CrossMark

ORIGINAL ARTICLE

Ischemic index changes in diabetic retinopathy after intravitreal dexamethasone implant using ultra-widefield fluorescein angiography: a pilot study

Lea Querques[1,2] · Mariacristina Parravano[2] · Riccardo Sacconi[1,3] ·
Alessandro Rabiolo[1] · Francesco Bandello[1] · Giuseppe Querques[1]

Abstract

Aims To investigate the effect of dexamethasone intravitreal implant on peripheral ischemia in patients affected by diabetic macular edema (DME).

Methods Patients with treatment-naïve diabetic retinopathy (DR) undergoing intravitreal dexamethasone implant for DME between October 2015 and March 2017 were enrolled. Patients underwent a comprehensive ocular examination at baseline (<2 weeks before treatment) and 10 ± 2 weeks after dexamethasone implant including best-corrected visual acuity (BCVA), intraocular pressure, optical coherence tomography, ultra-widefield (UWF) retinography and UWF fluorescein angiography (UWFA).

Results Nine eyes of seven consecutive patients (five males; mean age 66.4 ± 6.7 years) were enrolled. Mean duration of DR was 12.3 ± 8.4 years. Mean interval between UWFA acquisitions was 12.1 ± 2.1 weeks, and the mean interval between intravitreal injection and UWFA acquisition was 11.0 ± 1.6 weeks. Mean pre- and post-injection BCVA was 0.30 ± 0.20 and 0.21 ± 0.14 logMAR ($p = 0.06$), respectively. Mean pre- and post-injection central macular thickness was 449.8 ± 92.5 and 356.3 ± 52.4 μm ($p = 0.03$), respectively. Mean pre- and post-injection ischemic index was 24.0 ± 25.0 and $9.8 \pm 12.1\%$ ($p = 0.0427$), respectively.

Conclusions Intravitreal dexamethasone implant reduces peripheral retina ischemia in patients with DR.

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

✉ Giuseppe Querques
  giuseppe.querques@hotmail.it

  Lea Querques
  Querques.lea@hsr.it

  Mariacristina Parravano
  criparra@tin.it

  Riccardo Sacconi
  r.sacconi@studenti.unisr.it

  Alessandro Rabiolo
  rabiolo.alessandro@hsr.it

  Francesco Bandello
  bandello.francesco@hsr.it

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

[2] G. B. Bietti Foundation-IRCCS, Rome, Italy

[3] Eye Clinic, Department of Neurological and Movement Sciences, University of Verona, Verona, Italy

Introduction

Diabetic retinopathy (DR) is the most common complication of diabetes mellitus (DM) and is a threatening cause of legal blindness among working-age people worldwide. The risk of developing significant visual impairment due to DR may be reduced with adequate control of systemic disease and prompt treatment of retinal complications [1].

Diabetic macular edema (DME) is a major cause of vision loss in patients with DR and may occur at any stage of diabetes. Retinal ischemia and microvascular changes are frequent complications of DR. Areas of capillary nonperfusion are clearly visualized with fluorescein angiography (FA); under optimal conditions, traditional FA can capture approximately 30° of the retina at once [2].

More than 25 years ago, the Early Treatment of Diabetic Retinopathy Study (ETDRS) developed the seven-standard fields (7SF) protocol in which seven areas of the retina obtained in different phases of retinal angiography were combined to give 75° visualization [3]. This technique makes difficult to evaluate capillary nonperfusion because of changing vascular fluorescence, imprecise field overlap and extravascular leakage of the fluorescein dye in the late phases of angiography [4].

The advent of ultra-widefield fluorescein angiography (UWFA) has provided the opportunity to capture a single high-resolution 200° retinal field, covering 82% of the retinal surface, where all vessels are in the same angiographic phase, allowing visualization of both central and peripheral retina. The ability to obtain full-field angiographic data in a single frame allows the ready visualization of peripheral nonperfusion and vascular leakage. This rapid acquisition system also requires less photographic expertise and less patient cooperation providing additional information about the severity of DR compared to traditional FA giving significant contribution to the management of diabetic patients.

Although UWFA has been extensively studied as a diagnostic tool, it may also have a role on DR treatment. Research results [5] have shown the important role of vascular endothelial growth factor (VEGF) in the pathogenesis of DR; retinal ischemia stimulates the production of VEGF, which can lead to the breakdown of blood–retinal barriers and may cause DME through an increase in vascular permeability in the macula. Anti-VEGF intravitreal injections have proven efficacy in suppressing VEGF load and improve DME. Moreover, Campochiaro et al. [6] reported that monthly injections of ranibizumab in patients with DME suppress VEGF load and consequently slow progression of retinal nonperfusion. A randomized clinical trial [7] by the Diabetic Retinopathy Clinical Research Network (DRCR.net) determined that 4 mg of intravitreal triamcinolone acetonide can reduce the risk of progression of diabetic retinopathy through 3 years. Lower rate of worsening in diabetic retinopathy severity may prevent development of retinal ischemia.

To the best of our knowledge, there is no evidence of dexamethasone intravitreal implant (Ozurdex[TM], DEX Implant) efficacy in reducing retinal nonperfusion in patients with DR. DEX implant demonstrated efficacy in the treatment of DME and has showed a favorable safety profile [8]. Therefore, secondary analyses of clinical trials have shown that suppression of VEGF slows progression of retinal nonperfusion in patients with DME, and it is uncertain as to whether DEX implant would have the same ameliorative effect on retinal ischemia. This analysis was designed to evaluate this potential effect by means of UWFA.

Materials and methods

A prospective interventional case series was carried out including nine eyes of seven patients with diagnosis of DME that presented at the Medical Retina and Imaging Unit of the Department of Ophthalmology, University Vita-Salute, San Raffaele Hospital in Milan and Bietti Foundation, IRCCS, in Rome, between October 2015 and March 2017. This study adhered to the tenets of the Declaration of Helsinki. All patients signed a written general consent to participate to studies, which was approved by the ethics committee of San Raffaele Hospital.

The inclusion criteria were: (1) patients 18 years of age or older with diabetes mellitus (type 1 or 2), (2) diagnosis of nonproliferative DR, (3) decreased vision from DME, (4) central macular thickness (CMT) ≥ 275 μm. The exclusion criteria were: (1) ocular comorbidities such as retinal arterial or venous occlusion, age-related macular degeneration, inherited macular disease and posterior segment inflammation, (2) any previous treatment (e.g., laser photocoagulation, photodynamic therapy, intravitreal injections of anti-VEGF or steroids), (3) presence of significant media opacities (e.g., cataract or corneal opacity).

All patients underwent a complete ophthalmologic examination at baseline (<2 weeks before treatment) and 10 ± 2 weeks after DEX Implant, including best-corrected visual acuity (BCVA) using Early Treatment Diabetic Retinopathy Study (ETDRS) charts, slit-lamp biomicroscopy, lens status examination, intraocular pressure, indirect fundus ophthalmoscopy, structural spectral domain optical coherence tomography (SD-OCT), ultra-widefield color fundus images and UWFA. Optical coherence tomography examinations were performed using Spectralis (Heidelberg Engineering, Heidelberg, Germany). 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 degrees by 15 degrees. 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 color fundus images and UWFA were performed using the Optos California (Optos, PLC, Dunfermline, Scotland). This device combines both an ellipsoid mirror and a scanning laser ophthalmoscope to obtain panoramic fundus images up to the ora serrata. After standard intravenous infusion of 5 cc of sodium fluorescein 10%, UWFA images were obtained during the early (45 s), middle (2 min and 39 s) and late (5 min) phases of the angiography. In addition to a central image centered on the macula, the FA images were steered superiorly, temporally, nasally and inferiorly to allow clear

visualization of the peripheral edge of the visible retinal vasculature. Peripheral retinal ischemia in all eyes included in the analyses was quantified by ischemic index (ISI) at UWFA baseline and 10 ± 2 weeks after intravitreal DEX implant (this timeline period was chosen on the basis of the pharmacodynamic of the drug) [9]. In order to quantify capillary nonperfusion, a single operator (AR) calculated ISI on early macula-centered UWFA frames, as described elsewhere [10–12]. Briefly, images were exported in Joint Photographic Experts Group (jpeg) format with no change in contrast, gamma or brightness and imported on ImageJ software (National Institutes of Health, Bethesda, Maryland, USA). Total retinal surface and nonperfused areas were manually outlined, and ISI was calculated as the ratio between ischemic retina and total retinal area. DR grading was performed on ultra-widefield color fundus images using the severity scale proposed by Wilkinson and colleagues [13].

Prism 6.0 software (GraphPad Software, San Diego, CA) was used to analyze the data. Results of descriptive analyses were expressed as means $\pm$ standard deviations for quantitative variables and as counts and percentages for categorical variables.

Results

The UWFA images of nine eyes from seven consecutive patients (five males; mean age 66.4 ± 6.7 years) with type 2 DM were evaluated at baseline and 10 weeks after intravitreal dexamethasone implant. All patients were in good control of systemic metabolism. Two patients had DME in both eyes, and one fellow eye was excluded because of previous macular laser treatment. The mean duration of DR was 12.3 ± 8.4 years. The mean interval between the UWFA acquisition was 12.1 ± 2.1 weeks, and the mean interval between intravitreal injection and UWFA acquisition was 11.0 ± 1.6 weeks. Table 1 shows demographics of the patients included.

Mean BCVA at baseline was 0.30 ± 0.20 logMAR and improved to 0.21 ± 0.14 logMAR at 10-week follow-up ($p = 0.06$). The mean baseline CMT was 449.8 ± 92.5 μm, which reduced to 356.3 ± 52.4 μm 10 weeks following intravitreal injection ($p = 0.03$).

The mean ISI as evaluated on UWFA at baseline was $24.0 \pm 25.0\%$ and reduced to $9.8 \pm 12.1\%$ at 10-week follow-up (2.4-fold mean reduction, $p = 0.0427$). Figure 1 shows UWFA images of peripheral ISI before and after intravitreal dexamethasone implant in patient #2. Patient #2 also improved DR grade from severe to moderate after intravitreal DEX implant. Table 2 shows main clinical findings of the patients included in the study. One patient

Table 1 Patient demographics and main clinical findings

Patients/eyes	7/9
Age (years, mean $\pm$ SD)	66.4 ± 6.7
Race (Caucasian)	7
Sex (male/female)	5/2
Diabetes type (type 1/type 2)	0/7
Insulin-dependent (yes/no)	4/3
Duration of disease (years, mean $\pm$ SD)	12.3 ± 8.4
HbA1c (%, mean $\pm$ SD)	7.9 ± 0.7
Study eye (right/left)	4/5
Lens status (phakic/pseudophakic)	6/3

IOP intraocular pressure, *SD* standard deviation, *HbA1c* hemoglobin A1c

developed intraocular pressure (IOP) rising to 32 mmHg after DEX implant which normalized to 19 mmHg with application of topical dorzolamide/timolol fixed combination (Cosopt™) bid.

Discussion

In this pilot study, DEX implant provided reduction in peripheral retinal nonperfusion and improvement in vision and macular edema in patients with DR. Overall, the findings of the current study confirm the role of UWFA in assessing the DR extension and retinal changes associated with DME, which may be definitely considered as a valuable tool for identifying peripheral nonperfusion. Several studies in diabetic eyes have already demonstrated greater detection, compared to conventional FA, in visualizing peripheral retinal ischemia in DR.

Detection and delineation of retinal vascular nonperfusion in the retinal periphery may be of clinical value. Wessel et al. [12] reported a significant correlation between diabetic macular edema and peripheral retinal ischemia evaluated by UWFA. Moreover, Patel et al. [10] found a correlation between recalcitrant DME with larger areas of retinal nonperfusion in UWFA and greater severity of DR. Sim et al. [14] investigated the association between peripheral retinal ischemia in UWFA images and central ischemia in DR. They observed a positive correlation between these two variables indicating how both conditions share a common pathogenesis, such as capillary nonperfusion. This pilot study demonstrates the feasibility of quantifying retinal nonperfusion treatment response by means of ISI; moreover, DEX implant resulted effective not only in reducing breakdown of the blood–retinal barrier but also in improving ISI in all patients included (2.4-fold mean reduction).
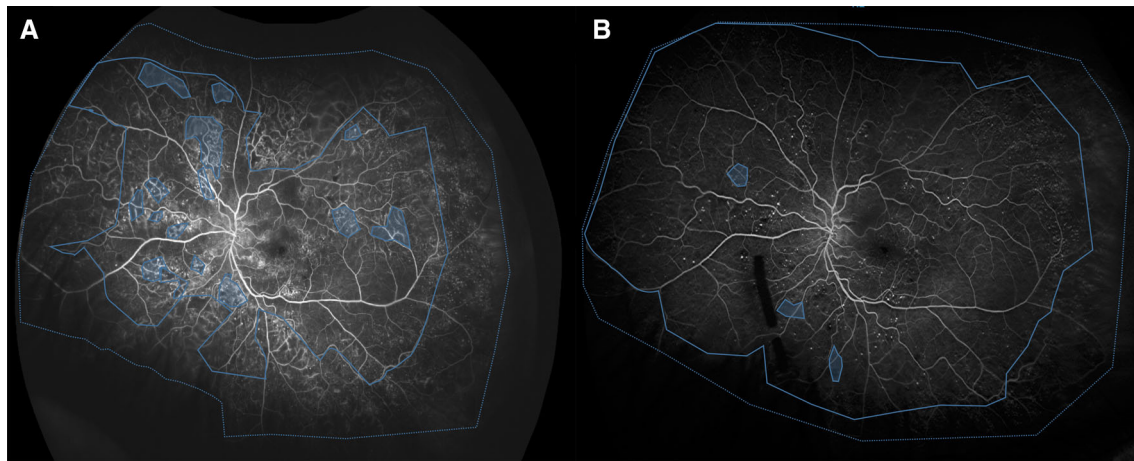
Fig. 1 Ultra-widefield fluorescein angiography images of peripheral ischemic index before (**a**) and after (**b**) dexamethasone intravitreal implant in a patient affected by diabetic retinopathy. Total fundus area was encircled (*dotted line*), and the limit between perfused and nonperfused retina was delineated (*solid line*). Nonperfused areas inside the perfused retina were encircled (*solid lines, transparent blue areas*). Ischemic index was calculated as the ratio of the area of nonperfusion over the total retinal area

Table 2 Selected variables before and after dexamethasone IV

Patient	Eye (R/L)	Baseline visit					Follow-up visit				
		DR grade	BCVA (logMAR)	IOP (mmHg)	CMT (micron)	ISI (%)	DR grade	BCVA (logMAR)	IOP (mmHg)	CMT (micron)	ISI (%)
#1	R	Moderate	0.4	16	399	72.37	Moderate	0.4	16	450	20.83
	L	Moderate	0.22	16	495	44.61	Moderate	0.22	16	418	34.66
#2	L	Severe	0.7	14	648	47.63	Moderate	0.4	32	347	12.59
#3	R	Mild	0.15	14	320	6.64	Mild	0.22	14	328	1.12
	L	Mild	0.4	14	427	16.44	Mild	0.22	14	399	15.40
#4	L	Moderate	0.1	12	395	11.64	Moderate	0	17	311	0.49
#5	R	Moderate	0.1	14	489	1.41	Moderate	0	17	307	0.59
#6	R	Moderate	0.22	17	403	15.42	Moderate	0.22	16	328	2.38
#7	L	Moderate	0.4	14	472	0.06	Moderate	0.22	15	319	0.51

IV intravitreal, *R* right, *L* left, *BCVA* best-corrected visual acuity, *logMAR* logarithm of the minimal angle of resolution, *IOP* intraocular pressure, *CMT* central macular thickness, *ISI* ischemic index

In patients with DME, the neutralization of intraocular VEGF levels by anti-VEGF improves macular edema and reverses the worsening in retinal nonperfusion. [6].

Similarly, corticosteroids can reduce the risk of progression of diabetic retinopathy through 3 years [7]. In fact, corticosteroids have been shown to down-regulate VEGF production and to reduce a large number of vasoactive factors [15, 16]. There are some patients in whom intravitreal anti-VEGF injections are not sufficient to reduce DME and this suggests there are other pro-permeability factors in addition to VEGF that play a role in patients with DME [17]. Lower rate of worsening in diabetic retinopathy severity may prevent development of retinal ischemia.

The obvious limitation of this study is the small sample size given its pilot design, and further studies with larger number of patients are needed to confirm our preliminary findings. Moreover, ISI quantification was carried out by one single operator and this could represent another study limitation. The present study should be considered as a starting point to promote prospective clinical trials in order to better analyze the effect of DEX implant on recovering retinal nonperfusion and avoiding worsening of DR progression in patients with DME.

Compliance with ethical standards

California, USA), Hoffmann-La-Roche (Basel, Switzerland), Nova-galiPharma (Évry, France), Novartis (Basel, Switzerland), Sanofi-Aventis (Paris, France), Thrombogenics (Heverlee, Belgium), Zeiss (Dublin, USA). Giuseppe Querques consultant for: Alimera Sciences (Alpharetta, Georgia, USA), Allergan Inc (Irvine, California, USA), Heidelberg (Germany), Novartis (Basel, Switzerland), Bayer Shering-Pharma (Berlin, Germany), Zeiss (Dublin, USA).

References

1. Wessel MM, Nair N, Aaker GD, Ehrlich JR, D'Amico DJ, Kiss S (2012) Peripheral retinal ischaemia, as evaluated by ultra-wide-field fluorescein angiography, is associated with diabetic macular oedema. Br J Ophthalmol 96(5):694–698. doi:10.1136/bjophthalmol-2011-300774

2. Witmer MT, Kiss S (2013) Wide-field imaging of the retina. Surv Ophthalmol 58(2):143–154. doi:10.1016/j.survophthal.2012.07.003

3. Diabetic retinopathy study (1981) Report number 6. Design, methods, and baseline results. Report number 7. A modification of the Airlie House classification of diabetic retinopathy. Prepared by the Diabetic Retinopathy. Invest Ophthalmol Vis Sci 21(2):1–226

4. Soliman AZ, Silva PS, Aiello LP, Sun JK (2012) Ultra-wide field retinal imaging in detection, classification, and management of diabetic retinopathy. Semin Ophthalmol 27(5–6):221–227. doi:10.3109/08820538.2012.708812

5. Nguyen QD, Brown DM, Marcus DM et al (2012) Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology 119(4):789–801. doi:10.1016/j.ophtha.2011.12.039

6. Campochiaro PA, Wykoff CC, Shapiro H, Rubio RG, Ehrlich JS (2014) Neutralization of vascular endothelial growth factor slows progression of retinal nonperfusion in patients with diabetic macular edema. Ophthalmology 121(9):1783–1789. doi:10.1016/j.ophtha.2014.03.021

7. Bressler NM, Edwards AR, Beck RW et al (2009) Exploratory analysis of diabetic retinopathy progression through 3 years in a randomized clinical trial that compares intravitreal triamcinolone acetonide with focal/grid photocoagulation. Arch Ophthalmol 127(12):1566–1571. doi:10.1001/archophthalmol.2009.308

8. Malcles A, Dot C, Voirin N et al (2016) Real-life study in diabetic macular edema treated with dexamethasone implant: the reldex study. Retina. doi:10.1097/IAE.0000000000001234

9. Haller JA, Bandello F, Belfort R Jr et al (2011) Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion twelve-month study results. Ophthalmology 118(12):2453–2460

10. Patel RD, Messner LV, Teitelbaum B, Michel KA, Hariprasad SM (2013) Characterization of ischemic index using ultra-wide-field fluorescein angiography in patients with focal and diffuse recalcitrant diabetic macular edema. Am J Ophthalmol 155(6):1038–1044 e1032. doi:10.1016/j.ajo.2013.01.007

11. Tan CS, Sadda SR, Hariprasad SM (2014) Ultra-widefield retinal imaging in the management of diabetic eye diseases. Ophthalmic Surg Lasers Imaging Retina 45(5):363–366. doi:10.3928/23258160-20140909-07

12. Wessel MM, Aaker GD, Parlitsis G, Cho M, D'Amico DJ, Kiss S (2012) Ultra-wide-field angiography improves the detection and classification of diabetic retinopathy. Retina 32(4):785–791. doi:10.1097/IAE.0b013e3182278b64

13. Wilkinson CP, Ferris FL 3rd, Klein RE et al (2003) Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 110(9):1677–1682. doi:10.1016/S0161-6420(03)00475-5

14. Sim DA, Keane PA, Rajendram R et al (2014) Patterns of peripheral retinal and central macula ischemia in diabetic retinopathy as evaluated by ultra-widefield fluorescein angiography. Am J Ophthalmol 158(1):144–153 e141. doi:10.1016/j.ajo.2014.03.009

15. Edelman JL, Lutz D, Castro MR (2005) Corticosteroids inhibit VEGF-induced vascular leakage in a rabbit model of blood-retinal and blood-aqueous barrier breakdown. Exp Eye Res 80(2):249–258. doi:10.1016/j.exer.2004.09.013

16. Tamura H, Miyamoto K, Kiryu J et al (2005) Intravitreal injection of corticosteroid attenuates leukostasis and vascular leakage in experimental diabetic retina. Invest Ophthalmol Vis Sci 46(4):1440–1444. doi:10.1167/iovs.04-0905

17. Dugel PU, Bandello F, Loewenstein A (2015) Dexamethasone intravitreal implant in the treatment of diabetic macular edema. Clin Ophthalmol 9:1321–1335. doi:10.2147/OPTH.S79948