Clinical and imaging biomarkers of response to intravitreal dexamethasone implant in eyes with non-infectious uveitic macular oedema

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Article

Keywords: Macular oedema, non-infectious uveitis, dexamethasone implant, optical coherence tomography

Posted Date: June 16th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2927148/v1

Additional Declarations: There is no conflict of interest

Version of Record: A version of this preprint was published at Eye on October 30th, 2023. See the published version at https://doi.org/10.1038/s41433-023-02802-7.

Abstract

Objective

To investigate the clinical and spectral-domain optical coherence tomography (SD-OCT) biomarkers correlating with pre-injection visual acuity (VA), post-injection VA, and the likelihood of macular oedema (MO) regression after dexamethasone (DEX) implant injection in patients with non-infectious uveitic (NIU).

Methods

Patients' data were collected on the date of DEX injection (pre-injection visit), and after three months (post-injection visit). Qualitative and quantitative features were assessed on pre-injection SD-OCT scans.

Results

Data from 173 DEX were analyzed, obtained from 103 eyes of 80 patients; 38 eyes (37%) received repeated DEX. Absent ellipsoid zone (EZ) layer and disorganization of the inner retinal layers (DRIL) were associated with worse pre- (+ 0.19 LogMAR, 95% CI 0.01–0.38, p = 0.06, and + 0.10 LogMAR, 95% CI 0.02–0.21, p = 0.01) and post-injection VA (+ 0.33 LogMAR, 95% CI 0.08–0.57, p = 0.01, and + 0.17 LogMAR, 95% CI 0.01–0.32, p = 0.04). EZ disruption and DRIL increased (p = 0.01 and p = 0.04) and the chance of gaining ≥ 5 letters decreased in eyes undergoing repeated DEX (p = 0.002). The rate of MO regression after each DEX was 67%. Longer MO duration (OR = 0.75 for year, p = 0.02) was associated with lower chance of MO regression. Subretinal fluid was associated with higher rate of MO regression (OR = 6.09, p = 0.01).

Conclusion

Integrity of the inner and outer retina is associated with better visual response to DEX. Long-standing or recurrent MO is associated with less chance of both visual and anatomic response. Timely treatment is necessary to maximize the outcomes of MO in NIU patients.

Introduction

Macular oedema (MO) is the leading cause of visual impairment in intermediate and posterior uveitis.[1] Its pathogenesis is multifactorial and includes inflammation and ischemia, eventually leading to blood-retinal barrier (BRB) disruption and intra- or extracellular fluid accumulation within the macula. If not adequately treated, persistent MO may cause irreversible inner retina and photoreceptor atrophy, with permanent vision loss.[2]

Local and systemic corticosteroids and immunosuppressive therapy (IMT) are effective for MO secondary to non-infectious uveitis (NIU).[3] In the HURON study, NIU MO eyes randomized to the 0.7-mg bioerodable intravitreal implant of dexamethasone (DEX; Ozurdex; Abbvie, Chicago, Illinois USA) had a 6-

fold higher chance of visual improvement than sham treatment.[4] Subsequent real-world studies showed that functional and anatomic responses to DEX are not always favourable,[5] and MO may persist in up to 50% of cases.[6–10] There is a knowledge gap regarding the clinical and morphologic factors predicting the response to intravitreal DEX in NIU MO patients.

Optical coherence tomography (OCT) allows a repeatable evaluation of central macular thickness (CRT) and retinal layers' integrity.[11] Previous studies showed only a moderate correlation between visual acuity (VA) and CRT;[12] thus, alternative biomarkers explaining VA variability in NIU MO patients must be identified. Ellipsoid zone (EZ) damage, hyperreflective foci (HRF), disorganization of retinal inner layers (DRIL), cystoid spaces in the outer (ONL) or inner nuclear layer (INL), subretinal fluid (SF), and presence of vitreoretinal abnormalities, such as an epiretinal membrane (ERM), have been evaluated in other macular diseases.[13] A comprehensive analysis in NIU MO is lacking.

This study investigates the clinical and spectral-domain OCT (SD-OCT) features correlating with pre-injection VA, post-injection VA, and the likelihood of MO regression after DEX in patients with NIU MO. This analysis may assist general ophthalmologists and uveitis specialists forecast the prognosis of NIU patients undergoing intravitreal treatment for MO.

Methods

This was a retrospective, multicenter, noncomparative study on patients seen at the Uveitis Service of the Department of Ophthalmology, San Raffaele Hospital (Milan, Italy), the Department of Ophthalmology of Pitié Salpêtrière University Hospital (Paris, France), and the Department of Ophthalmology of Charité-Universitätsmedizin (Berlin, Germany). The Institutional Review Board (IRB) approved the study design at each centre. All study procedures conformed with the tenets of the Health Insurance Portability and Accountability Act and the Declaration of Helsinki for research involving human subjects.

The initial pool of patients was retrieved from all those receiving the 0.7 mg DEX for NIU between October 2011 and July 2022. We included NIU patients older than 18 years, with VA better than counting fingers, and both clinical data and SD-OCT available for review at the time of DEX. All patients had MO as the main indication for treatment. We excluded patients with MO secondary to infectious uveitis (except for uveitis secondary to tuberculosis hypersensitivity), corneal or lens opacity affecting vision or impeding imaging assessment. We also excluded patients with MO secondary to other retinal diseases (e.g., retinal vein occlusion [RVO], diabetic macular oedema [DMO]), or vision-threatening comorbidities. Both eyes of the same patients were included if eligible.

Patients' data were collected from the visit immediately before each DEX (pre-injection visit) with a maximum time interval of 6 weeks. Demographics, medical history, uveitis diagnosis, decimal VA values, and anterior- and posterior-segment findings were gathered. Patients were defined as non-naïve if they had received any local (periocular or intraocular) treatment before DEX. All patients were managed by experienced uveitis specialists, who made the diagnosis based on a combination of clinical, laboratory,

and imaging findings and undertook treatment decisions. As per clinical practice shared between centres, DEX was administered in cases of uveitic MO unresponsive to systemic treatment, as a bridge therapy before systemic IMT became effective, or in patients with contraindications to systemic medications and no history of steroid response or advanced glaucoma.

Follow-up visits were scheduled within three months from each DEX (post-injection visit), and VA values were collected. Co-registered SD-OCT scans were used to assess MO regression, defined as the absence of intraretinal or subretinal fluid at that visit. Repeated DEX was allowed with a minimum interval of 4 months.

Optical Coherence Tomography Analysis

All SD-OCT scans were acquired with a digital confocal scanning laser ophthalmoscope device (Spectralis HRA, Heidelberg Engineering; Heidelberg, Germany); a raster SD-OCT pattern centred on the fovea was obtained using an enhanced depth imaging technique.

The horizontal SD-OCT scan passing through the fovea acquired during the pre-injection visit was analyzed for the presence of: (1) ERM; (2) DRIL, defined as the impossibility of distinguishing inner retinal layers boundaries in the central 1-millimetre area;[14] (3) HRF, defined as discrete and well-circumscribed dots of identical reflectivity as the RPE band;[15] (4) EZ disruption under the fovea; (4) SF; (5) cysts in the ONL; (6) cysts in the INL (Fig. 1). Quantitative parameters included CRT (μm) in the foveal 1-mm area, subfoveal choroidal thickness (CT, μm), and the vertical diameter of the largest intraretinal cyst (μm). Features that were not assessable because of artefacts or poor visualization were left blank and managed as missing data.

All measurements were carried out by a trained grader at each centre, masked to demographic and clinical characteristics of the study eyes. A senior uveitis specialist (MVC, ST, or DP) solved disagreements between readers.

Statistical Analysis

All statistical analyses were performed with the open-source programming language R (version 1.2.5033). Inferential statistics with a $p < 0.10$ were considered clinically significant.

The sample size was calculated using the wp.mrt2arm function from the WebPower R package,[16] which provided the sample size for a two-level hierarchical linear model, where the main covariate was the first level, and the subject/eye clustering was the second level. For the effect size, we used the posthoc analysis of the VISUAL-1 trial, testing the correlation between different SD-OCT parameters and VA in NIU MO. The study found a mean difference of 0.17 LogMAR (95% confidence interval [CI] 0.07–0.27) between eyes with foveal DRIL and those without DRIL.[17] The between-subjects variance ($\sigma = 0.0027$) and the within-subjects variance ($\sigma = 0.13374$) were calculated in a sample of randomly chosen eyes ($n = 50$) from our data, with a linear mixed regression having pre-injection VA as the dependent variable and DRIL

as the predictor. A sample size of 100 subjects, each contributing with 1.60 eyes, was powered enough to detect a difference of 0.17 LogMAR with a power of 0.8 and significance of 0.05 (assuming an ICC of 0.1).

Descriptive statistics are presented as means, medians, or proportions; group comparisons were performed with linear or logistic regression models.

Firstly, we investigated the correlation between pre-injection VA and clinical and morphologic biomarkers. We used a multiple linear regression model having the LogMAR VA values as the dependent variable and different demographic or SD-OCT features as covariates, adjusted for the lens status (phakic vs. pseudophakic). The covariates were selected with a parsimonious approach, using a least absolute shrinkage and selection operator regression (LASSO).[18] Multi-collinearity issues were excluded by computing the variance inflation factor of each covariate. Nested random factors, including patients' and eye' identification numbers, were included to account for patients being treated bilaterally and some eyes receiving repeated injections. Effect sizes were interpreted while holding constant all other independent variables. Missing data in regression predictors were imputed with multiple imputations.

Secondly, we compared pre- and post-injection VA values. We investigated post-injection VA correlations with a multivariable regression model adjusted for pre-injection VA values, lens status (phakic vs. pseudophakic), systemic treatment, and clustered observations. Regression estimates and their 95% CI were provided.

Finally, we scrutinized the factors associated with MO regression after DEX with multivariable logistic regression models. The exponential logit of each factor was interpreted as the odds ratio (OR) for the binary outcome (regressed vs. persistent MO).

Results

Overall, 103 eyes from 80 patients with NIU MO were included in the study. Each eye received a median of 2 (interquartile range [IQR] 1–3) DEX; 65 eyes (63%) received only one DEX, while 38 eyes (37%) received two or more implants, up to a maximum of 8. Cumulatively, pre- and post-injection data from 173 DEX were analyzed. The median follow-up time was 13 (IQR 5 to 24) months after the first DEX.

Patients' demographics

Demographic and clinical characteristics of the study patients collected at first DEX are shown in Table 1.

Table 1
Demographic and clinical characteristics of the study patients at the time of the first DEX injection.

	Overall (N = 80)
Age (years)	
Mean (SD)	59.4 (15.1)
Median [Min, Max]	61.0 [26.0, 95.0]
Gender	
Female	41 (51%)
Male	39 (49%)
Anatomic location of uveitis^	
Anterior uveitis	4 (5%)
Intermediate uveitis	25 (31%)
Posterior uveitis	20 (25%)
Panuveitis	31 (39%)
Etiology of uveitis	
JIA	1 (1.3%)
Behçet	1 (1.3%)
Birdshot chorioretinopathy	6 (7.4%)
Drug-induced uveitis	1 (1.3%)
Crohn's Disease	1 (1.3%)
HLA-B27	2 (2.5%)
Idiopathic	37 (46.2%)
Psoriasis	2 (2.5%)
Sarcoidosis	21 (26.2%)
Sympathetic ophthalmia	2 (2.5%)

N: number; %: percentage; SD: standard deviation; Min: minimum; Max: maximum; JIA: Juvenile idiopathic arthritis; HLA: human leukocyte antigen; TB: Tuberculosis; IMT: immunosuppressive therapy.

^ The location was given for the worse eye in patients with bilateral disease

	Overall (N = 80)
Age (years)	
TB-hypersensitivity uveitis	4 (5.0%)
Vogt-Koyanagi-Harada	2 (2.5%)
Duration of uveitis (months)	
Mean (SD)	15.9 (11.0)
Median [Min, Max]	12.0 [0, 63]
Systemic IMT	
No	36 (45%)
Yes	44 (55%)
N: number; %: percentage; SD: standard deviation; Min: minimum; Max: maximum; JIA: Juvenile idiopathic arthritis; HLA: human leukocyte antigen; TB: Tuberculosis; IMT: immunosuppressive therapy.	
^ The location was given for the worse eye in patients with bilateral disease	

All patients were of Caucasian ancestry. Most of them had panuveitis (31 patients, 39%), with idiopathic (37 patients, 46%) and sarcoid uveitis (21 patients, 26%) being the most common diagnoses. One patient had persistent uveitis and QuantiFERON-gold positive test, but no active Tuberculous infection. None had undergone vitrectomy.

Thirty-six patients (45%) were under systemic IMT, and 5 patients were started on systemic medications after the first DEX. Systemic treatments included oral corticosteroids (10 patients), methotrexate (9 patients), adalimumab (5 patients), mycophenolate mofetil (2 patients), or a combination of these drugs (10 patients).

Twenty-seven eyes (26%) were pseudophakic. Sixty-four eyes (62%) were treatment-naïve; the remaining eyes had received periocular or intravitreal triamcinolone for MO before DEX.

Clinical and SD-OCT characteristics associated with pre-injection VA

The SD-OCT characteristics, stratified between those recorded at the first DEX and those recorded at subsequent DEX, are shown in Table 2. NIU eyes had higher CRT ($p = 0.05$) and presented with SF and HRF more frequently ($p = 0.002$ and $p = 0.07$) at the time of the first DEX than subsequent DEX. The proportion of eyes with disrupted or absent EZ considerably increased from the second treatment ($p =$

0.01). DRIL, as well, was seen more frequently in eyes receiving more than one DEX ($p = 0.04$). The prevalence of ERM remained stable over follow-up ($p = 0.7$).

Table 2
SD-OCT characteristics of study eyes stratified between those recorded at first DEX and those recorded at subsequent DEX injections.

	First DEX (N = 101 SD-OCT scans)	Subsequent DEX (N = 72 SD-OCT scans)	Overall (N = 173 SD-OCT scans)
CRT (µm)			
Mean (SD)	510 (154)	464 (127)	485 (144)
Median [Min, Max]	485 [225, 985]	449 [190, 755]	469 [190, 985]
CT (µm)			
Mean (SD)	323 (150)	309 (183)	316 (167)
Median [Min, Max]	296 [60, 785]	276 [50, 807]	289 [50, 807]
Largest intraretinal cyst diameter (µm)			
Mean (SD)	316 (128)	299 (119)	308 (124)
Median [Min, Max]	321 [44, 588]	304 [86, 575]	315 [44, 588]
Subretinal fluid			
No	33 (33%)	51 (71%)	84 (49%)
Yes	40 (39%)	21 (29%)	61 (35%)
N/A	28 (28%)	0 (0%)	28 (16%)
Ellipsoid zone appearance			
Continuous	73 (72%)	33 (46%)	106 (61%)
Disrupted	25 (25%)	31 (43%)	56 (32%)
Absent	3 (3%)	8 (11%)	11 (7%)
Hyperreflective foci			
No	58 (57%)	52 (72%)	110 (64%)
Yes	43 (43%)	20 (28%)	63 (36%)

^This variable has missing data

N: number; %: percentage; SD: standard deviation; Min: minimum; Max: maximum; N/A: not available; DEX: dexamethasone; CRT: central retinal thickness; CT: choroidal thickness; DRIL: disorganisation of the inner retinal layers; ONL: outer nuclear layer; INL: inner retinal layer.

	First DEX (N = 101 SD-OCT scans)	Subsequent DEX (N = 72 SD-OCT scans)	Overall (N = 173 SD-OCT scans)
CRT (µm)			
DRIL			
No	57 (56%)	45 (63%)	102 (59%)
Yes	16 (16%)	27 (37%)	43 (25%)
N/A	28 (28%)	0 (0%)	28 (16%)
Epiretinal membrane			
No	69 (68%)	53 (74%)	122 (70%)
Yes	32 (32%)	19 (26%)	51 (30%)
ONL cysts^			
No	21 (21%)	11 (15%)	32 (19%)
Yes	79 (79%)	61 (85%)	140 (81%)
INL cysts			
No	8 (8%)	2 (3%)	10 (6%)
Yes	92 (91%)	70 (97%)	162 (93%)
N/A	1 (1%)	0 (0%)	1 (1%)
^This variable has missing data			

N: number; %: percentage; SD: standard deviation; Min: minimum; Max: maximum; N/A: not available; DEX: dexamethasone; CRT: central retinal thickness; CT: choroidal thickness; DRIL: disorganisation of the inner retinal layers; ONL: outer nuclear layer; INL: inner retinal layer.

The VA was worse at first DEX than on subsequent treatments (0.48 ± 0.34 vs. 0.44 ± 0.28 LogMAR, p = 0.001). Pre-injection VA was associated with CRT (p = 0.008). Notably, the relationship between VA and CRT was best explained by an exponential fit rather than a linear one (Fig. 2.**A**).

The multiple linear regression analysis revealed that eyes with absent EZ layer and those with DRIL had worse pre-injection VA, with an estimated difference of + 0.19 (p = 0.04) and + 0.10 (p = 0.01) LogMAR over eyes with continuous EZ and no DRIL, respectively. Patients not receiving systemic IMT for NIU also had worse pre-injection VA values (+ 0.11 LogMAR, p = 0.07) (Table 3). The model explained 23% of the variance in pre-injection VA values (marginal R^2 = 0.23).

Table 3
Associations between pre-injection visual acuity (LogMAR) and clinical and morphologic biomarkers. CI: confidence interval; IMT: Immunosuppressive therapy; DRIL: disorganisation of the inner retinal layers; CRT: Central retinal thickness.

Characteristic	Regression estimates	95% CI	p-value
Female gender (vs. male)	0.12	-0.04, 0.28	0.15
Systemic IMT	-0.11	-0.22, 0.01	0.07
Ellipsoid zone:			
Disrupted (vs. continuous)	0.03	-0.08, 0.13	0.60
Absent (vs. continuous)	0.19	0.01, 0.38	0.04
DRIL	0.10	0.02, 0.21	0.01
CRT (µm) (exponential)	0.02	0.00, 0.03	0.01

CI: confidence interval; IMT: Immunosuppressive therapy; DRIL: disorganisation of the inner retinal layers; CRT: Central retinal thickness.

Clinical and SD-OCT characteristics associated with post-injection VA

Mean post-injection VA was 0.34 ± 0.27 LogMAR; post-injection VA was associated with pre-injection VA, with an increase of 0.42 LogMAR for each unitary increase in pre-injection VA values ($p < 0.001$).

The average VA improvement after each DEX was 0.13 ± 0.25 LogMAR ($p = 0.003$). The rate of 5-, 10-, and 15-letter improvement was 21 (12%), 12 (7%), and 38 (22%) over the 173 DEX analyzed; the chance of gaining at least 5 letters was higher after the first DEX than subsequent DEX (50/101 [52%] vs. 19/72 [26%], $p = 0.002$).

In the multiple linear regression analysis, post-injection VA was associated with the presence of DRIL, EZ disruption, and ERM, with VA being on average 0.17 ($p = 0.04$), 0.33 ($p = 0.01$), and 0.12 ($p = 0.04$) LogMAR worse than eyes with no DRIL, EZ disruption, or ERM, respectively (Fig. 2.**B-C**). The plotted values of post-injection VA suggested the effect of ERM was greater in eyes with worse pre-injection VA (Fig. 2.**D**) (Table 4). The model explained 50% of the variance in post-injection VA values (marginal $R^2 = 0.50$).

Table 4

Associations between post-injection visual acuity (VA, LogMAR) and clinical and morphologic biomarkers. CI: confidence interval; DRIL: disorganisation of the inner retinal layers.

Characteristic	Beta	95% CI	p-value
Pre-injection VA (LogMAR)	0.42	0.25, 0.60	< 0.001
Age (for 10 years)	0.04	-0.04, 0.01	0.16
Systemic treatment	0.11	-0.02, 0.24	0.37
Epiretinal membrane	0.12	0.001, 0.23	0.04
DRIL	0.17	0.01, 0.32	0.04
Ellipsoid zone:			
Disrupted (vs. continuous)	0.14	0.02, 0.26	0.02
Absent (vs. continuous)	0.33	0.08, 0.57	0.01

CI: confidence interval; DRIL: disorganisation of the inner retinal layers.

Clinical and SD-OCT characteristics associated with MO regression

Three-month follow-up SD-OCT was available after 134 DEX. The rate of MO regression was 90 (67%). Eyes with MO regression had significantly better post-injection VA (-0.15 LogMAR, p = 0.002) than eyes with persistent MO.

The multiple logistic regression analysis showed that older age (OR = 0.95 for each 10 years, p = 0.049) and longer MO duration (OR = 0.75 for each year, p = 0.02) were associated with a lower chance of MO regression after DEX. A higher pre-injection CRT (OR = 0.58 for each 100 µm, p = 0.03) and the presence of HRF (OR = 0.12, p = 0.004) were also independent risk factors of persistent MO. The presence of SRF was associated with higher rates of MO regression (OR = 6.09, p = 0.01)(Table 5).

Table 5
Factors associated with macular oedema (MO) regression three months after DEX.

Characteristic	OR	95% CI	p-value
Age (for 10 years)	0.95	0.90, 0.99	0.049
Duration of ME (for 1 year)	0.75	0.53, 0.91	0.02
CRT (100 µm)	0.58	0.36, 0.94	0.03
DRIL	1.31	0.34, 5.04	0.70
Subretinal fluid	6.09	1.69, 22.0	0.01
Hyperreflective foci	0.12	0.03, 0.50	0.004

OR: odds ratio; CI: confidence interval; CRT: central retinal thickness; DRIL: disorganisation of the inner retinal layers.

Discussion

This study assessed the associations between pre-injection VA, post-injection VA, and clinical and SD-OCT characteristics in NIU MO eyes treated with intravitreal DEX. We identified EZ damage, the presence of DRIL, and a thicker macula as biomarkers of worse pre-injection VA. EZ disruption and DRIL were also predictors of poor visual outcomes, and their prevalence increased significantly in eyes requiring multiple treatments. Older age, longer MO duration, higher CRT, and the presence of HRF were risk factors for persistent MO after each DEX.

According to randomized clinical trials and real-life data, the magnitude of visual improvement in eyes being treated for NIU and MO varies widely. In the HURON trial, the percentage of 15-letter gainers after intravitreal DEX was 42% at 3 months and 38% at 6 months.[4] Real-world studies showed that up to 40% of eyes failed to improve 3 EDTRS lines after DEX treatment.[5,19,20] The patients included in this study globally gained vision after each DEX, but visual gains were heterogenous, with 60% of eyes improving less than 5 letters. There is limited data availability on morpho-functional correlations in eyes with NIU MO.[21] Studies examining the effect of single or repeated DEX in NIU were based on a small number of eyes, and only a few analyzed morphologic predictors of visual and anatomic outcomes.[6,8,22,23] Our study is uniquely positioned to analyze data from nearly 200 DEX in NIU patients undergoing serial SD-OCT imaging in an attempt to identify the factors affecting DEX response.

Ciulla et al. investigated the relationship between VA and CRT in eyes with NIU MO.[12] The authors found VA and CRT were weakly associated, and CRT values accounted only for a negligible part of VA scores variability.[12] We found that pre-injection VA and CRT values followed an exponential relationship, suggesting that very low (e.g., < 300 µm) and very high (e.g., > 600 µm) CRT values were both associated with poor VA. While high CRT values suggest worse MO, low CRT values may correspond to macular atrophy with extensive retinal damage, a common end-stage disease of exudative macular disorders.[24]

Nonetheless, CRT values alone (considering either linear or quadratic fits) explained less than 7% of the pre-injection VA variance in our cohort, implying the existence of other structural biomarkers contributing to VA.

DRIL and EZ disruption were associated with worse VA, before and after DEX. DRIL indicates the loss of inner retinal layers' lamination on SD-OCT, and it is a surrogate of irreversible damage of amacrine, bipolar, and horizontal cells.[17] Conversely, the EZ band reflects the integrity of the photoreceptor outer segments. DRIL correlates with poorer treatment response in eyes with DMO,[25,26] RVO,[14,27] and idiopathic ERM.[28] The presence of DRIL and its extent has also been associated with worse visual outcomes in eyes with NIU treated with systemic IMT (Adalimumab).[17] On the other hand, the posthoc analysis of the PEACHTREE and AZALEA trials assessing the efficacy of suprachoroidal triamcinolone acetonide in NIU eyes showed the EZ status had the strongest association with baseline and post-treatment VA (explaining up to 25% of the total variation).[29] Our data confirmed the robustness of DRIL and EZ disruption as independent negative prognostic biomarkers for VA in real-life practice.

A multicenter French study observed that patients who were naïve at baseline (n = 6/22, 27%) had a higher chance of visual improvement after DEX than previously treated patients (n = 8/46, 17%).[30] MO duration was not directly correlated with VA in our study; however, the chance of at least 5-letter improvement was higher after the first DEX than subsequent DEX. A regression toward the mean plausibly biases this finding. However, we speculate progressive retinal damage occurs with recurrent MO. In fact, the prevalence of DRIL and EZ disruption increased with repeated DEX. Moreover, we found a possible inverse association between systemic IMT and pre-injection VA, suggesting worse vision in subjects not receiving systemic IMT. Prolonged inflammation and, probably, undertreatment is the most likely cause of cumulative retinal damage.

The effect of DEX was lower in eyes with ERM. Epiretinal membranes are relatively common in NIU, with an estimated prevalence of 41%.[31] Eyes with ERM tend to have worse VA than eyes without ERM,[31] and may obtain limited visual gains after surgical ERM removal.[32] Munk et al. and Khurana and Porco investigated the treatment outcomes in NIU MO presenting with ERM. Both groups found that intravitreal treatments had limited visual effects in eyes with ERM compared to eyes without ERM.[6,33] Our data also showed a possible interaction between VA and ERM, with eyes with ERM and poor pre-injection VA having worse post-injection vision than eyes without ERM. We hypothesize ERM may exert additive harm on the macular structures, which does not revert with medical treatment.

A delayed anatomic response was associated with suboptimal visual recovery after suprachoroidal triamcinolone acetonide treatment.[29] In our study, the persistence of intraretinal or subretinal fluid was associated with worse post-injection VA. A few studies reported the rate of persistent or recurrent MO in NIU.[5,7,8,10]A retrospective case series of 18 eyes treated with DEX found MO resolved in 72% of cases,[6] comparable to our study rate of 67%. Older age, longer MO duration, and a higher pre-injection CRT were associated with a lower chance of MO regression. The presence of HRF was also a risk factor for less

responsive MO. Although there is no definitive consensus, HRF may derive from lipoproteins extravasation from a halted inner blood-retinal barrier. HRF may also represent microglial activation, and their presence may imply active intraretinal inflammation.[34] The presence of SF was associated with a 6-fold higher chance of MO regression, in line with a US retrospective study of 101 eyes with uveitic MO.[35] SF tends to occur in MO of shorter duration and may suggest intact connections between Müller cells and foveal cones.[33] Therefore, it may be regarded as a sign of good response to local or systemic treatments.

We acknowledge the retrospective design and the presence of missing data as limitations of this study. Patients seen at tertiary uveitis centres could have worse expected outcomes by the referring physicians, and the study may be limitedly generalizable. There was heterogeneity in patients' follow-up time due to discrepancies in post-injection visits scheduled between centres. In fact, post-injection SD-OCT scans were available in 75% of the cases. We cannot exclude data were not missing at random; patients not returning for follow-up SD-OCT could be those with very good or very poor responses to DEX. Similarly, we defined persistent MO as intraretinal or subretinal fluid on follow-up SD-OCT. The post-injection assessment was done at 3 months, so we could not discern eyes with persistent fluid from those with early MO recurrence. We did not include clinical variables potentially affecting VA in the regression analyses, such as anterior segment inflammation, cataract grading, and vitritis severity. Hence, a large quote of VA variability was still not explained by our models.

In conclusion, this study assessed the relationship between clinical and SD-OCT biomarkers and VA in NIU patients with MO treated with DEX. Our analysis revealed that integrity of the inner and outer retina is associated with a better visual response to treatment, independently from the severity of macular thickening. Long-standing and recurrent MO are likely to cause cumulative retinal damage and are associated with less chance of both visual and anatomic improvement. We conclude that timely treatment with local and systemic IMT is necessary to maximize the outcomes of MO in NIU patients.

Declarations

ACKNOWLEDGMENTS

- Funding/Support: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

- Financial disclosures: Claudia Gerosolima, Pierluigi Scandale, Elisabetta Miserocchi: No financial disclosures

- Maria Vittoria Cicinelli, Sarah Touhami, Dominika Pohlmann, Audrey Giocanti, Amir Rosenblatt previously received travel grants from Allergan as International Retinal Panel members

- Francesco Bandello consultant for: Allergan Inc (Irvine, California, USA), Bayer Shering-Pharma (Berlin, Germany), Hoffmann-La-Roche (Basel, Switzerland), Novartis (Basel, Switzerland), Sanofi-Aventis

(Paris, France), Thrombogenics (Heverlee, Belgium), Zeiss (Dublin, USA), Boehringer-Ingelheim, Fidia Sooft, Ntc Pharma, Sifi

- Anat Loewenstein consultant for: Allergan, Bayer health care, Beyeonics, Forsightlabs, NotalVision, Novartis, Roche, WebMD, Syneos, Xbrane, Nanoretina, Ocuterra, Ripple Therapeutics, Annexon, MJHEvents, Iveric Bio, Biogen, Johnson & Johnson, Ophtimedrx, Ocuphire Pharma, Iqvia

- Other acknowledgements: None

COMPETING INTERESTS STATEMENT: The authors have no competing interest in publishing the present work

CONTRIBUTORSHIP STATEMENT

All the authors contributed to the conception or design of the work, the acquisition, analysis, and interpretation of data, drafting the work, and revising it critically for intellectual content. Each coauthor has seen and agrees with how his or her name is listed.

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Figures

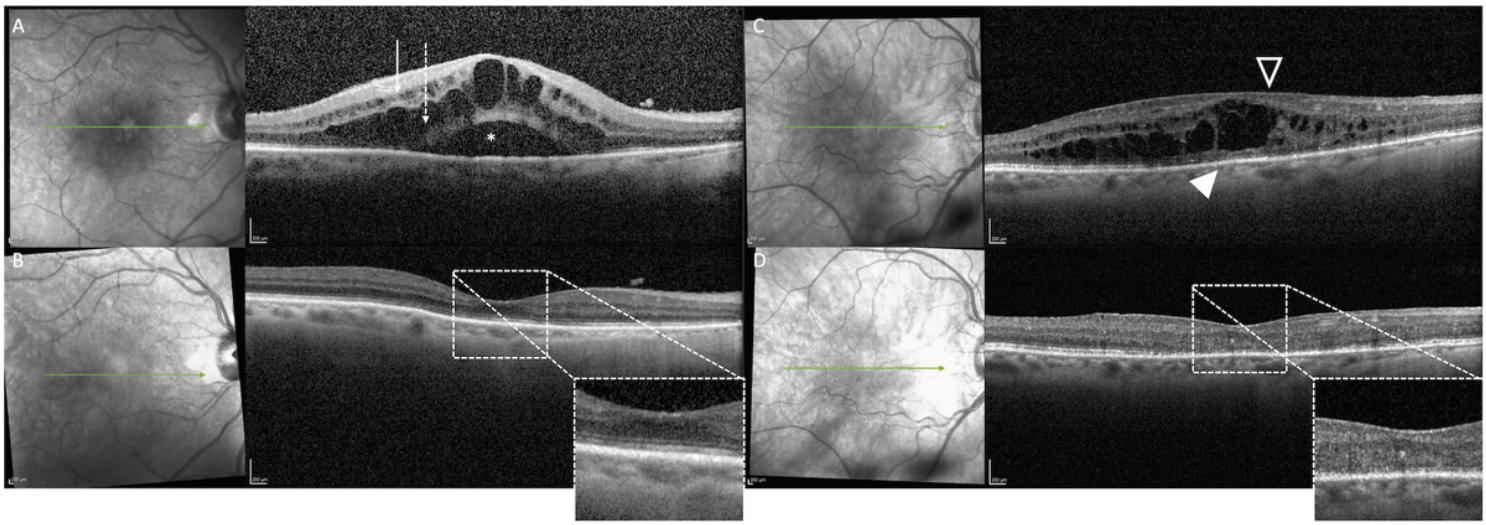

Figure 1

Qualitative assessment of spectral-domain optical coherence tomography (SD-OCT).

A) Horizontal SD-OCT scan acquired before dexamethasone implant injection (DEX) in a patient with idiopathic panuveitis. The scan shows intra-retinal fluid, with cystoid spaces in the outer (solid arrow) and inner nuclear layer (dashed arrow), and subretinal fluid (asterisk).

B) Horizontal SD-OCT scan acquired after DEX acquired with a follow-up mode. The scan shows complete regression of macular oedema. The ellipsoid zone (EZ) under the fovea is preserved, as shown in the enlarged panel.

C) Horizontal SD-OCT scan acquired before DEX in a patient with Behçet disease. The scan shows intra-retinal fluid, with cystoid spaces in the outer and inner nuclear layer. There is disorganization of retinal inner layers (DRIL) in the central 1-millimetre area. The EZ band is absent under the fovea.

D) Horizontal SD-OCT scan acquired after DEX acquired with a follow-up mode. The scan shows regression of macular oedema, but persistence of DRIL. The EZ band is absent under the fovea.

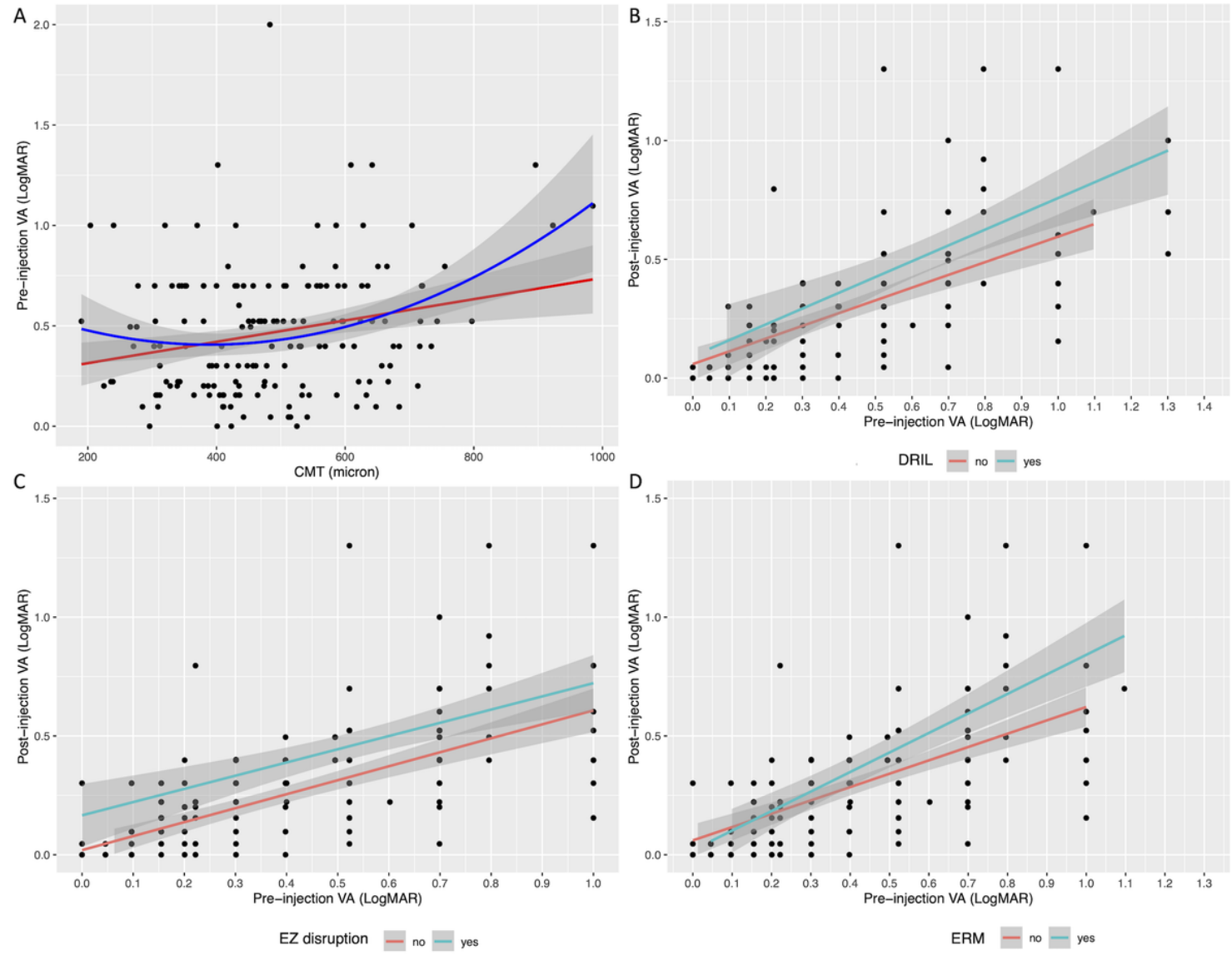

Figure 2

Correlation between pre- and post-injection visual acuity (VA).

A) Scatterplot showing the association between pre-injection VA (expressed as LogMAR) and central retinal thickness (CRT). The relationship between VA and CRT was best explained by an exponential fit (blue line) rather than a linear one (red line). The grey shadow shows the confidence interval of the interpolating line.

B) Scatterplot showing the association between pre-injection and post-injection VA (expressed as LogMAR), according to the presence of disorganization of retinal inner layers (DRIL) in the central 1-millimetre area. Eyes with DRIL had worse pre-injection and post-injection VA. No interaction is seen. The grey shadow shows the confidence interval of the interpolating line.

C) Scatterplot showing the association between pre-injection and post-injection VA (expressed as LogMAR), according to the presence of ellipsoid zone (EZ) under the fovea. Eyes with EZ had worse pre-

injection and post-injection VA. No interaction is seen. The grey shadow shows the confidence interval of the interpolating line.

D) Scatterplot showing the association between pre-injection and post-injection VA (expressed as LogMAR), according to the presence of epiretinal membrane (ERM). A possible interaction is noticeable, suggesting that the effect of ERM is negligible in eyes with good pre-injection VA and greater in eyes with worse pre-injection VA. The grey shadow shows the confidence interval of the interpolating line.