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Short-term peripapillary structural and vascular changes following anti-VEGF vs. Dexamethasone intravitreal therapy in patients with DME

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Abstract

Purpose: To evaluate short-term peripapillary structural and vascular changes in DME after treatment with dexamethasone implant (DEX-I) and anti-VEGFs using OCT-A.

Methods: Sixty-five patients with naïve center-involving DME were enrolled. 33 of sixty five patients (group 1) underwent with single DEX-I 0.7 mg (Ozurdex, Allergan, Inc., USA), 32 of sixty-five (group 2) underwent with intravitreal injection of aflibercept 0.5 mg (Eylea, Bayer, Genentech, San Francisco, USA). The OCT acquisition was completed at the following visits: (i) "T1 visit" corresponding to the intravitreal injection of DEX-I or aflibercept in patients with naïve center-involving DME (ii) "T2 visit" corresponding to the examination performed 2 weeks after intravitreal injection of aflibercept and 1 month after DEX-I. The parameters analyzed were: (i) RPC vasculature density (VD); (ii) peripapillary retinal nerve fiber layer (pRNFL) thickness, and (iii) intraocular pressure (IOP).

Results: The RPC analysis showed a VD increase at T2 in both groups, although values did not reach statistical significance (48.12± 4.17 and 49.04 ± 4.23; P = 0.081 in Group 1 and 46.93± 3.16 and 47.17 ± 3.70; P = 0.087 in Group 2). Likewise, the pRNFL thickness and IOP fluctuations did not show statistically significant changes in in both groups among the different study visits.

Conclusions: After intravitreal injection (anti-VEGF or DEX-I), no significant short-term changes were found in peripapillary microvasculature, IOP and pRNFL thickness in diabetic eyes treated with anti-VEGF or DEX-I.

Keywords

optical coherence tomography angiography. diabetic macular oedema, diabetic retinopathy, pharmacology, retinal disorder

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Introduction

The incidence of diabetes mellitus (DM) is expected to increase in the adult population from 4.7% in 1980 to 8.5% in 2014.[1] Diabetic retinopathy (DR) is one the most frequent conditions of DM and it represents a dominant cause of visual loss worldwide.[2,3] Macular ischemia and diabetic macular edema (DME) are considered as the primary causes of DR-associated visual loss.[4–6] Treatment of DME aims to reduce exudation caused by

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release of cytokine that disrupts the inner blood-retinal barrier.[7]

Current first-line treatment options for DME include anti-VEFG intravitreal injections or dexamethasone implant (DEX-I). VEGFs are known to have an significant role in increasing vascular permeability in DR patients.[8] Intravitreal anti-VEGF therapy proved to improve visual acuity and decrease macular exudation in patients with DME.[9] Likewise, DEX-I (Ozurdex®, Allergan, Inc., CA, USA) has displayed a favorable long-term safety profile,[10] with mild side effects including cataract formation and increasing in intraocular pressure (IOP). Anti-VEGF and corticosteroids therapies target diverse pathways in the DME pathogenesis.[11]

The debut of optical coherence tomography angiography (OCTA) has expanded our capacity to analyze the perfusion in the peripapillary and macular regions.[12–14] In the latter region, previous studies have accurately measured the radial peripapillary capillary (RPC) plexus in several diseases including glaucoma, optic neuropathy, uveitis, and retinitis pigmentosa.[15–17] Importantly, various authors have combined structural OCT and OCTA to assess the peripapillary region and they demonstrated a significant and early reduction in perfusion and retinal nerve fiber layer (RNFL) thickness.[18–20] However, these studies failed to assess anatomic and vascular changes in the peripapillary region following intravitreal therapy of anti-VEGF vs. DEX-I.

Therefore, in this study, we aimed to assess short-term peripapillary vascular and anatomical changes in DME after treatment with DEX-I and anti-VEGFs by means of OCT-A.

Methods

Study design and participants

This prospective study analyzed 65 eyes of 65 patients with naïve center-involving DME undergoing intravitreal injection at the Department of Translational Biomedicine Neuroscience, University of Bari "Aldo Moro".

Thirty-three out of 65 patients (group 1) underwent with either single DEX-I 0.7 mg (Ozurdex, Allergan,USA), while thirty-two out of 65 subjects (group 2) underwent with adminsitraton of IVT of alfibercept 0.5 mg (Eylea, Bayer, Genentech, San Francisco, USA) at the Medical Retina service between January and May 2022.

All patients were imaged with the RTVue XR Avanti spectral-domain (SD)-OCT (Optovue, Inc., Fremont, CA). The OCT acquisition was completed at the following visits: (i) "T1 visit" corresponding to the intravitreal injection of DEX-I or aflibercept in patients with naïve center-involving DME (ii) "T2 visit" corresponding to the examination performed 2 weeks after intravitreal injection of aflibercept and 1 month after DEX-I.

Moreover, images with either relevant motion artifacts and erroneous segmentation were not included in the analysis.[21] Insufficient signal strength (<6/10) images were removed from the analysis.[22]

Inclusion criteria were: age > 40 years; diagnosis of non-proliferative diabetic retinopathy (NPDR) with naïve center-involving DME and/or subfoveal neuro-retinal detachment (SND); increased central macular thickness (CMT ≥ 300 μm); Exclusion criteria were: cataract surgery within 6 months,history for any retinal treatment; glaucoma or ocular hypertension (IOP > 21 mmHg); neurodegenerative disorders (e.g., Alzheimer or Parkinson disease); any retinal disease other than DME; increased ocular axial length greater (>26 mm); refractive error > 6 diopters (D); and significant media opacities that may affect the image quality.

Documented anamnestic data were documented for each patient, including value of glycated hemoglobin (HbA1c), previous ocular surgery, use of antidiabetic and antihypertensive agents. Each patients enrolled received a ophthalmologic inspection, which involved the best-corrected visual acuity (BCVA) and intraocular pressure (IOP) measurments, and OCT acquisitiopn before and after treatment using standard ETDRS protocol.

This study respected the tenets of the Helsinki Declaration and was approved by our institutional review board of Department of Translational Biomedicine Neuroscience, University of Bari "Aldo Moro". Patients gave their written consent to be included in the study.

Imaging analysis

Subjects underwent SD-OCT imaging system (RTVue XR; Optovue, Inc., Fremont, CA, USA) before and after treatment.

Optic nerve head imaging was performed as a 4.5 × 4.5 mm angiography scan centered on the Optovue instrument (Figure 1). The peripapillary area was described as a 750-μm wide ring extending from the optic disc boundary.

To calculate the RPC vascular plexus, the Avanti RTVue (AngioVue) automatically segments the ILM and the posterior border of RNFL providing a vascular density quantification, both in the peripapillary region and in the whole scan (Figure 2). We applied a manual correction when the segmentation was altered. To delineate the pRNFL thickness, ONH acquisition (glaucoma protocol) was used.

In details, the RNFL thickness is determined as the distance between the ILM and the outer border of the IPL. Therefore, the average RNFL thickness was calculated.

Statistical analysis

Statistical evaluation was performed using SPSS (IBM SPSS Statistic 25). To study the Distribution analysis of data, Shapiro–Wilk test was performed. Paired t-test was used to

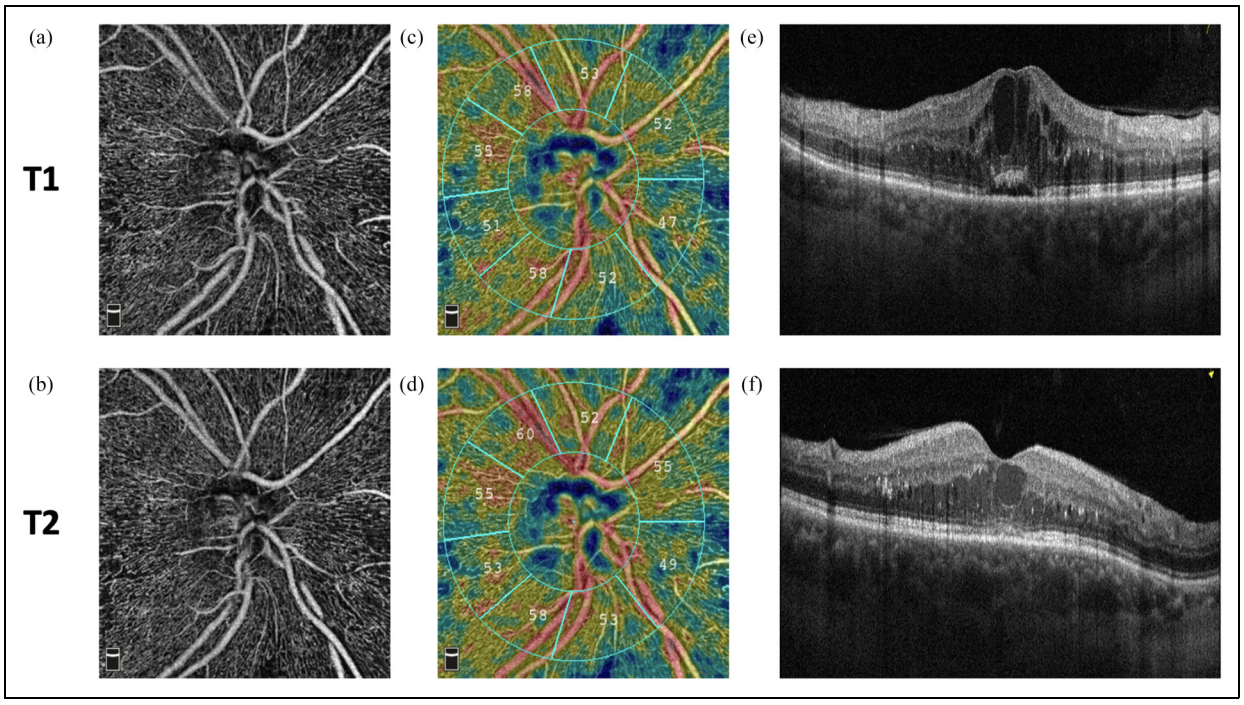

Figure 1. OCT and OCTA imaging of a representative case before (T1) and one month (T2) after dexamethasone injection. OCTA scan 4,5 × 4,5 mm centered on ONH before and after treatment (a-b). Color-coded density maps and automatized vessel density measurements of the RPC before and after dexamethasone injection (c-d). Optical coherence tomography of a patient with DME before and after dexamethasone injection (e-f).

compare data analysis before and after intravitreal injections. Moreover, we compared the mean change of the main outcomes changes between the two groups (I-DEX and anti-VEGF), expressed as a percentage, using Student t test. Means and standard deviation (SD) were computed for all quantitative metrics. A P value less than 0.05 was considered significant.

Results

Characteristics of subjects included in the analysis

Sixty-five eyes (65 individuals) including 35 females and 30 males with a mean age of 65.75 ± 6.4 years were included. Of the 65 subjects (65 eyes) included, 33 were treated with DEX-I 0.7 mg (Ozurdex, Allergan, Inc., Irvine, California, USA), while 32 were treated with intravitreal injection of aflibercept 0.5 mg (the first of the loading phase (LP)). The characteristics of subjects included in the analysis are shown in Table 1.

OCT-OCTA analysis

The peripapillary microvasculature analysis did not show statistically significant changes in in both groups between following visits. In detail, the RPC showed a slight increase in peripapillary perfusion at T2 in both groups, although values did not reach statistical significance (48.12± 4.17 and 49.04 ± 4.23; P = 0.081 in Group 1 and 46.93± 3.16 and 47.17 ± 3.70; P = 0.087 in Group 2). (Table 2).

Likewise, the pRNFL thickness and IOP fluctuations did not show statistically significant changes in in both groups between study visits (Table 2).

Furthermore, after the comparison between two groups, all the variables analyzed did not change significantly (Table 3).

Discussion

We presented a study of 65 eyes imaged with structural OCT and OCTA, in which the pRNFL thickness, IOP and peripapillary capillary network were studied. We compared these variables before and after intravitreal injection of aflibercept versus single DEX-I. In addition, no relevant modifications were found in peripapillary microvasculature, IOP and pRNFL thickness in both groups. To summarize, these findings indicate that both DEX-I and anti-VEGF treatment did not have short-term significant effects on the structural and vascular peripapillary plexus in DME-naive patients. In a cross sectional study of 155 eyes, Rodrigues et colleagues[19] have analyzed the pRNFL thickness and RPC density in patients with DM2

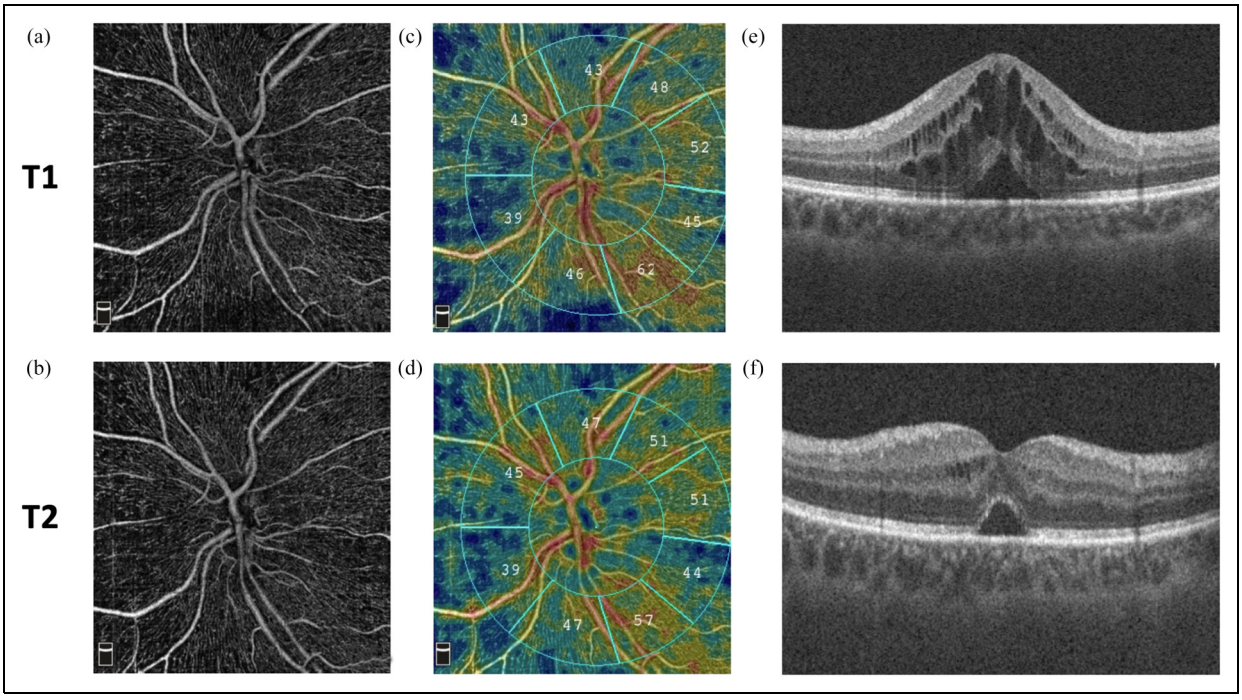

Figure 2. OCT and OCTA imaging of a representative case before (T1) and one month (T2) after anti-VEGF (aflibercept) injection. OCTA scan 4,5 × 4,5 mm centered on ONH before and after treatment (a-b). Color-coded density maps and automatized vessel density measurements of the RPC before and after aflibercept injection (c-d). Optical coherence tomography of a patient with DME before and after aflibercept injection (e-f).

Table 1. The clinical characteristics of subjects included in the analysis. Quantitative data are presented as mean ± SD (standard deviation).

Variables	Group 1 DEX-I (n = 33)	Group 2 Alfibercept (n = 32)	P value
Age (years)	64.3 ± 5.7	67.2 ± 8.9	0.093
Gender (male,%)	15 (46%)	15 (45%)	0.297
Laterality (right,%)	19 (59%)	23 (70%)	0.342
Duration of diabetes (years)	14.5 ± 7.7	16.2 ± 8.5	0.126
BCVA (logMAR)	0.43 ± 0.12	0.45 ± 0.23	0.117

Table 2. OCT angiography, pRNFL thickness and IOP changes, data and comparisons (T1 vs T2).

	T1	T2	P value
Group 1 (DEX-I)			
RPC VD (%)	48.12 ± 4.17	49.04 ± 4.23	0.081
pRNFL thickness (μm)	97.1 ± 9.11	98.2. ± 9.6	0.142
IOP changes (mmhg)	18.4 ± 2.0	19.1 ± 1.8	0.075
Group 2 (Alfibercept)			
RPC VD (%)	46.93 ± 3.16	47.17 ± 3.70	0.087
pRNFL thickness (μm)	96.8 ± 8.8	97.4. ± 9.13	0.121
IOP changes (mmhg)	19.2 ± 1.9	18.2 ± 1.8	0.098

Data are presented as Mean ± SD. RPC radial peripapillary capillaries VD vessel density; pRNFL peripapillary retinal nerve fiber layer; IOP intraocular pressure.
T1 before intravitreal injection; T2 after anti-VEGF or DEX-I therapy.

Table 3. Comparison between groups.

	Group 1 (DEX-I)	Group 2 (Alfibercept)	P value
RPC VD (%)	2.3± 3.9	2.8± 4.3	0.093
pRNFL thickness (μm)	1.4± 2.1	1.2.± 2.0	0.137
IOP changes (mmhg)	0.79 ± 1.1	−0.24 ± 0.8	0.085

Data are delta percentages (Mean ± SD). The Student t-test was performed to obtain P-values.
RPC radial peripapillary capillaries VD vessel density; pRNFL peripapillary retinal nerve fiber layer; IOP intraocular pressure.

without DR highlighting a significantly peripapillary damage already in the early phase of the disease. These results suggest that peripapillary area is notably susceptible to damage from DM. For this reason, we focused on the ONH region response to the anti-VEGF or DEX-I treatment in eyes with DME-naïve.

The anti-VEGF impact on retinal vascular flow has not a clear interpretation, several studies displayed conflicting findings. In a recent OCTA study, Falavarjani et al.[23] evaluated the retinal vessel changes after a single anti-VEGF injection for DME. The authors highlighted that anti-VEGF therapy did not worsen capillaries perfusion. Other authors have shown that the retinal capillaries already present became evident after DME resolution.[24] In this retrospective cohort study,[25] the authors analyzed the retinal perfusion modfications in response to repeated DEX-I therapy over a 1-year period. They found a retinal reperfusion still maintained at 1 year after starting treatment with DEX-Is. An important limitation of these findings is the quality of the image due to signal attenuation and the segmentation altered of the retinal plexuses in patients with severe DME.

Therefore, this study was intended to define the morphological and vascular short-terms effects of anti-VEGF and DEX-I on the ONH before and after treatment for DME naïve.

Despite the pathogenesis is different from DR, Nicolai et al. proved that peripapillary VD measurements were characterized by an increase after intravitreal anti-VEGF injection in patients with central retinal vein occlusion.[26] Our study displayed that the peripapillary vasculature seemed to be increased after aflibercept injection, although it did not reach a statistical significance. In agreement with our results, Toto et al.[27] also described no significant difference in peripapillary VD after intravitreal anti-VEGF injection.

Furthermore, our results relayed no IOP fluctuations and pRNFL thickness changes at T2 visit. According to a recent study,[28] long-term therapy with anti-VEGF agents did not lead to relevant RNFL thickness changes in eyes with wet AMD. On the contrary, the IOP fluctuations after anti-VEGF therapy is known. Multiple studies[29,30] displayed that there is an IOP elevation associated with anti-VEGF injections presenting a potential risk of damage to RNFL thickness. In the present study, no IOP and RNFL changes was documented. Our results not show statistically significant differences in RNFL thickness before and after use of anti-VEGF agents.

As above mentioned, we also assessed OCT and OCTA parameters after DEX-I treatment in eyes with DME-naïve. Our results showed that DEX-I seems to have no side effects on RNFL thickness, IOP and peripapillary VD in a 1-month period. Similarly, Ozcalıskan et al.[31] found macular reperfusion after DEX-I with no significant impact on peripapillary capillaries in DME patients. The long-term DEX-I effects on the RNFL are not well known. Evaluating RNFL thickness and peripapillary microvascular changes is a way to assess the effect of the intravitreal drug on retinal ganglion cells. This is the first study assessing short-term optic head changes in DME before and after treatment with DEX-I and anti-VEGFs by means of OCT-A.

Importantly, DEX-I implant is a sustained release drug which does not allow for a drug- free period compared to intravitreal anti-VEGF drugs. Therefore, we performed OCT and OCTA analysis during the period of maximum efficacy of both drugs. Furthermore, we enrolled only patients with naïve DME. In our study, the difference between RNFL thickness, peripapillary VD and IOP fluctuations before and after the intravitreal treatment (anti-VEGF or DEX-I) was not statistically significant. These findings suggest the safety of dexamethasone therapy in patients with ONH disease (e.g., glaucoma). This aspect is important to highlight, in fact the DEX impact on neural cells may show both neurodegenerative and neuroprotective effects. In detail, steroids are thought to have neuroprotective effect by reducing extracellular glutamate and microglial activity.[32,33] Collectively, these data suggest that although DEX-l may be directly toxic to neural cells, our findings did not show short-terms negative effects.

Besides, this study is not without limitations. First, the cross-sectional design and short-term follow up do not allow to evaluate prognostic parameters of response to intravitreal treatment. Second, the sample size was moderate, although sufficiently adequate for the primary outcome. Third, the automated segmentation of RPC en face OCTA may not be reliable in diseased eyes although we applied a manual correction when the segmentation was altered.

In summary, this study documents no significant changes in peripapillary microvasculature, IOP and pRNFL thickness in DME eyes treated with anti-VEGF or DEX-I. This finding supports that the short-term effects of drugs (anti-VEGF or DEX-I) on neural cells, IOP fluctuations and ONH vasculature are equivalent. Further studies with prospective design including longer follow-up duration are needed to confirm the findings of our study.

Authors' contribution

PV, MOG, GB: Data collection and analysis, GB, EB and AF: results Interpretation, PV and FB: Drafting manuscript, GA, MGM and AF: review.

Declaration of conflicting interests

No potential conflicts of interest declared from the authors.

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