Microvascular Changes In The Recurrent Cystoid Macular Edema Secondary to Posterior Noninfectious Uveitis on Optical Coherence Tomography Angiography

Valeria Albano (valeria.albano12@gmail.com)
Universita degli Studi di Bari Aldo Moro https://orcid.org/0000-0002-6193-3299
Silvana Guerriero
University of Bari: Universita degli Studi di Bari Aldo Moro
Claudio Furino
University of Bari: Universita degli Studi di Bari Aldo Moro
Giancarlo Sborgia
University of Bari: Universita degli Studi di Bari Aldo Moro
Alessandra Sborgia
University of Bari: Universita degli Studi di Bari Aldo Moro
Rosanna Dammacco
University of Bari: Universita degli Studi di Bari Aldo Moro
Francesco Boscia
University of Bari: Universita degli Studi di Bari Aldo Moro
Giovanni Alessio
University of Bari: Universita degli Studi di Bari Aldo Moro

Research Article

Keywords: non-infectious posterior uveitis, cystoid macular edema, optical coherence tomography angiography.

Posted Date: September 28th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-790122/v1

Abstract

BACKGROUND: Posterior uveitis represents the second most frequent type of uveitis (15-30% of all uveitis). Non-infectious posterior uveitis complicated with secondary cystoid macular edema (CME) negatively affected the visual prognosis.

The objective of the current study is to determine possible microvascular changes that can cause a relapsing uveitis-CME through optical coherence tomography angiography (OCTA).

METHODS: This is a case-control study, an evaluation of patients with secondary CME noninfectious posterior uveitis-related undergoing dexamethasone (DEX) implant. The visits following the DEX-implant were carried out after 1 month, 2-months, 4-months, 6-months, and for up 1-year.

A total of 76 eyes of 38 consecutive patients with noninfectious posterior uveitis were enrolled (consecutive sample). Complicated noninfectious posterior uveitis with secondary CME was diagnosed in 56 eyes of uveitis patients (24.3%) reviewed.

RESULTS: Our investigation showed a reduction in superficial vessel plexus (SVP) measurements already within 2-month (84%), reaching 96.4% for up 1-year, however displaying an irregular profile in 69.6% of cases, persisting for up 1-year; the relapsing uveitis-CME eyes with irregular superficial foveal avascular zone (FAZ) profile were in 51%, while the SVP measurements reestablished in 100% of cases. Conversely, the deep vascular plexus (DVP) parameters restored occurred in a lower number of eyes within the 2-month (39.3%), remaining abnormal in 46.4% of cases for up 1-year; despite DVP restored in 53.6% of cases for up 1 year, a capillary rarefaction ring around the FAZ appeared in 80.4% of cases; the relapsing uveitis-CME eyes with abnormal DVP parameters were in 41% of cases, of which 92.1% showed a rarefaction ring had abnormal DVP.

CONCLUSIONS: The use of OCTA allows to evaluate the retinal microvascular features, which could be the cause of the recurrence of CME in uveitis patients, despite the DEX-implant treatment. We suggested that the possibility of the recurrence of the uveitis-CME depends on the persistence of modifications of the superficial and deep layers, which we therefore consider appropriate to investigate. With this purpose it would be useful to introduce OCTA into the current imaging armamentarium in follow-up of patients with noninfectious uveitis-CME.

Introduction

Posterior uveitis represents the second most frequent type of uveitis (15–30% of all uveitis).[1]

These forms cause unilateral visual impairment in 14–50 % of cases, and bilateral in 4–40%.[2] Posterior uveitis are infectious or noninfectious beginning. Noninfectious posterior uveitis is several entities that can be associated with autoinflammatory, or autoimmune diseases,[3] affecting the retina, and choroid,

sometimes involving adjacent structures, such as the vitreous, optic nerve.[4] The treatment with systemic steroid, or immunosuppressive therapy, depends on the underlying disease.[5]

In some cases, noninfectious posterior uveitis is complicated with secondary cystoid macular edema (CME), estimated in various studies about 20–70%, negatively affecting the visual prognosis.[6]

CME in uveitis depends on the intraretinal accumulation of fluid, due to the alteration of the integrity of the blood-retinal barrier (BRB).[7] If the inflammatory stimulus is fleeting, then BRB restores spontaneously, while if it enduring, focal or diffuse leakage occurring in the extracellular space of the retina, mainly at the level of the external plexiform layer (layer of Henle).[8]

A negative correlation between CME, macular thickness, and visual acuity was revealed in the study by Iannetti *et al.*;[9] the positive correlation between CME and duration of uveitis was also described.[10]

CME was studied employing imaging techniques commonly used, such as fluorangiography (FA), indocyanine green angiography (ICG-A), and optical coherence tomography (OCT).[11] Latest technological developments have led to the innovative introduction of optical coherence tomography with angiography modules (OCT-A), which accurately detecting ultrastructural details of the retinal capillaries, not otherwise identified.[12]

For the treatment of CME related to noninfectious posterior uveitis, the biodegradable dexamethasone 0.7 mg with the intravitreal implant has been approved by the US Food and Drug Administration (US-FDA) in 2010,[13] and by NICE (and Care Excellence National Institute) in 2017[14,15] for the treatment of the persistent noninfectious uveitis-CME.

Previous studies have investigated the benefits and limits of dexamethasone implantation (DEX-implant) in uveitis were either prospective and retrospective.[16–19]

Since the trial by Lowder *et al.* in 2011,[20] the safety, tolerability, and efficacy of the DEX-implant in non-infectious uveitic macular edema (ME) was reported.[21–24]

However, the treatment was not always lasting in the long-term, and some cases of recurrent CME associated with uveitis were recorded.[25]

The pathogenesis of the recurrence of CME in uveitis may be anatomical and functional changes of the retinal vessels.[26]

This study aims to evaluate the microvascular changes following the DEX-implant in patients who presented secondary CME non-infectious posterior uveitis-related.

Methods

STUDY DESIGN

This is a case-control study, an evaluation of patients with secondary CME noninfectious posterior uveitis-related undergoing DEX-implant. The current article does not contain any personal information that could identify the patient. The data were treated consistent with the tenets of the Declaration of Helsinki. All participants signed the informed consent before the surgery. The Standards for Reporting Diagnostic Accuracy (STARD) statement was developed.[27]

Participants

From January 2020 to December 2020 a total of 76 eyes of 38 consecutive patients with noninfectious posterior uveitis referred to Uveitis University Ophthalmology Center of the Bari Polyclinic were selected. Complicated noninfectious posterior uveitis with secondary CME was diagnosed in 56 eyes of uveitis patients (24.3%) reviewed. All patients with uveitis-CME was treated with a single shot of DEX-implant.

The age range of the sample was 24–84 years (mean 54 ± 42.4 years).

The inclusion criteria were (1) confirmed diagnosis of uni- or bilateral noninfectious posterior uveitis, (2) new referral to Uveitis University Ophthalmology Center of the Bari Polyclinic, (3) the presence of the secondary CME of recent onset confirmed by the OCT findings, and (4) CME not previously treated with intravitreal drugs. All patients enrolled meeting the criteria were included.

Conversely, study exclusion criteria were (1) noninfectious posterior uveitis without related secondary edema, (2) previous intravitreal DEX-implant, (3) previously intravitreal injections of other substances, (4) ocular hypertonus, (5) presence of serous retinal detachment, and (6) previous retinal intraocular surgery.

Demographic characteristics of the study sample were summarized in Table 1.

Table 1
Demographic characteristics of the study sample.

	Sample size (n = 56 eyes)	P *value*
Age (y, range)		0.05
20–35, n (%)	3 (7.9)	
36–50, n (%)	17 (44.7)	
51–60, n (%)	16 (42.1)	
≥ 60, n (%)	2 (5.3)	
Gender		0.22
Female, n (%)	18 (47.4)	
Male, n (%)	20 (52.6)	
Eyes		0.18
Right, n (%)	24 (42.9)	
Left, n (%)	32 (57.1)	
Laterality		0.04
Unilateral, n (%)	12 (31.8)	
Bilateral, n (%)	22 (57.9)	
State of eye		0.08
Phakic,n (%)	31 (55.4)	
Pseudophakic, n (%)	25 (44.6)	
Course of uveitis		0.06
Acute, n (%)	8 (21)	
Recurrent, n (%)	18 (47.4)	
Chronic, n (%)	12 (31.6)	
Etiology of uveitis		0.06
Uveitis not associated with systemic disease, n (%)	8 (21)	
Uveitis associated with systemic disease, n (%)	18 (47.4)	
Idiopathic uveitis, n (%)	12 (31.6)	

Abbreviations: Y, years; N, number; %, percent; BCVA, best corrected visual acuity; IOP, intraocular pressure; OCT, optical coherence tomography; CME, cystoid macular edema.

	Sample size (n = 56 eyes)	P *value*
Previous systemic treatment		0.07
Corticosteroids, n (%)	25 (65.8)	
Immunosuppressors, n (%)	13 (34.2)	
BCVA (logMAR) at inclusion, range		0.04
< 0.1, n (%)	4 (7.1)	
0.1–0.4, n (%)	15 (26.8)	
0.5–1.0, n (%)	28 (50)	
> 1.0, n (%)	9 (16.1)	
IOP (mmHg) at inclusion		0.18
8–14	32 (57.1)	
15–21	24 (42.9)	
OCT macular findings		0.06
CME with the epiretinal membrane, n (%)	20 (35.7)	
CME without the epiretinal membrane, n (%)	36 (64.3)	
Abbreviations: Y, years; N, number; %, percent; BCVA, best corrected visual acuity; IOP, intraocular pressure; OCT, optical coherence tomography; CME, cystoid macular edema.		

Patients were previously treated with systemic therapy, immunosuppressive drugs, or corticosteroids, depending on the underlying disease.

In all those eyes in which CME was diagnosed they received a sustained-release 0.7 mg intravitreal DEX-implant (DEX-implant, Ozurdex®, Allergan, Inc.).

Clinical Examination

The visits following the DEX-implant were carried out after 1 month (M1), 2-months (M2), 4-months (M4), 6-months (M6), and for up 1-year (Y1).

Examinations were performed as following: the best-corrected visual acuity (BCVA, logMAR), *in vivo* biomicroscopy, measurement of intraocular pressure (IOP, mmHg) using Perkins applanation tonometer, spectral domain optical coherence tomography (SD-OCT, RTVue XR Spectral Domain OCT, Optovue Inc, Fremont, USA), optical coherence tomography angiography (OCT-A, SS OCT Angio ™ into Swept Source DRI OCT Triton ™, Topcon Medical Systems, Inc.).

The central macular thickness (CMT) was indagated through SD-OCT by MM6 scanning.

The foveal avascular zone (FAZ), the superficial vessel plexus (SVP), and the deep vessel plexus (DVP) were examined by OCTA data analysis into a 3x3 mm^2 parafoveal window. (see Fig. 1).

Faz Area Measurements

FAZ area outlined after importing image records to Adobe Photoshop (Adobe Photoshop CC 2018 (19.0), Adobe Systems, San José, California, USA) as JPEG-file. The borders of FAZ were defined in red color. Area quantification was also performed in Adobe Photoshop.

Statistical Analyses

The statistical analyses were performed using SPSS Statistics for Windows, version 23.0 (SPSS Inc., Chicago, Ill., USA).

Comparisons between groups were performed using the non-parametric Mann–Whitney U-test. Categorical comparison of the was made using a Pearson's Chi-squared test.

We have assumed statistical significance at $p < 0.05$.

Results

A significant improvement in BCVA during the 1-year follow-up from T0 to 1Y (mean 0.3 ± 0.2 logMAR, range 0.8–0.1 logMAR, p = .001) has been recorded.

There were no significant increases in IOP up the 1-year following the DEX implantation (mean 14.5 mmHg ± 9.2, range 8–21 mmHg, p = .006).

OCT data were reported in Table 2.

Table 2
OCT and OCTA data of the study sample during follow-up.

	T0	M1	M2	M4	M6	Y1
CMT, mean (SD), μm	514.96 (141.87)	329.85 (157.43)	326.75 (123.01)	331.07 (141.56)	332.78 1 (171.06)	245.56 (124.78)
SVP, mean (SD), mm^2	1.01 (0.28)	0.55 (0.39)	0.54 (0.34)	0.52 (0.28)	0.51 (0.36)	0.31 (0.22)
DVP, mean (SD), mm^2	0.71	0.55 (0.16)	0.52 (0.18)	0.51 (0.19)	0.51 (0.18)	0.48 (0.15)
Abbreviations: CMT, central macular thickness; SVP, superficial vessel plexus; DVP, deep vessel plexus; T0, inclusion; M1, 1 month, M2, 2-month; M4, 4-month; M6, 6-month; Y1, 1 year.						

In the sample size examined, the mean CMT was decreased from baseline (514.96 ± 141.88 μm) to the 1-year follow-up (245.65 ± 143.81 μm), range 215.43–650.14 μm (p = .001).

The CME recovery was established after DEX implant, as following: in 27 eyes (48.2%) the CME at M1, in 15 eyes (26.8%) at M2, in 6 eyes (10.7%) at M4, in 5 eyes (8.9%) at M6, in 3 eyes (5.4%) at Y1.

CME recurred in 30 eyes (53.6%) treated with one single shot of DEX implant; of these 18 (32.1%) had an ERM at inclusion. The relapsing CME occurred at M4 in 21 eyes (37.5%), and M6 in 9 eyes (16.1%).

All of these relapsed eyes replanted as soon as CME reappeared. At 1 year, 28 eyes (93.3%) had a complete resorption, in the absence of a recurrence of uveitis.

Superficial, And Deep Faz Area Changes

OCTA data were showed in Table 2.

The enlargement of the FAZ in the SVP was restored, as following: in 32 eyes (57.1%) at M1, in 15 eyes at M2 (26.9%), in 3 eyes at M4 (5.3%), 3 eyes (5.3%) at M6, ad in 1 eye (1.8%) at 1Y; in 2 eyes (3.6%) it remained enlarged despite the DEX implant.

The mean superficial FAZ area was significatively reduced from baseline 1 ± 0.28 mm^2 to 0.31 ± 0.22 mm^2 at the end of the 1-year follow-up (range 0.12–1.23 mm^2, p = .001).

The FAZ area in SVP was irregular in 39 eyes (69.6%) at the end of 1-year follow-up

The FAZ diameter was reestablished in DVP, as following: in 10 eyes (17.9%) at M1, in 12 eyes (21.4%) at M2, in 4 eyes (7.1%) at M4, in 2 eyes (3.6%) at M6, and in 2 eyes at 1Y (3.6%); in 26 eyes (46.4%) it remained enlarged despite the DEX implant.

The mean deep FAZ area was not significatively reduced from baseline 0.71 ± 0.17 mm^2 to 0.48 ± 0.15 mm^2 at the end of the 1-year follow-up (range 0.25–0.86, p = .001).

In the deep FAZ, a capillaries rarefaction appeared around the FAZ in 45 eyes (80.4%).

Discussion

One of the most common complications of noninfectious posterior uveitis is CME.[28]

In 2004, Markomichelakis *et al.* have identified two main patterns of ME, with no statistical significance in relation to the location, or etiology of uveitis: 1) diffuse type (DME), and 2) cystoid type (CME).[29]

The incidence of CME has been estimated in various studies about 33% of uveitis patients.[30] In recent reports, the use of OCT has revealed the CME type in 25–69% of patients with uveitic ME examined.[9,29]

In essence, the presence of CME was observed especially in higher age of patients at the onset of uveitis, insidious onset of uveitis, persistent duration of an attack of uveitis, a chronic course of uveitis, bilateral involvement. In accord with previous studies,[31,32] the occurrence of CME in noninfectious posterior uveitis seems to be associated with systemic disease, or idiopathic uveitis (p = .001), lower BCVA (p = .001), and a refractory course despite the treatment, while no significant association of CME with gender (p = .065) emerged.

It was proven how a single injection of dexamethasone is effective in reducing CMT, which doing a significant gain in visual acuity (AV).[33–43]

As described by Pleyer *et al.*,[44]from our data analysis there was a significant reduction in CMT at M1 (p = 0.001), associated with an improvement in BCVA (p = .002).

No significant difference was observed between the resolution of CME in non-infectious posterior uveitis with known cause (either not associated with systemic disease, and those associated with systemic disease) compared to non-infectious posterior uveitis of idiopathic origin (p = .087).

On the other hand, the CME has reappeared over time in a significant percentage of cases, in 37.5% after 4-month, and 16.1% after 6-month. For instance, Nobre-Cardoso *et al.*[45]documented the reappearance of CME in 31.3% of cases treated after 3-month, and Khurana *et al.*[15] described a recurrence of CME after the 6-month in 65% of cases.

If CME persists, getting damaged photoreceptors, with possible serious complications such as macular ischemia, epiretinal membranes (ERM), macular hole.[46] In turn, the presence of ERM has a negative correlation with lower visual acuity and CME relapsing.[32]

Our study is consistent with the OCT data found in the literature for defining the uveitis macular ME features,[47] such as the CMT,[31] different patterns of edema,[29] the associated vitreoretinal interface.[48]

CMT was very thick (> 300μm) at inclusion and significantly reduced after the 1-month DEX-implant (p = .001). Only the cystoid form of uveitic ME was included in the study, which the most difficult entity to resolve.[32] The presence of ERM associated with CME in a certain percentage of patients (35.7%). Of these, uveitis-CME recurrence despite the DEX-implant occurred in 32.1% of cases of ERM associated.

Regarding the persistence, or the recurrence of uveitis-CME, it was hypothesized the microstructural disruption of the inner and outer blood-retinal-barrier as the result of the release of inflammatory cytokines.[49–51] It has already been revealed that the possibility of anatomical and functional modifications of the retinal capillary network can be negatively correlated with the CME recurrence, but it has been demonstrated in diabetic patients.[26]

To our knowledge, no other studies in the literature estimated the microvascular changes of the retinal capillaries in CME posterior noninfectious uveitis after the DEX-implant have been found. Most of the studies, as seen, were based on follow-up through OCT, widely used in clinical practice.

Although OCT has dramatically transformed the understanding and management of uveitis-CME, it does not allow to evaluate the retinal microvascular characteristics, which could be the cause of the recurrence of CME in uveitis patients.[52]

OCTA previously has proven being an interesting imaging tool in diagnosis, and management of retinal vasculitis,[53–55] and choriocapillaritis,[56–57]as it allowed to visualize in detail the retinal microvascular changes, which can be so easily assessed and quantified, to accurately identify the area of the FAZ,[58] or the parafoveal capillary telangiectasia and shunting vessels,[59] or the rarefaction of the perifoveal capillary network.[60]

The current study suggests use of OCTA among the imaging techniques for identifying microvascular changes during the course treatment with DEX-implant in noninfectious posterior uveitis, whereas the other instruments fail to detect the retinal capillary plexuses.

Although the complete intraretinal and subretinal fluid resorption observed though OCT images after DEX-implant, some microvascular anatomical and functional changes were revealed by OCTA findings.

Our investigation showed a reduction in SVP measurements already within 2-month (84%), reaching 96.4% for up 1-year, however displaying an irregular profile in 69.6% of cases, persisting for up 1-year.

The relapsing uveitis-CME eyes with irregular superficial FAZ profile were in 51%, while the SVP measurements reestablished in 100% of cases.

Conversely, the DVP parameters restored occurred in a lower number of eyes within the 2-month (39.3%), remaining abnormal in 46.4% of cases for up 1-year.

Despite DVP restored in 53.6% of cases for up 1 year, a capillary rarefaction ring around the FAZ appeared in 80.4% of cases.

The relapsing uveitis-CME eyes with abnormal DVP parameters were in 41% of cases, of which 92.1% showed a rarefaction ring had abnormal DVP.

Enlarged deep FAZ was found in patients with posterior uveitis, both in the presence and absence of ME.[61] Significant changes in DVP parameters were previously detected in uveitis-CME, matching with the site of intraretinal cystoid spaces in the inner retina (inner nuclear and plexiform layers).[62] The enlarged deep FAZ coupled with the rarefaction of the perifoveal capillary network was described in other ocular diseases as microstructural damage to the retinal barrier.[63,64]

Persistent damage of the retinal capillary layers, both of the superficial, and particularly of the deep plexuses, may further explain the reason of the relapsing uveitis-CME.

Limits

In using the OCTA of the patient with uveitis, we also encountered some difficulties to be taken into account, such as the possibility of the presence of synechiae, vitreous turbidity, dense cataracts, which may hinder good quality in image acquisition; to these limitations it is necessary to add age heterogeneity and patient collaboration, which were also crucial for a good quality of acquisition.

Conclusions

Currently, OCT-A adds significant value to the multimodal imaging armamentarium in noninfectious posterior uveitis. It can be useful in monitoring complications such as the uveitis-CME, and predictive of the relapsing CME. By embracing the hypothesis of the persistence of microvascular modifications of BRB in relapsing uveitis-CME cases, the OCTA plays a decisive role to provide a microstructural analysis of the retinal capillary plexuses, representing a valid option for prognosis.

Declarations

Ethics approval and consent to participate

The study was performed in accordance with the Declaration of Helsinki and

approved by the institution’s review board. Each patient signed the informed

consent form.

Consent for publication

Written informed consent was obtained for publication of this study.

Availability of data and materials

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

There is no financial support for this study.

Authors' contributions

Concept and design: VA, SG, CF, RD.

Acquisition, analysis, or interpretation of data: VA, SG, CF.

Drafting of the manuscript: VA, SG, CF.

Critical revision of the manuscript for important intellectual content: VA, SG, CF.

Statistical analysis: VA, SG, CF, AS, RD, CP, FB, GA.

Administrative, technical, or material support: VA, SG, CF, AS, RD, CP, FB, GA.

Supervision: VA, SG, CF, AS, CP, FB, GA.

All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

References

1. Tsirouki T, Dastiridou A, Symeonidis C et al. A Focus on the Epidemiology of Uveitis. Ocular Immunology and Inflammation. 2018 Jan 2;26(1):2–16
2. Uy HS, Yu-Keh E, Chan PS. Posterior Uveitis. In: Nguyen QD, Rodrigues EB, Farah ME, Mieler WF, Do DV, editors. Developments in Ophthalmology [Internet]. Karger S AG (2015) [cited 2020 Dec 8]. p. 163–6. Available from: https://www.karger.com/Article/FullText/438968

3. Forrester JV, Kuffova L, Dick AD (2018 May) Autoimmunity, Autoinflammation, and Infection in Uveitis. Am J Ophthalmol 189:77–85
4. Biswas J, Sudharshan S, Ganesh S (2010) Current approach in the diagnosis and management of posterior uveitis. Indian J Ophthalmol 58(1):29
5. Castiblanco C, Foster CS (2014 Dec) Review of Systemic Immunosuppression for Autoimmune Uveitis. Ophthalmol Ther 3(1–2):17–36
6. Lardenoye CWTA, van Kooij B, Rothova A (2006 Aug) Impact of Macular Edema on Visual Acuity in Uveitis. Ophthalmology 113(8):1446–1449
7. Chung Y-R. Insights into the pathogenesis of cystoid macular edema: leukostasis and related cytokines. Int J Ophthalmol. 2019 Jul 18;12(7):1202–8
8. Bringmann A, Reichenbach A, Wiedemann P (2004) Pathomechanisms of Cystoid Macular Edema. Ophthalmic Res 36(5):241–249
9. Iannetti L, Accorinti M, Liverani M, Caggiano C, Abdulaziz R, Pivetti-Pezzi P. Optical Coherence Tomography for Classification and Clinical Evaluation of Macular Edema in Patients with Uveitis. Ocular Immunology and Inflammation. 2008 Jan;16(4):155–60
10. Okhravi N, Lightman S (2003 Jan) Cystoid macular edema in uveitis. Ocular Immunology Inflammation 11(1):29–38
11. Onal S, Tugal-Tutkun I, Neri P, Herbort P (2014 Apr) C. Optical coherence tomography imaging in uveitis. Int Ophthalmol 34(2):401–435
12. Pichi F, Sarraf D, Arepalli S et al (2017 Jul) The application of optical coherence tomography angiography in uveitis and inflammatory eye diseases. Prog Retin Eye Res 59:178–201
13. Saraiya NV, Goldstein DA (2011 May) Dexamethasone for ocular inflammation. Expert Opin Pharmacother 12(7):1127–1131
14. Couret C, Poinas A, Volteau C et al. Comparison of two techniques used in routine care for the treatment of inflammatory macular oedema, subconjunctival triamcinolone injection and intravitreal dexamethasone implant: medical and economic importance of this randomized controlled trial. Trials. 2020 Feb 10;21(1):159
15. Khurana RN, Porco TC. EFFICACY AND SAFETY OF DEXAMETHASONE INTRAVITREAL IMPLANT FOR PERSISTENT UVEITIC CYSTOID MACULAR EDEMA: Retina. 2015 Aug;35(8):1640–6
16. Ong DN, Lim LL (2019 Dec) The efficacy of intravitreal dexamethasone implants for non-infectious posterior segment uveitis: Increasing the uveitis armamentarium. Clin Experiment Ophthalmol 47(9):1119–1121
17. Squires H, Poku E, Bermejo I et al (2017 Nov) A systematic review and economic evaluation of adalimumab and dexamethasone for treating non-infectious intermediate uveitis, posterior uveitis or panuveitis in adults. Health Technol Assess 21(68):1–170
18. Hasanreisoğlu M, Özdemir HB, Özkan K et al (2019 Oct) Intravitreal Dexamethasone Implant in the Treatment of Non-infectious Uveitis. Turk J Ophthalmol 24(5):250–257 49(

19. González MM, Solano MM, Porco TC et al. Epidemiology of uveitis in a US population-based study. J Ophthalmic Inflamm Infect. 2018 Apr 17;8(1):6
20. Lowder C Jr, Lightman RB (2011) S, et al. Dexamethasone Intravitreal Implant for Noninfectious Intermediate or Posterior Uveitis. ARCH OPHTHALMOL 129(5):9
21. Yap YC, Papathomas T, Kamal A (2015) Results of intravitreal dexamethasone implant 0.7 mg (Ozurdex®) in non-infectious posterior uveitis. Int J Ophthalmol 8(4):835–838
22. Tsang AC, Virgili G, Abtahi M, Gottlieb CC. Intravitreal Dexamethasone Implant for the Treatment of Macular Edema in Chronic Non-infectious Uveitis. Ocular Immunology and Inflammation. 2017 Sep 3;25(5):690–7
23. Frère A, Caspers L, Makhoul D et al (2017 May) Single Dexamethasone Intravitreal Implant in the Treatment of Noninfectious Uveitis. J Ocul Pharmacol Ther 33(4):290–297
24. Ryder S, Iannetta D, Bhaleeya S, Kiss S. Efficacy and tolerability of bilateral sustained-release dexamethasone intravitreal implants for the treatment of noninfectious posterior uveitis and macular edema secondary to retinal vein occlusion. OPTH. 2015 Jun;1109
25. Shulman S, Azem N, Gepstein R. Use of Intravitreal Dexamethasone Implant (Ozurdex) Prior to Cataract Surgery in Uveitic Patients. J Clin Exp Ophthalmol [Internet]. 2017 [cited 2021 Jan 6];08(05). Available from: https://www.omicsonline.org/open-access/use-of-intravitreal-dexamethasone-implant-ozurdex-prior-to-cataract-surgery-in-uveitic-patients-2155-9570-1000680-93908.html
26. Mastropasqua L, Di Staso S, D'Aloisio R et al (2019) Anatomical and functional changes after dexamethasone implant and ranibizumab in diabetic macular edema: a retrospective cohort study. Int J Ophthalmol 12(10):1589–1597
27. Cohen JF, Korevaar DA, Altman DG et al. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. BMJ Open. 2016 Nov 14;6(11):e012799
28. Invernizzi A, Cozzi M, Staurenghi G (2019 Apr) Optical coherence tomography and optical coherence tomography angiography in uveitis: A review. Clin Experiment Ophthalmol 47(3):357–371
29. Markomichelakis NN, Halkiadakis I, Pantelia E et al (2004 May) Patterns of macular edema in patients with uveitis: qualitative and quantitative assessment using optical coherence tomography. Ophthalmology 111(5):946–953
30. Rothova A, Suttorp-van Schulten MS, Frits Treffers W, Kijlstra A (1996) Causes and frequency of blindness in patients with intraocular inflammatory disease. British Journal of Ophthalmology. Apr 1;80(4):332–6
31. Grajewski RS, Boelke AC, Adler W et al (2016 Nov) Spectral-domain optical coherence tomography findings of the macula in 500 consecutive patients with uveitis. Eye 30(11):1415–1423
32. Markomichelakis NN, Halkiadakis I, Pantelia E et al (2007 Apr) Course of macular edema in uveitis under medical treatment. Ocul Immunol Inflamm 15(2):71–79
33. LeHoang P (2012) The gold standard of noninfectious uveitis: corticosteroids. Dev Ophthalmol 51:7–28

34. Robinson BH, Mattingly D, Cope CL. Adrenal function after prolonged corticosteroid therapy. Br Med J. 1962 Jun 9;1(5292):1579–84
35. Stanbury RM, Graham EM (1998 Jun) Systemic corticosteroid therapy–side effects and their management. Br J Ophthalmol 82(6):704–708
36. Fardeau C, Simon A, Rodde B et al (2017 May) Interferon-alpha2a and Systemic Corticosteroid in Monotherapy in Chronic Uveitis: Results of the Randomized Controlled BIRDFERON Study. Am J Ophthalmol 177:182–194
37. Fabiani C, Vitale A, Lopalco G, Iannone F, Frediani B, Cantarini L (2016 Nov) Different roles of TNF inhibitors in acute anterior uveitis associated with ankylosing spondylitis: state of the art. Clin Rheumatol 35(11):2631–2638
38. Fabiani C, Vitale A, Emmi G et al (2017 Jan) Efficacy and safety of adalimumab in Behçet's disease-related uveitis: a multicenter retrospective observational study. Clin Rheumatol 36(1):183–189
39. Fabiani C, Sota J, Tosi GM et al (2017 Oct) The emerging role of interleukin (IL)-1 in the pathogenesis and treatment of inflammatory and degenerative eye diseases. Clin Rheumatol 36(10):2307–2318
40. Fabiani C, Vitale A, Emmi G et al (2017 Jan) Interleukin (IL)-1 inhibition with anakinra and canakinumab in Behçet's disease-related uveitis: a multicenter retrospective observational study. Clin Rheumatol 36(1):191–197
41. Fardeau C, Champion E, Massamba N, LeHoang P (2016 Oct) Uveitic macular edema. Eye (Lond) 30(10):1277–1292
42. Fabiani C, Alió JL. Local (topical and intraocular) therapy for ocular Adamantiades – Behçet's disease: Current Opinion in Ophthalmology. 2015 Nov;26(6):546–52
43. Hoerauf H, Feltgen N, Weiss C et al (2016 Sep) Clinical Efficacy and Safety of Ranibizumab Versus Dexamethasone for Central Retinal Vein Occlusion (COMRADE C): A European Label Study. Am J Ophthalmol 169:258–267
44. Pleyer U, Klamann M, Laurent T-J et al (2014) Fast and Successful Management of Intraocular Inflammation with a Single Intravitreal Dexamethasone Implant. Ophthalmologica 232(4):223–229
45. Nobre-Cardoso J, Champion E, Darugar A, Fel A, Lehoang P, Bodaghi B. Treatment of Non-infectious Uveitic Macular Edema with the Intravitreal Dexamethasone Implant. Ocular Immunology and Inflammation. 2017 Jul 4;25(4):447–54
46. Karim R, Sykakis, Lightman S, Fraserbell. Interventions for the treatment of uveitic macular edema: a systematic review and meta-analysis. OPTH. 2013 Jun;1109
47. Tran THC, de Smet MD, Bodaghi B, Fardeau C, Cassoux N, Lehoang P. Uveitic macular oedema: correlation between optical coherence tomography patterns with visual acuity and fluorescein angiography. British Journal of Ophthalmology. 2008 Jul 1;92(7):922–7
48. Lehpamer B, Moshier E, Pahk P et al (2014 May) Epiretinal membranes in uveitic macular edema: effect on vision and response to therapy. Am J Ophthalmol 157(5):1048–1055
49. Freeman G. Cystoid macular oedema in uveitis: An unsolved problem. Eye. 2001 Jan 1;15(1):12–7

50. Howes EL, Cruse VK (1978) The Structural Basis of Altered Vascular Permeability Following Intraocular Inflammation. Archives of Ophthalmology. Sep 1;96(9):1668–76
51. Rotsos TG, Moschos MM. Cystoid macular edema. Clin Ophthalmol. 2008 Dec;2(4):919–30
52. Hagag A, Gao S, Jia Y, Huang D (2017) Optical coherence tomography angiography: Technical principles and clinical applications in ophthalmology. Taiwan J Ophthalmol 7(3):115
53. Emre S, Güven-Yılmaz S, Ulusoy MO, Ateş H (2019 Oct) Optical coherence tomography angiography findings in Behcet patients. Int Ophthalmol 39(10):2391–2399
54. Dingerkus VLS, Munk MR, Brinkmann MP et al (2019 Dec) Optical coherence tomography angiography (OCTA) as a new diagnostic tool in uveitis. J Ophthal Inflamm Infect 9(1):10
55. Tian M, Tappeiner C, Zinkernagel MS, Huf W, Wolf S, Munk MR (2019 Sep) Evaluation of vascular changes in intermediate uveitis and retinal vasculitis using swept-source wide-field optical coherence tomography angiography. Br J Ophthalmol 103(9):1289–1295
56. Marchese A, Agarwal A, Moretti AG et al (2020 Jan) Advances in imaging of uveitis. Ophthalmol Eye Dis 12:251584142091778
57. Khochtali S, Dridi T, Abroug N, Ksiaa I, Lupidi M, Khairallah M (2020 Jun) Swept-Source Optical Coherence Tomography Angiography Shows Choriocapillaris Flow Reduction in Multiple Evanescent White Dot Syndrome. J Curr Ophthalmol 32(2):211–215
58. Tranos P, Karasavvidou E-M, Gkorou O, Pavesio C (2019 Dec) Optical coherence tomography angiography in uveitis. J Ophthal Inflamm Infect 9(1):21
59. Karti O, Saatci AO (2019) Optical Coherence Tomography Angiography in Eyes with Non-infectious Posterior Uveitis; Some Practical Aspects. Med Hypothesis Discov Innov Ophthalmol 8(4):312–322
60. Khairallah M, Abroug N, Khochtali S et al. OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY IN PATIENTS WITH BEHÇET UVEITIS: Retina. 2017 Sep;37(9):1678–91
61. Waizel M, Todorova MG, Terrada C, LeHoang P, Massamba N, Bodaghi B (2018 Oct) Superficial and deep retinal foveal avascular zone OCTA findings of non-infectious anterior and posterior uveitis. Graefes Arch Clin Exp Ophthalmol 256(10):1977–1984
62. Kim AY, Rodger DC, Shahidzadeh A et al (2016 Nov) Quantifying Retinal Microvascular Changes in Uveitis Using Spectral-Domain Optical Coherence Tomography Angiography. Am J Ophthalmol 171:101–112
63. Cennamo G, Montorio D, Santoro C et al. The Retinal Vessel Density as a New Vascular Biomarker in Multisystem Involvement in Fabry Disease: An Optical Coherence Tomography Angiography Study. J Clin Med. 2020 Dec 18;9(12)
64. Carnevali A, Sacconi R, Corbelli E et al (2017 Jul) Optical coherence tomography angiography analysis of retinal vascular plexuses and choriocapillaris in patients with type 1 diabetes without diabetic retinopathy. Acta Diabetol 54(7):695–702

Figures

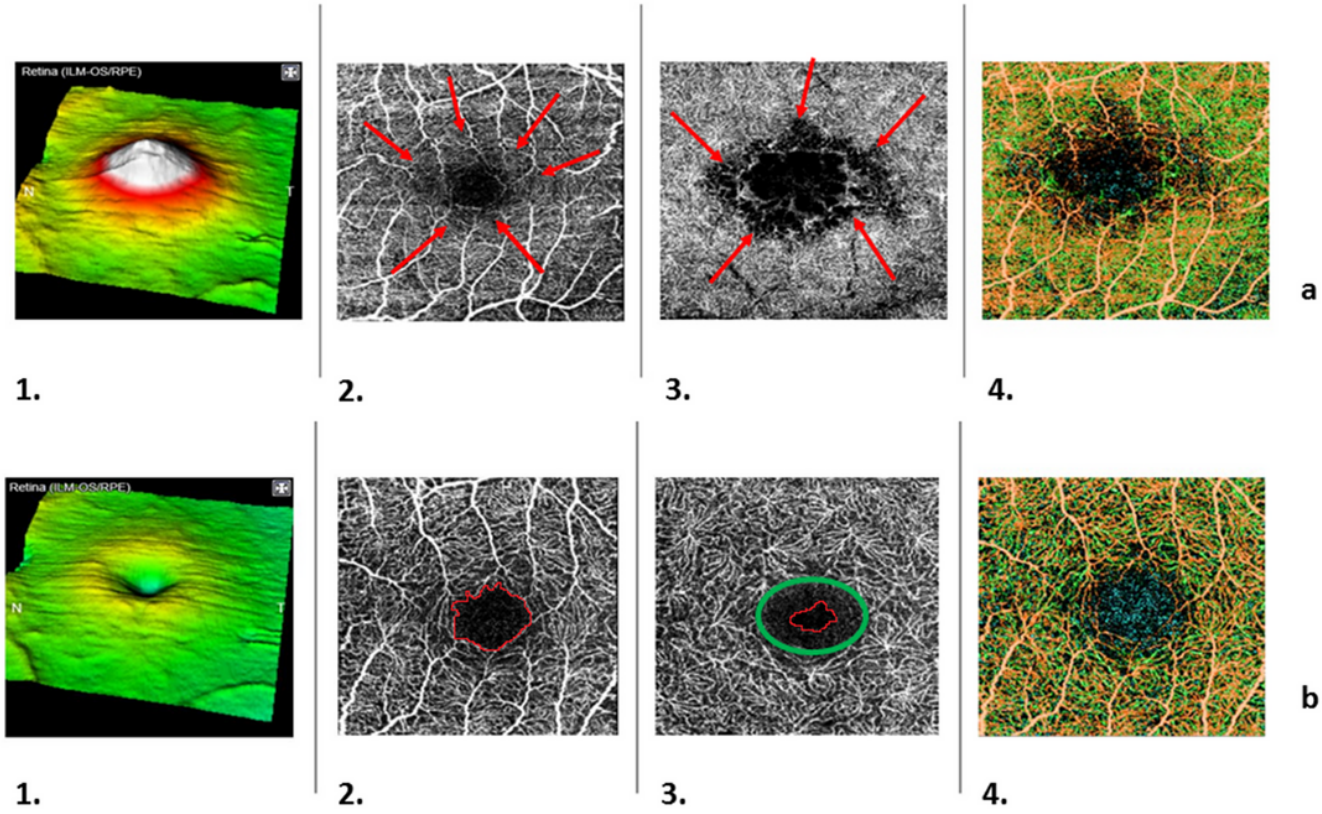

Figure 1

Representative images on a uveitis-CME eye of the sample study before the DEX-implant treatment (a) and after follow-up 6-month (b) showed. 1. The 3D map of the CMT (SD-OCT) 2. The SVP scan centered on the FAZ (SS-OCTA). 3. The DVP scan centered on the FAZ (SS-OCTA). 4. En face image with montage scanning protocol (SS-OCTA). The increase of the CMT before the DEX-implant (a, 1) and the reduction of the CMT after the DEX-implant (b, 1) are illustrated. The cystic fluid is outlined by red arrows around the FAZ area in the SVP (a,2) and DVP (a,3) layers. The irregular FAZ profile in the SVP (b,2) and DVP (b,3) layers are marked in the red line. The capillary rarefaction ring in the DVP network is pointed out with a green circle (b,3).