentioned that the assessment of these biomarkers was mainly qualitative and was performed retrospectively with short-term follow-up time in the majority of the studies so far.

Considering the above, the purpose of this study was to evaluate if qualitative and quantitative changes in retinal layers may affect treatment response in patients with DME treated with anti-VEGF agents. Additionally, this study aims to determine factors, which may define patients who do not respond to anti-VEGF treatment after 12 months of follow-up.

Methods

Participants in this prospective study were 110 treatment-naïve patients (110 eyes) with type 2 DM and center involved DME (CI-DME), who were treated with anti-VEGF agents at the Second Department of Ophthalmology, University of Athens, Athens, Greece, from November 2015 to November 2018 and had at least 12 months of follow-up. Patients with age-related macular degeneration, retinal vein occlusion, other retinal diseases except for DME, vitreomacular interface disorders, intraocular inflammation, cornea disorders, media opacities, uncontrolled glaucoma, myopia >6D, previous trauma, and intraocular surgery within the last 6 months were excluded from the study. The study was in accordance with the Tenets of Helsinki Declaration and was approved by the Institutional Review Board of our hospital.

Data related to demographic characteristics, DM duration, comorbidities (hypertension, hyperlipidemia), and HbA1c levels were recorded for all included patients. All participants underwent a complete ophthalmological examination at the time of DME diagnosis (baseline), including best corrected visual acuity (BCVA) measurement, slit-lamp biomicroscopy, dilated fundoscopy, SD-OCT, and fluorescein angiography using Spectralis (Spectralis HRA + OCT, Heidelberg Engineering, Germany).

For each patient, BCVA was converted to the logarithm of the minimum angle of resolution (logMAR) for statistical purposes. Regarding SD-OCT examination, 6 radial scans which were 3 mm long were performed at equally spaced angular orientations centered on the foveola. Additionally, the OCT volume scan was performed on a 20 × 20° cube, which consisted of 49 horizontal B-scans with 20 averaged frames per B-scan centered over the fovea. OCT scans were evaluated for central retinal thickness (CRT) measurement. In addition, we used the software Heidelberg Eye Explorer (version 6.013.0) to perform individual retinal layer segmentation, while the automated segmentation lines were examined by the graders for the verification of proper segmentation. Individual retinal layers were defined as follows: ganglion cell layer (GCL; distance between outer edge of RNFL and outer edge of GCL), inner plexiform layer (IPL; distance between outer edge of GCL and outer edge of IPL), inner nuclear layer (INL; distance between outer edge of IPL and outer edge of INL), outer plexiform layer (OPL; distance between outer edge of INL and outer edge of OPL), and outer nuclear layer (ONL; distance between outer edge of OPL and external limiting membrane). The thickness of individual layers was measured in the central subfield ring of the Early Treatment Diabetic Retinopathy Study (ETDRS) grid, which was classified as a central 1 mm ring of the ETDRS grid. In addition, the qualitative structural condition of EZ was determined by examining the retina at a diameter of 2,500 μm around the foveola and was categorized qualitatively as intact (if it was continuous and completely visible) or disrupted (if it was partially absent or attenuated because of pathological changes). All images were assessed by 2 masked trained graders (I.C., D.K.), using the same methodology, and the interobserver reliability of measurements was calculated by comparing the results of the 2 separate graders. The intraclass correlation coefficient (ICC) was computed to estimate the interrater reliability, with the value of ICC >0.7 to be considered as an acceptable agreement.

All patients were treated with at least 3 intravitreal anti-VEGF injections, either 0.5 mg/0.05 mL ranibizumab or 2.0 mg/0.05 mL aflibercept. Intravitreal injections were performed under sterile conditions. Installation of proparacaine hydrochloride was used as topical anesthesia, while povidone iodine (5%) was applied to the lids and eyelashes and instilled in the conjunctiva before draping. Intravitreal injection was done using a 30-gauge needle, 4 or 3.5 mm posterior to the limbus inferotemporally for phakic or pseudophakic eyes, respectively. Finally, a drop of 5% povidone iodine was instilled at the injection site.

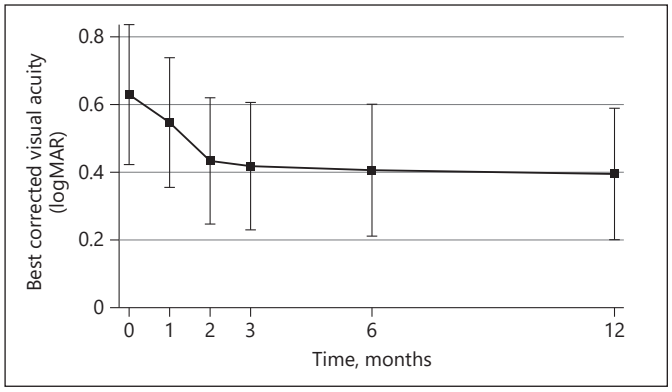

Fig. 1. Evolution of BCVA over time. BCVA, best corrected visual acuity.

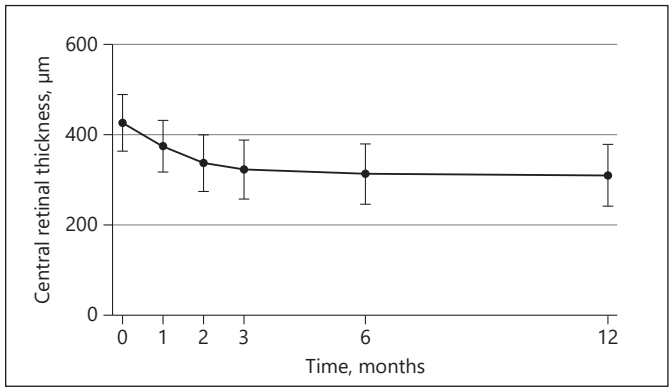

Fig. 2. Evolution of CRT over time. CRT, central retinal thickness.

All patients were followed up at a pro re nata basis, with monthly monitoring for at least 12 months. At each monthly visit, all patients underwent BCVA measurement and SD-OCT assessment, while reinjection was performed if the height of macular edema was ≥320 μm and if a decrease in VA ≥ 1 Snellen line was noticed.

The primary outcomes were the changes in retinal layers at month 12 compared to baseline and the prognostic factors for the visual outcome. Secondary outcomes were the percentage of nonresponders to anti-VEGF treatment at month 12 and factors affecting this outcome.

Statistical Analysis

At baseline, mean ± standard deviation was used for continuous variables and counts with percentages for categorical variables for the description of patients' characteristics. Normal distribution for all variables was tested by the Shapiro-Wilk test. The Wilcoxon matched-pairs signed-ranks test was used for the longitudinal comparisons of BCVA and retinal layers' thickness between baseline and each time point, while Bonferroni correction was adopted, since multiple comparisons were done. For the comparison of categorical binary variables (EZ) at each time point versus baseline, the McNemar test was performed, as appropriate.

Generalized Least Squares (GLS) random-effects linear regression analysis was used to assess the potential association between retinal layers and VA since observation may be intercorrelated in such datasets. VA was the dependent variable, while CRT, thickness of GCL, INL, IPL, ONL, OPL, and EZ condition were the independent variables in models adjusted for time (in months) and treatment. The beta coefficients with their 95% confidence intervals (CIs) are given in the manuscript.

Furthermore, patients with CRT ≥320 μm at month 12 were defined as nonresponders. Multivariate logistic regression analysis with backward selection was performed to evaluate factors at baseline, which could affect nonresponse to treatment. Factors assessed were age, gender, hypertension, hyperlipidemia, DM duration, HbA1c levels, and baseline VA. The respective odd ratios (ORs) with their 95% CIs are provided in the manuscript.

Statistical analysis was performed using STATA/SE 13 statistical software (Stata Corporation, College Station, TX, USA). A p value <0.05 was considered as statistically significant, apart from cases where the Bonferroni correction was adopted, as declared above.

Table 1. Demographic and clinical characteristics of our study sample at baseline

Patients with DME (n = 110)	
Age (mean±SD), years	64.7±8.8
Gender, *n* (%)	
Male	61 (55.5)
Female	49 (45.5)
HbA1c, *n* (%)	
<7.5%	63 (57.3)
≥7.5%	47 (42.7)
DM duration (mean±SD), years	11.6±4.6
Hypertension, *n* (%)	83 (75.5)
Hyperlipidemia, *n* (%)	35 (31.8)
Anti-VEGF agent, *n* (%)	
Ranibizumab	49 (44.5)
Aflibercept	61 (55.5)

DME, diabetic macular edema; DM, diabetes mellitus; anti-VEGF, anti-vascular endothelial growth factor; SD, standard deviation.

Results

Table 1 shows the demographic and clinical characteristics of our study sample at baseline. At baseline, the mean BCVA was 0.63 ± 0.20 logMAR. There was a statistically significant improvement in BCVA at all time points (month 1, 2, 3, 6, and 12) compared to baseline ($p < 0.001$ for all comparisons). Figure 1 shows the evolution of BCVA over time.

At baseline, the mean CRT was 427 ± 62.5 μm. There was a statistically significant decrease in CRT at all time points (month 1, 2, 3, 6, and 12) compared to baseline ($p < 0.001$ for all comparisons). Figure 2 depicts the evo-

Table 2. Quantitative changes in CRT and individual retinal layers over time

	μm, mean±SD					
	CRT	GCL	IPL	INL	OPL	ONL
Baseline	427±62.5	15.1±1.4	24.3±1.8	22.9±1.8	33.3±1.7	116.2±6.9
Month 1	375.2±57.4	14.3±1.2	22.8±2.0	21.6±1.8	31.3±1.4	110.1±7.5
Month 2	337.3±62.9	14.2±1.3	22.3±2.0	20.9±2.0	30.4±1.8	105.9±8.6
Month 3	323.0±65.6	14.1±1.3	22.2±2.0	20.6±2.1	30.1±1.9	104.1±8.9
Month 6	313.5±67.5	14.0±1.3	22.0±2.0	20.5±2.2	29.7±2.0	102.8±9.5
Month 12	309.7±68.5	13.9±1.3	21.9±2.0	20.4±2.3	29.6±2.1	103.4±13.4

CRT, central retinal thickness; GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; SD, standard deviation.

Table 3. Results of the GLS linear regression analysis of retinal layers, potentially affecting visual acuity

Variable	Category/increment	Coefficient (95% CI)	*p* value
CRT thickness	100 μm increase	+0.18 (+0.17 to +0.20)	**<0.001**
GCL thickness	10 μm increase	+0.01 (−0.07 to +0.10)	0.794
IPL thickness	10 μm increase	+0.03 (−0.05 to +0.11)	0.424
INL thickness	10 μm increase	+0.18 (+0.10 to +0.26)	**<0.001**
OPL thickness	10 μm increase	+0.23 (+0.16 to +0.31)	**<0.001**
ONL thickness	10 μm increase	+0.03 (+0.02 to +0.04)	**<0.001**
EZ	Disrupted versus intact	+0.18 (+0.15 to +0.20)	**<0.001**

CRT, central retinal thickness; GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; EZ, ellipsoid zone; GLS, generalized least squares; CI, confidence interval; SD, standard deviation. Bold values indicate statistical significance.

lution of CRT over time. Accordingly, all retinal layers (GCL, IPL, INL, OPL, and ONL) showed a significant decrease at all time points (month 1, 2, 3, 6, and 12) compared to baseline ($p < 0.001$ for all comparisons). Table 2 demonstrates the quantitative changes in CRT and retinal layers separately during the 12-month follow-up. Regarding the qualitative assessment of EZ, 62 out of 110 patients (56.4%) had intact EZ at baseline, which remained intact at the end of the 12-month follow-up period. However, 48 patients (43.6%) had disrupted EZ at baseline, 34 of whom (30.9% of the whole study sample) presented restoration of EZ at month 12 and 14 (12.7% of patients) had disrupted EZ until the end of the follow-up period. The qualitative improvement of EZ at month 12 compared to baseline was statistically significant ($p < 0.001$). For interobserver agreement, we found high inter-rater agreement between the evaluations of the second investigator and the first investigator for all assessments (ICC > 0.92; $p < 0.001$ for all comparisons).

Results of the GLS linear regression analysis, examining the retinal layers associated with BCVA (logMAR), are presented in Table 3. Increased CRT (coefficient = +0.18, 95% CI = +0.17 to +0.20, $p < 0.001$), increased INL thickness (coefficient = +0.18, 95% CI = +0.10 to +0.26, $p < 0.001$), increased OPL thickness (coefficient = +0.23, 95% CI = +0.16 to +0.31, $p < 0.001$), increased ONL thickness (coefficient = +0.03, 95% CI = +0.02 to +0.04, $p < 0.001$), and disrupted EZ (coefficient = +0.18, 95% CI = +0.15 to +0.20, $p < 0.001$) were associated with lower BCVA.

The mean number of intravitreal injections at the end of the 12-month follow-up was 6.0 ± 1.6 and did not differ significantly between the 2 treatment alternatives, that is, ranibizumab (6.9 ± 1.1 injections) and aflibercept (5.9 ± 1.3 injections), $p = 0.072$. At month 12, 57 of 110 patients (51.8%) presented persistent/recurrent macular edema, which was defined as CRT ≥320 μm. Based on multivariate regression analysis, factors, which were

found to be associated with persistent macular edema at month 12, were baseline HbA1c levels (OR = 3.78, 95% CI: 1.15–9.22, $p = 0.003$) and baseline BCVA (OR = 1.56, 95% CI: 1.24–1.97, $p < 0.001$), while borderline association was found for male sex (OR = 2.32, 95% CI: 0.96–5.64, $p = 0.063$). No association was found with age ($p = 0.514$), hypertension ($p = 0.441$), hyperlipidemia ($p = 0.604$), and DM duration ($p = 0.915$).

Discussion

Our study showed that there was a statistically significant reduction in CRT and in individual retinal layers at the end of the 12-month follow-up period compared to baseline, which was accompanied by significant improvement in visual acuity. It is worthy to mention that the greater improvement in visual acuity was observed after the loading phase of 3 intravitreal injections.

Our results were in accordance with previous studies, which have also demonstrated reduction in retinal thickness, either as a whole or in individual layers separately, after treatment with anti-VEGF agents [7, 8, 23, 24]. It is worthy to note that this study examined the inner and outer retinal layers individually, while previous studies were focused in retinal nerve fiber layer of ganglion cell layer, having small sample size as well [24]. On the contrary, this study has a relatively large sample size and analyzes the changes of retinal layers in a long-term follow-up of 12 months.

In addition, our study evaluated if changes in retinal layers could predict long-term visual acuity. Previous studies have tried to define prognostic factors of final visual outcome after anti-VEGF treatment of DME. The main factors, which have been found as predictive of visual outcome, were OCT biomarkers, such as CRT, HF, DRIL, EZ condition, and the presence of intraretinal cysts [19–26]. Interestingly, individual layers have not been examined as potential predictors of visual outcome. The present study showed that apart from CRT, changes in INL, OPL, ONL, and EZ may affect visual acuity. This could be explained based on retinal anatomy and physiology since outer retinal layers are considered to play a significant role in visual acuity due to their direct relation to photoreceptors.

Another interesting finding of this study was the percentage of patients, who did not respond adequately to anti-VEGF treatment. Protocol I and T from DRCR.net reported that about 30–40% of DME patients, treated with anti-VEGF, were nonresponders and presented persistent DME [12]. In our study, the percentage of nonresponders at month 12 was 52%, greater than that of previous studies. This could be partially explained by the lower number of injections in our study since our data were real-life and patients received about 6 injections, contrary to the large trials where a fixed regimen is used with a greater number of injections, especially in the first year of follow-up. Furthermore, it should be mentioned that in patients with persistent macular edema, the most significant factor affecting its presence was HbA1c levels, suggesting that control of DM is crucial for treatment response.

Treatment response is a matter of controversy between studies since there is no univocal definition of responsiveness to treatment and there are different criteria of "successful" treatment response or "nonresponse," while the time to assess treatment response varies among studies [27]. Although anti-VEGF agents were found to be effective in DME treatment, reducing retinal thickness as a whole and in all separate retinal layers and improving visual acuity in the 12-month follow-up, the definition of factors affecting visual outcome is significant to determine treatment response and consider early switch in treatment in cases of "nonresponders." Although it has been supported that there may be a delayed treatment response and that patients with DME may benefit from sustained anti-VEGF treatment [28], a recent study by Ruiz-Medrano et al. [29] has shown that in eyes with insufficient response to anti-VEGF agents, switching to dexamethasone implant after 3 intravitreal anti-VEGF injections provided better functional results than receiving >3 injections and then switching, supporting early switch in "nonresponders."

It should be also noted that the management of DME requires repeated measurements of retinal thickness from OCT devices. In the last decade, SD-OCT is mainly used in retinal research, addressing limitations of time domain-OCT as it has better reproducibility of measurements and accurate handling of data. More recently, the development of swept-source OCT allows the scanning of wider areas and the deeper penetration in the retinal and choroidal structures than SD-OCT [30, 31]. Therefore, in order to avoid misinterpretation of data and have a reliable comparison between measurements, the same type of OCT instrument is recommended to be used, while clinical validation of OCT technology is required for new devices [31, 32]. In our study, all measurements were performed using the same SD-OCT machine to obtain more accurate comparisons.

In conclusion, this study has shown that there is a significant improvement in retinal thickness, as a whole or in individual retinal layers, after anti-VEGF treatment for

DME. Of note, changes in retinal thickness and outer retinal layers may affect visual acuity. However, a significant percentage of patients did not respond adequately to treatment, presenting with persistent macular edema. The current study also pointed out the significance of factors, which could affect visual outcome and treatment response in patients treated with anti-VEGF, so as to predict prognosis and probably early switch to other treatment alternatives in "nonresponders." It is important to identify prognostic factors since some of them could be modified, such as DM control, leading to better results and providing individualized treatment.

Statement of Ethics

The study was in accordance with the Tenets of Helsinki Declaration and was approved by the institutional review board of our hospital. Inform consent was obtained from all participants before entering the study.

Conflict of Interest Statement

The authors declare no conflict of interest.

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The authors did not receive any funding.

Author Contributions

Irini Chatziralli conceived the idea, designed the study, collected data, interpreted data, and drafted the manuscript. Dimitrios Kazantzis collected data, interpreted data and drafted the manuscript. George Theodossiadis and Panagiotis Theodossiadis critically revised the manuscript. Theodoros Sergentanis performed the statistical analysis and critically revised the manuscript. All authors have read and approved the current version of the manuscript.

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