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ORIGINAL ARTICLE

One-year follow-up of ischemic index changes after intravitreal dexamethasone implant for diabetic macular edema: an ultra-widefield fluorescein angiography study

Enrico Borrelli[1] · Mariacristina Parravano[2] · Lea Querques[1] · Riccardo Sacconi[1] · Paola Giorno[2] · Daniele De Geronimo[2] · Francesco Bandello[1] · Giuseppe Querques[1]

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Abstract

Aim To investigate late changes in peripheral ischemia in patients affected by diabetic macular edema (DME) and treated with repeated dexamethasone (DEX) intravitreal implants over a 1-year period.

Methods In this retrospective cohort study, patients older than 18 years of age and with type 2 non-proliferative treatment-naïve diabetic retinopathy (DR) and DME at baseline were included. All patients were treated with two intravitreal DEX implants within 1 year of follow-up. A minimum of two annual ultra-widefield fluorescein angiography (UWF FA) were required to ensure that all cases had a baseline UWF FA (< 2 weeks before first treatment with dexamethasone) and a UWF FA performed at 12 months of follow-up. On baseline and 1-year UWFA images, peripheral retinal ischemia was quantified using the ischemic index (ISI).

Results Six eyes of five patients (two males, three females) met the inclusion criteria and were enrolled in this study. Best-corrected visual acuity was 0.34 ± 0.22 LogMAR at baseline and improved to 0.21 ± 0.14 logMAR at the 1-year follow-up visit ($P = 0.050$). Mean ± SD central macular thickness was 467.6 ± 63.0 µm at baseline and 272.0 ± 14.7 µm at the 1-year follow-up visit ($P = 0.043$). Mean ± SD ISI was 26.7 ± 14.1% at baseline and reduced to 12.2 ± 5.0% at the 1-year follow-up visit ($P = 0.012$).

Conclusions Improvement in retinal perfusion is still maintained 1 year after starting treatment with DEX implants. This improvement in retinal perfusion might be related to DEX implant-related positive effects on leukostasis.

Keywords Diabetic retinopathy · Diabetic macular edema · Ultra-widefield fluorescein angiography · Ischemic index · Intravitreal dexamethasone implant

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✉ Giuseppe Querques
giuseppe.querques@hotmail.it

Enrico Borrelli
borrelli.enrico@yahoo.com

Mariacristina Parravano
mcparravano@gmail.com

Lea Querques
querques.lea@hsr.it

Riccardo Sacconi
ric.sacconi@gmail.com

Paola Giorno
paolagio@fastwebnet.it

Daniele De Geronimo
danieledegeronimo@gmail.com

Francesco Bandello
bandello.francesco@hsr.it

[1] Department of Ophthalmology, University Vita-Salute, IRCCS Ospedale San Raffaele, Via Olgettina 60, 20132 Milan, Italy

[2] IRCCS - Fondazione Bietti, Rome, Italy

Introduction

Diabetic retinopathy (DR) is the leading cause of vision loss among working-age individuals in the Western world [1–3]. Diabetic macular edema (DME) is a major cause of vision decrease in these patients and may occur at any stage of DR. The occurrence of DME is strictly dependent on the increase in vascular permeability which affects diabetic eyes [4]. Elevated levels of vascular endothelial growth factor (VEGF) in these eyes were demonstrated to promote permeability of retinal vasculature [5]. In addition, several evidences highlighted the important role of inflammation in DR pathogenesis and progression, as well as in DME development, taking into consideration that chronic inflammation may also promote vascular dysfunction and occlusion [6–8].

Assuming that DME pathophysiology is thus complicated and multifactorial, different pharmacological treatments have been successfully introduced. Anti-VEGF agents represented a milestone in the management of DME, and they act by lowering intraocular VEGF levels and thereby reducing vascular permeability [9, 10]. Among the other treatments, the dexamethasone intravitreal implant (Ozurdex™, DEX Implant) has been demonstrated to be effective in the treatment of DME with a significant improvement in macular function and a favorable safety profile [11, 12]. The latter treatment is efficacious on the assumption that it suppresses inflammation, reduces extravasation of fluid from leaking blood vessels, and down-regulates production of VEGF [13].

Ultra-widefield (UWF) fluorescein angiography (FA) has become a useful imaging tool in the diagnosis and management of patients with DR. The UWF FA images were demonstrated to display 3.9 times more nonperfusion in comparison with traditional Early Treatment of Diabetic Retinopathy Study (ETDRS) seven-field images [14]. Furthermore, recent advances in UWF image processing software yielded an accurate quantification of the nonperfusion area (NPA), after imaging compensation for nonlinear distortion. Therefore, previous notable studies quantified the ischemic index (ISI = NPA/retinal area) in eyes with DR on UWF FA images [15–18].

Our group recently reported on the modifications in ISI occurring after a single dexamethasone intravitreal implant, and we demonstrated that this treatment reduces peripheral retina ischemia in eyes with DR [19]. The aim of this pilot study is to present data on ISI variations after repeated DEX intravitreal treatments for DME over a 1-year period.

Methods

In this retrospective cohort study, patients older than 18 years of age and with type 2 non-proliferative treatment-naïve DR and DME in at least one eye were enrolled at Bietti Foundation-IRCCS, Rome, Italy. The study adhered to the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants included in the study and it was approved by the Local Institutional Review Board (IRB).

The authors in this study identified patients with DME (central macular thickness [CMT] ≥ 275 µm on spectral domain optical coherence tomography [SD-OCT] images) who were treated with two DEX implants over a 1-year period. A minimum of two annual UWF FA were required to ensure that all cases had a baseline UWF FA (< 2 weeks before first treatment with dexamethasone) and a UWF FA at 12 months of follow-up. All patients received a complete ophthalmologic examination at each visit, which included the measurement of best-corrected visual acuity (BCVA), intraocular pressure (IOP), dilated ophthalmoscopy, and SD-OCT.

Exclusion criteria were: (i) ocular comorbidities such as retinal arterial or venous occlusion, age-related macular degeneration, inherited macular disease, posterior segment inflammation, (ii) any previous treatment (e.g., laser photocoagulation, photodynamic therapy, intravitreal injections of anti-VEGF, or steroids), (iii) presence of significant media opacities.

Patients underwent SD-OCT imaging using the Heidelberg Spectralis device (Heidelberg Engineering, Heidelberg, Germany) with high-resolution (HR) mode. The structural SD-OCT minimum acquisition protocol included 19 horizontal raster linear B-scans, each composed by nine averaged OCT B-scans (1024 A-scans per line) at 240 µm intervals, covering an area of 20° by 15°. CMT in the central 1-mm-diameter circle of the ETDRS thickness map was recorded with the Spectralis Software (Heidelberg Eye Explorer, Version 1.9.11.0, Heidelberg Engineering, Germany).

Ultra-widefield fluorescein angiography and pseudocolor fundus images were obtained using the Optos California (Optos PLC, Dunfermline, Scotland, UK). These images were obtained by a trained physician, as previously described [20, 21]. In brief, subjects were seated in front of the Optos device and instructed to look at a green fixation target. Once the correct position and focus was achieved, the examiner was able to press a button to capture the image. The image could be immediately viewed by the examiner and repeated if necessary. In order to obtain UWFA images, after standard intravenous infusion of 5 cc of sodium fluorescein 10%, images were captured during the early (45 s), middle (2 min and 39 s), and late (5 min) phases of the angiography. Moreover, each patient had several images obtained for each of the gaze position (ahead, superior, inferior, right, left), in order to obtain a clear visualization of the peripheral edge of the visible retinal vasculature.

On UWFA images, peripheral retinal ischemia was quantified using the ischemic index at both baseline and

1-year follow-up images. The ISI was calculated as previously described [15–18]. Briefly, images were exported in Joint Photographic Experts Group (jpeg) format with no change in contrast, gamma or brightness and then imported into ImageJ software version 1.50 (National Institutes of Health, Bethesda, MD; available at http://rsb.info.nih.gov/ij/index.html). Total retinal surface and nonperfused areas were manually outlined, and ISI was calculated as the ratio between NPA and total retinal area.

DR grading was performed on ultra-widefield pseudocolor images using to the severity scale proposed by Wilkinson and colleagues [22].

Quantitative variables are expressed as mean and standard deviation (SD), while categorical variables are presented as counts. The paired samples T test was used to compare values at the following visits. Statistical calculations were performed using Statistical Package for Social Sciences (version 20.0, SPSS Inc., Chicago, IL, USA). The chosen level of statistical significance was $P < 0.05$.

Results

Six eyes of five patients (two males, three females) met the inclusion criteria and were enrolled in this study. Mean ± SD age was 58.7 ± 9.2 years [range 48–69 years]. The mean duration of DR was 19.2 ± 6.1 years. All patients were in good control of systemic metabolism. Five out of six eyes were phakic, while one eye was pseudophakic. All patients were treated with two DEX implants during the 1-year follow-up period, with a mean interval of 7.7 ± 2.3 months [range 5–11 months] between the two following treatments. Therefore, the 1-year UWFA was performed 4.3 ± 2.3 months after the second DEX implant. Regarding the DR stage at baseline, four eyes were affected by mild DR, while one eye had moderate DR, and one eye was graded as severe DR. No changes in DR grading were noted at the 1-year follow-up visit.

BCVA was 0.34 ± 0.22 LogMAR at baseline and improved to 0.21 ± 0.14 logMAR at the 1-year follow-up visit ($P = 0.050$). Mean ± SD CMT was 467.6 ± 63.0 µm at baseline and 272.0 ± 14.7 µm at the 1-year follow-up visit ($P = 0.043$). Mean ± SD ISI was 26.7 ± 14.1% at baseline and reduced to 12.2 ± 5.0% at the 1-year follow-up visit ($P = 0.012$) (Table 1, Fig. 1).

Table 1 Ischemic index values changes in the enrolled eyes

	Baseline	12 months
Case #1	9.3	6.7
Case #2	16.1	9.3
Case #3	19.9	9.5
Case #4	29.9	10.9
Case #5	40.2	18.2
Case #6	45.0	18.6

Discussion

In this pilot study, we described ischemic index changes in response to dexamethasone intravitreal treatment over a 1-year period. Overall, we observed that this treatment is associated with a sustained reduction in retinal nonperfusion. Nonetheless, we confirmed the role of UWFA in quantifying peripheral nonperfusion in eyes with diabetic retinopathy.

Retinal nonperfusion is a key feature of diabetic retinopathy and may characterize both the posterior pole and the periphery. Several studies topographically quantified the amount of retinal nonperfusion in DR and displayed that the majority of nonperfusion in eyes with DR is located in the periphery [17, 23]. Taking into consideration that retinal nonperfusion and DME may coexist, the severity of DME was suggested to be potentially influenced by the extent of retinal ischemia by triggering VEGF overexpression [5]. More importantly, the amount of retinal nonperfusion is associated with the development of proliferative DR. The total area of retinal nonperfusion was demonstrated to be greater in eyes with proliferative DR [18]. Notably, differences in retinal ischemia between proliferative and non-proliferative DR eyes were predominantly detected in the periphery, while the extension of posterior pole nonperfusion was associated with the development of optic disk neovascularizations.

Using UWF FA, several previous notable studies have reported on the ischemic index in diabetic retinopathy. Fan et al. [17] prospectively investigated 29 patients (40 eyes) with treatment-naïve DME. The authors demonstrated that the ISI was not associated with CMT in these eyes. Successively, Fang and colleagues [15] displayed that the severity of DME is positively correlated with nonperfusion regions with leakage, but negatively correlated with NPR without leakage. They speculated that these regions of nonperfusion with leakage may be ischemic but still have viable tissue capable of producing VEGF, and therefore causing vascular leakage and edema.

In a previous prospective longitudinal study, our group investigated early changes in retinal nonperfusion after treatment with DEX implant for DME [19]. In the latter study, nine eyes of seven patients with non-proliferative diabetic retinopathy and DME were enrolled. In order to quantify changes in retinal nonperfusion occurring after DEX treatment, the ISI was measured at baseline and at 10 ± 2 weeks after the DEX intravitreal injection. Therefore, we demonstrated that eyes affected by DR and treated with a single DEX implant had a significant early improvement in retinal perfusion after treatment. The latter results might account

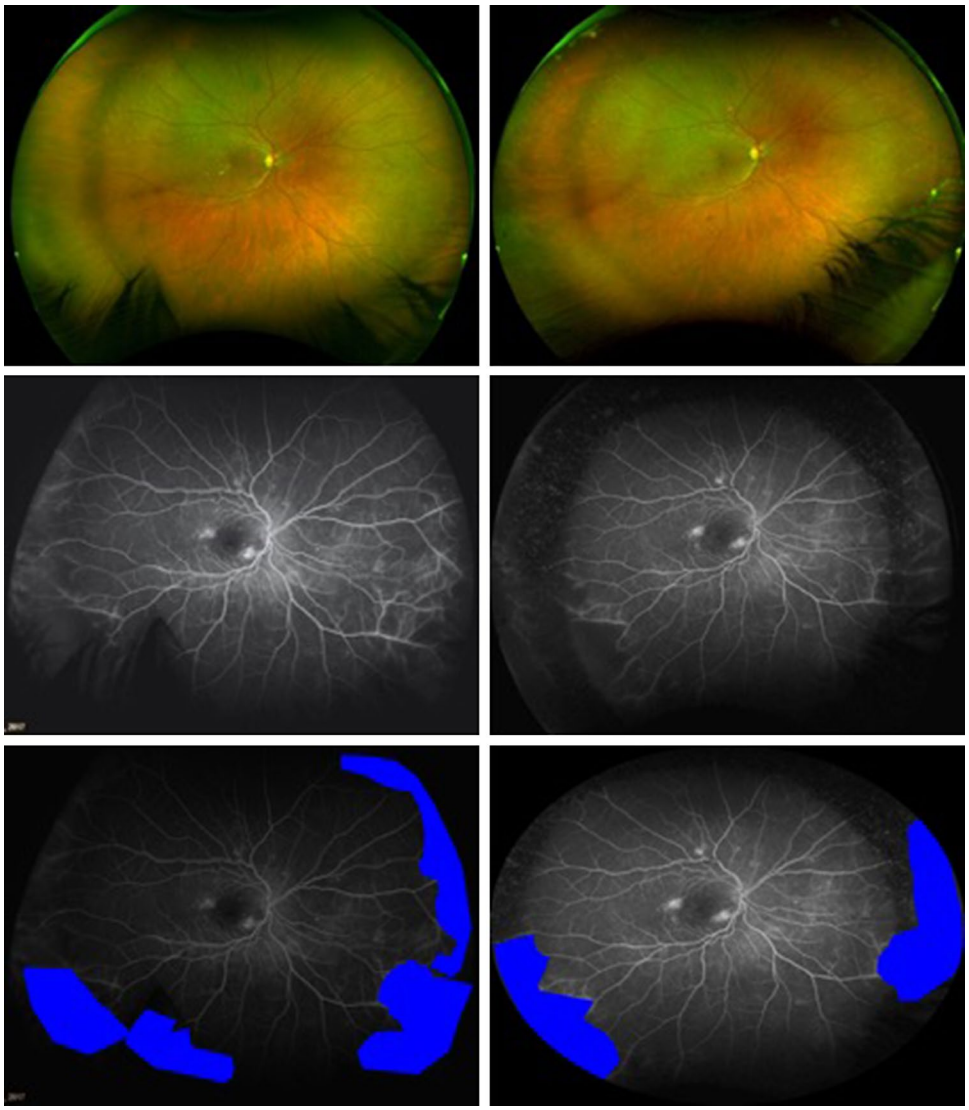

Fig. 1 Ultra-widefield fluorescein angiography images from a patient with diabetic retinopathy. Pseudocolor (first row) and ultra-widefield fluorescein angiography (UWFA—middle and bottom rows showing UWFA without and with highlighted ISI regions, respectively) images at baseline (left column) and at 1-year follow-up visit (right column) in a patient affected by treatment-naïve diabetic macular edema and treated with two dexamethasone intravitreal implants during the study period. The ischemic index (ISI) resulted reduced at the 1-year follow-up visit (color figure online)

for the corticosteroids effects on reducing the risk of progression of diabetic retinopathy through 3 years [24].

We add to the literature by proving that this amelioration in retinal ischemia is still maintained at 1 year after starting treatment with DEX implants. Considering that dexamethasone was demonstrated to be detected in the retina and vitreous humor for 6 months after intravitreal treatment [25] and assuming that patients in our cohort underwent the 1-year UWFA 4.3 ± 2.3 months after the second DEX implant, we may suppose that this reduction is dependent on the treatment. We speculate that this corticosteroid-related increase in retinal perfusion might be related to positive effects on leukocyte stasis (leukostasis). Leukostasis has been implicated in the pathogenesis and progression of DR as it triggers retinal nonperfusion and vascular leakage [26, 27]. In detail, diabetes was demonstrated to activate leukocytes with consequent increased adhesion to vascular endothelium of these cells [26]. Since decrease in retinal blood flow and increase in leukocyte adhesion are concomitant and are regulated by several metabolic factors in common, it was thus suggested that these two processes are strictly inter-related [27]. Assuming that the intravitreal injection of corticosteroids inhibits leukocyte recruitment in the diabetic retina [27], we may thus conclude that our results might be—at least in part—interpreted as a DEX implant-related decrease in leukocyte recruitment in the retinal vessels. Our results are even more relevant considering the recent evidences suggesting that the anti-VEGF treatment does not improve retinal perfusion in eyes with diabetic retinopathy [28, 29]. In addition, Bonnin and colleagues [29] also showed that the anti-VEGF treatment may cause narrowing of retinal vessels and disappearing of some small vessels. These effects were speculated to be secondary to the vasoconstrictive effect of this treatment. A reduced effect of anti-VEGF on leukostasis, which was demonstrated to transitorily increase after intravitreal anti-VEGF treatment [30], might also account

for such difference between anti-VEGF and dexamethasone treatments.

Our study has limitations including its retrospective nature and the relatively small sample size. Future larger prospective longitudinal studies will shed further light on the changes in retinal perfusion after treatment with DEX implants. In addition, we did not investigate changes in retinal ischemia within the posterior pole. Future reports may clarify whether this treatment may cause changes in the posterior ischemia. Finally, the recent introduction of ultra-widefield optical coherence tomography angiography (OCTA) [31] will further allow the assessment of peripheral retinal perfusion in eyes with DR.

In conclusion, this study investigated the retinal perfusion changes in response to repeated dexamethasone intravitreal treatment over a 1-year period. We displayed that an improvement in retinal perfusion is still maintained at 1 year after starting treatment with DEX implants. This improvement in retinal perfusion might be related to DEX implant-related positive effects on leukostasis.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to disclose.

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Ethical standard statement or human and animal rights disclosure All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent disclosure Informed consent was obtained from all patients for being included in the study.

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