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ORIGINAL ARTICLE

Real-world outcomes of non-responding diabetic macular edema treated with continued anti-VEGF therapy versus early switch to dexamethasone implant: 2-year results

Catharina Busch[1] · Samantha Fraser-Bell[2] · Matias Iglicki[3] · Marco Lupidi[4] · Aude Couturier[5] · Voraporn Chaikitmongkol[6] · Ermete Giancipoli[7,8] · Patricio J. Rodríguez-Valdés[9] · Pierre-Henry Gabrielle[10,11] · Inês Laíns[12,13,14] · Ana Rita Santos[13,15] · Zafer Cebeci[16] · Atchara Amphornphruet[17] · Valentin Degenhardt[1,18] · Jan-Darius Unterlauft[1] · Carlo Cagini[4] · Valérie Mané-Tauty[5] · Giuseppe D'Amico Ricci[7,8] · Isaac Hindi[19,20] · Kushal Agrawal[21] · Jay Chhablani[22,23] · Anat Loewenstein[19,20,24] · Dinah Zur[19,20] · Matus Rehak[1] · for the International Retina Group

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Abstract

Aims To provide 2-year follow-up data on eyes with diabetic macular edema (DME) that were non-responsive after three initial anti-vascular endothelial growth factor (VEGF) injections, comparing functional and anatomical outcomes under continued anti-VEGF therapy versus dexamethasone (DEX) implant.

Methods Multicenter, retrospective chart review comparing eyes with treatment-naïve DME and a suboptimal response to a loading phase of anti-VEGF therapy (3 injections given monthly) which were then treated with (a) further anti-VEGF ($n=72$) or (b) initially switched to DEX implant ($n=38$). Main outcome measures were change in visual acuity (VA) and central subfield thickness (CST) from the end of the loading phase to 24 months.

Results In 79% of the 12-month study population (87/110 eyes), 24-month data were available. One quarter of eyes in each group switched treatments during the second year. Eyes that were switched early to DEX implant maintained the functional and anatomical improvements at 24 months which were seen in the first year (from month 3: +8.9 letters, −214 µm). Eyes that were switched from anti-VEGF therapy to steroids in the second year improved VA and reduced CST at 24 months (from month 12: +6.8 letters, $p=0.023$; −226 µm, $p=0.004$). In eyes continued on anti-VEGF therapy, VA and CST were stable at 24 months (from month 3: +2.8 letters, $p=0.254$; −24 µm, $p=0.243$). Eyes that were non-responsive to anti-VEGF therapy for 12 months had similar chances to experience a VA gain from further therapy as eyes that were non-responsive for 3 months only (23.8 vs. 31.0%, $p=0.344$).

Conclusions The beneficial effect of an early switch to DEX implant in DME non-responders seen at month 12 was maintained during the second year. A later switch from anti-VEGF to steroids still provided significant improvement. Eyes continued on anti-VEGF over a period of 24 months maintained vision. A quarter of eyes, which had not improved vision at 12 months, exhibited a delayed response to treatment.

Keywords Refractory diabetic macular edema · Anti-VEGF therapy · Dexamethasone implant · Intravitreal therapy · Long-term outcome

Introduction

The increasing prevalence of diabetes has been labeled as an epidemic. The number of people being diagnosed with diabetes is expected to rise from 451 million cases in 2017 to 693 million cases in 2045 [1]. Diabetic retinopathy is a major health problem as it is a common cause of visual loss in working-aged individuals, mainly due to the development

Dinah Zur and Matus Rehak have contributed equally.

Managed By Giuseppe Querques.

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of diabetic macular edema (DME) [2]. The outcomes of patients with DME have significantly improved since the advent of intravitreal vascular endothelial growth factor (VEGF) inhibitors, which are the first-line therapy in most cases [3]. However, about 30–40% of patients do not respond to anti-VEGF during the loading phase (3 monthly injections) [4–6] with another half of those patients still not responding despite 12 months of continuous monthly treatment [4, 7]. Besides anti-VEGF agents, therapy with intravitreal corticosteroids, such as dexamethasone (DEX) intravitreal implant 0.7 mg (Ozurdex®, Allergan, Inc., Irvine, CA, USA), has been proven to be effective in DME [8–10]. Due to differences in pathophysiological targets, it stands to reason that intravitreal corticosteroids might be beneficial in eyes not responding to anti-VEGF therapy. Randomized control studies exploring the optimal treatment decision in patients with limited response to anti-VEGF loading phase are lacking so far.

Recently, our study group conducted a retrospective analysis of DME patients with suboptimal response to anti-VEGF loading phase, comparing the outcome of two treatment regimens: continued anti-VEGF treatment versus an early switch to DEX implant [11]. The previously reported 1-year results revealed that an early switch to DEX implant led to significant improvement in vision associated with reduction in central subfoveal thickness compared to eyes which continued anti-VEGF alone. We concluded that DME patients with limited response to anti-VEGF therapy during the loading phase might benefit more from an early switch to DEX implant than from continuation of anti-VEGF therapy. Since diabetes is a chronic disease and longer-term outcomes of the management of its complications are required, we now report on the 2-year outcomes of this cohort.

Methods

The study procedures and statistical methods have been reported previously and are summarized briefly [11]. Institutional review board (IRB) approval was obtained through the individual IRBs at the participating institutes for a retrospective consecutive chart review. This research adhered to the tenets of the Declaration of Helsinki.

Study participants

Fourteen study sites included 110 eyes from 105 diabetic patients (mean age: 61.4 ± 11.2 years, 54% women) with treatment-naïve DME causing visual loss, with study eye visual acuity (VA) of 0.1–1.0 logMAR (mean VA: 0.49 ± 0.24 logMAR); macular edema defined clinically and by retinal thickness of > 300 µm in the central subfield (CST) with intra ± subretinal fluid on spectral domain (SD) OCT (mean CST: 477 ± 124 µm). Eyes had to be treatment naïve on presentation and initially treated with 3 monthly anti-VEGF injections (aflibercept, ranibizumab or bevacizumab) (i.e., loading phase) leading to a suboptimal response: defined as ≤ 5 letter gain in VA (including vision loss), or reduction of less than 20% of CST on SD-OCT 1 month after the third anti-VEGF injection (M3) [7, 12] and received further treatment as follows: either (a) continued on anti-VEGF injections without switching agents for at least 12 months ($n = 72$ eyes) or (b) switched to DEX implant after ≤ 1 further anti-VEGF injection ($n = 38$ eyes).

Data collection

Medical charts of all included patients were reviewed for the following data: VA and CST at 18 and 24 months, DME treatment from month 12 to 24 (including further anti-VEGF injections, DEX implants, fluocinolone acetonide (FA) implant, macular laser), panretinal photocoagulation, pars plana vitrectomy, cataract surgery and reason for lost to follow-up where two-year data were not available. Patients were only included in the analysis if 24-month data were available.

OCT analysis for disruption of the foveal ellipsoid zone (EZ) was performed by three independent and masked graders (CB, DZ, MI) as previously described [11].

Outcome measures

Main outcome measures were the change in VA and CST from the end of the loading phase (month 3) to month 24. Secondary outcome measures included mean change in standardized area under the curve (AUC) of VA and CST from month 3 to month 24 and from month 12 to month 24, proportion of eyes with VA gain ≥ 5 letters, ≥ 10 letters and VA loss ≥ 5 letters.

Statistical Analysis

The 2-year analysis methods mirrored the 1-year analyses [11]. The demographic and clinical characteristics of our study cohort were evaluated using traditional descriptive methods. The standardized area under the curve (AUC) of VA and CST change was calculated by the trapezoidal rule [13]. Differences in baseline characteristics between matched anti-VEGF and DEX group were assessed by univariable logistic regression model. Differences in outcome measures were analyzed by multivariable regression model, including age, gender, stage of diabetic retinopathy, EZ disruption at baseline, lens status at baseline and after 24 months, status post-panretinal photocoagulation at baseline and after 24 months, and baseline visual acuity (for visual acuity outcomes) and baseline CST (for CST outcomes).

For continuous outcome variables, a linear regression model, and for a binary outcome, a logistic regression model were applied. The last observation carried forward method was used to impute missing data. Statistical analysis was performed with SPSS Statistics 22 (IBM, Armonk, NY, USA).

Results

Two-year data were available for 87 of the 110 initially included eyes (in total: 79%, anti-VEGF group: 81%, DEX group: 76%). Characteristics of those with and without 2-year data are displayed in Table 1. Reasons for incomplete 24-month follow-up were as follows: patients were scheduled but missed further appointments (11/23 eyes, 47.8%), patients continued follow-up outside of the study site (6/23 eyes, 25%), patients were not scheduled at 24-month follow-up time (3/23 eyes, 13.0%), data not available due to technical reasons (2/23 eyes, 8.6%), and death (1/23 eyes, 4.3%).

Details on the treatment received during the second year of the study period are shown in Table 2. Among patients continued on anti-VEGF therapy alone during the first year and available 24-month data ($n=58$), 44/58 eyes (75.9%) only received anti-VEGF therapy throughout the entire study period with a mean (± SD) number of 4.3 (± 3.7) anti-VEGF injections given during the second year. 6/44 eyes (13.6%) did not receive further injections

Table 1 Characterization of eyes with versus without 24-month follow-up

	Eyes with 24-M follow-up				Eyes without 24-M follow-up[a]		
	All eyes ($n=87$)	Only anti-VEGF during study period ($n=44$)	Anti-VEGF throughout 1st year + switch to steroids in 2nd year ($n=14$)	Early switch to DEX implant ($n=29$)	All eyes ($n=23$)	Anti-VEGF group ($n=14$)	DEX group ($n=9$)
Age, years, mean (SD)	61.7 (11.6)	60.0 (10.2)	62.1 (13.1)	64.0 (12.7)	60.4 (9.8)	60.4 (9.1)	60.4 (11.5)
Known duration of diabetes, months, mean (SD)	110 (121)	143 (117)	16 (37)	104 (133)	159 (145)	132 (132)	205 (163)
Proliferative diabetic retinopathy, *n* (%)	30 (34.5)	12 (27.3)	5 (35.7)	13 (44.8)	5 (21.7)	3 (21.4)	2 (22.2)
Pseudophakia at M0, *n* (%)	33 (37.9)	8 (18.2)	9 (64.3)	16 (55.2)	3 (13.0)	1 (7.1)	2 (22.2)
Prior PRP, *n* (%)	36 (41.4)	15 (34.1)	7 (50.0)	14 (48.3)	7 (30.4)	4 (28.6)	3 (33.3)
Ellipsoid zone disruption at M0, *n* (%)	47/85 (55.3)	23 (52.3)	5 (35.7)	19 (65.5)	10 (47.6)	6 (42.9)	4 (44.4)
VA at M0, logMAR, mean (SD)	0.52 (0.24)	0.47 (0.25)	0.59 (0.22)	0.57 (0.23)	0.39 (0.22)	0.35 (0.21)	0.44 (0.24)
VA at M3, logMAR, mean (SD)	0.50 (0.27)	0.45 (0.30)	0.58 (0.22)	0.55 (0.22)	0.39 (0.19)	0.33 (0.17)	0.48 (0.19)
VA at M12, logMAR, mean (SD)	0.45 (0.26)	0.45 (0.29)	0.57 (0.27)	0.39 (0.17)	0.45 (0.34)	0.44 (0.35)	0.46 (0.34)
CST at M0, µm, mean (SD)	482 (121)	451 (108)	496 (141)	522 (121)	460 (139)	467 (158)	450 (111)
CST at M3, µm, mean (SD)	444 (133)	389 (101)	527 (153)	488 (131)	399 (95)	385 (99)	422 (88)
CST at M12, µm, mean (SD)	427 (150)	419 (128)	561 (150)	374 (147)	396 (127)	392 (128)	401 (133)

M0—initiation of loading dose with 3 monthly anti-VEGF injections

CST, central subfield thickness; DEX, dexamethasone; M, month; PRP, panretinal photocoagulation; VEGF, vascular endothelial growth factor

[a]Includes loss of follow-up and death

Table 2 Treatment characteristics

	Anti-VEGF throughout 1st year		Early switch to DEX implant ($n=29$)
	Only anti-VEGF during study period ($n=44$)	Switch to steroids in 2nd year ($n=14$)	
M0–M12			
Anti-VEGF drug, *n* (%)			
Ranibizumab	29 (65.9)	2 (14.3)	12 (41.4)
Aflibercept	7 (15.9)	11(78.6)	14 (48.3)
Bevacizumab	8 (18.2)	1 (7.1)	3 (10.3)
No. of anti-VEGF injections, mean (SD)	6.9 (2.4)	6.9 (0.7)	3.3 (0.5)
No. of DEX implants, *n* (%)			
1	0	0	16 (55.2)
2	0	0	13 (44.8)
Mean (SD)	0	0	1.4 (0.5)
M12–M24			
No. of anti-VEGF injections M12–M24, mean (SD)	4.3 (3.7)	1.0 (2.2)	0.5 (1.3)
No. of steroid implants[a] M12–M24, *n* (%)			
0	44 (100)	0	7 (24.1)
1	0	4 (28.6)	9 (31.0)
2	0	10 (71.4)	12 (41.4)
3	0	0	1 (3.4)
Mean (SD)	0	1.7 (0.5)	1.2 (0.9)
Therapy with fluocinolone acetonide implant, *n* (%)	0	3 (21.4)	3 (10.3)
Switch between anti-VEGF agents, *n* (%)	5 (11.4)	0 (0)	2 (6.9)
No DME therapy received between M12 and M24, *n* (%)	6 (13.6)	0 (0)	6 (20.7)
Additional treatment			
M0–M12, *n* (%)			
Macular laser	2 (4.5)	1 (7.1)	1 (3.4)
Panretinal photocoagulation	7 (15.9)	11 (78.6)	0 (0)
Cataract surgery	4/36 (11.1)	1/5 (20.0)	4/13 (30.8)
Pars plana vitrectomy	0	0	0
M12–M24, *n* (%)			
Macular laser	1 (2.3)	1 (7.1)	1 (3.4)
Panretinal photocoagulation	2 (4.5)	0	1 (3.4)
Cataract surgery	4/32 (12.5)	0/4	2/9 (22.2)
Pars plana vitrectomy	0	0	0

M0—initiation of loading dose with 3 monthly anti-VEGF injections

DEX, dexamethasone; VEGF, vascular endothelial growth factor; M, month

[a]Including DEX and fluocinolone acetonide implants

in the second year, even though in 4/6 eyes (66.6%) CST was above 300 µm, indicating need for further therapy. In all cases, malcompliance of the patients was the reason for postponed treatment. In 14/58 eyes (24.1%), the therapy was switched from anti-VEGF to steroids with a mean (± SD) number of 1.7 (± 0.5) steroid implants in the second year. Mean time of switch to steroids in this group was 15.3 ± 2.9 months from baseline. In 11 eyes (78.6%), the therapy was switched from anti-VEGF to DEX implant at 13.9 ± 0.3 months after baseline, 38.1 ± 4.2 days after the last anti-VEGF injection, and after a mean of 7.2 ± 0.9 anti-VEGF injections. In 3 eyes (21.4%), the therapy was switched from anti-VEGF to fluocinolone acetonide due to DME recurrence at 19.0 ± 4.2 months after baseline, 6.6 ± 1.2 months after the last anti-VEGF injection, and after a mean of 8.3 ± 1.3 anti-VEGF injections.

Within the group of eyes which were switched early to DEX after anti-VEGF loading doses and available 24-month data ($n=29$), 76% (22/29 eyes) received further steroid implants (mean [± SD] number of steroid implants in the second year: 1.6 ± 0.6). Three eyes (10.3%) were switched to fluocinolone acetonide implant (mean [± SD]

number: 1.0 ± 0.0) at 13.3 ± 0.5 months after baseline (6.6 ± 0.9 months after last DEX implant). Four eyes (13.8%) received additional anti-VEGF injections in the second year (mean [± SD] number: 3.0 ± 1.5). Six eyes (20.7%) did not receive further DME therapy in the second year. In all 6 eyes, CST values were below 300 µm at all study visits in the second year. Cataract surgery was performed more frequently in eyes that were switched early to DEX compared those with anti-VEGF therapy alone (46.2% compared to 22.2%).

Functional and anatomical outcomes

Functional and anatomical outcomes for eyes stratified by treatment regimen are displayed in Fig. 1 and Table 3.

On average, eyes that were treated with anti-VEGF alone maintained VA. However, there was no significant improvement in their mean VA or reduction in CST after the loading phase (from month 3 to month 24: + 2.8 ± 12.9 letters, $p = 0.254$; − 24 ± 154 µm, $p = 0.243$). Eyes with anti-VEGF therapy in the first year that were switched to steroids in the second year experienced significant functional and anatomical improvements in the second year (from month 12 to month 24: + 6.8 ± 8.9 letters, $p = 0.023$; − 226 ± 188 µm, $p = 0.004$). Eyes that were switched to DEX early maintained the significant gain in VA during the first 12 months (+ 7.8 letters, $p < 0.001$, Table 3) at 24 months (+ 1.1 letters). CST continued to decrease during the second year in eyes switched early to DEX implant (− 66 µm, $p = 0.001$, Table 3, Fig. 1).

A matching procedure to balance baseline characteristics was performed in the initial analysis in order to compare the outcomes of eyes which were treated with anti-VEGF alone for 12 months compared to those switched early to DEX implant [11]. Follow-up data were available for 79% of these eyes. Baseline characteristics between both groups did not differ significantly (Table S1). In the matched anti-VEGF group, 30.3% (10 out of 33 eyes) were later switched to steroids (DEX: 7 eyes, fluocinolone acetonide: 3 eyes). Multivariable analysis revealed that functional and anatomical outcomes were better in the first and second years in the DEX group compared to the anti-VEGF group (VA change [AUC]: month 3–12: + 17.9 ± 20.6 letters vs. + 1.9 ± 17.6 letters, $p = 0.004$; month 12–24: + 138.0 ± 156.1 letters vs. + 38.8 ± 145.8 letters, $p = 0.035$; CST change [AUC]: month 3–12: − 246 ± 378 µm vs. − 38 ± 269 µm, $p = 0.020$; month 12–24: − 2318 ± 2664 µm vs. − 593 ± 2067 µm, $p = 0.007$, Fig. 2, Table 3).

Outcome of continued non-responders during anti-VEGF therapy

Among eyes with continued anti-VEGF therapy during the first year, most eyes (72.4%, 42/58 eyes) remained non-responsive (VA gain ≤ 5 letters and/or CST reduction < 20% from baseline) during the first 12 months. The likelihood of achieving a VA gain of > 5 letters from further therapy remained stable with increased duration a patient was non-responsive to anti-VEGF therapy. The likelihood of gaining > 5 letters from further anti-VEGF therapy was similar in eyes being non-responsive for 12 months compared to eyes being non-responsive for only 3 months (23.8 vs. 31.0%, $p = 0.344$) (Table 4).

Discussion

We previously reported better functional and anatomical 12-month outcomes in eyes non-responsive to anti-VEGF during the loading phase switched early to DEX implant compared to those continued on anti-VEGF agents alone

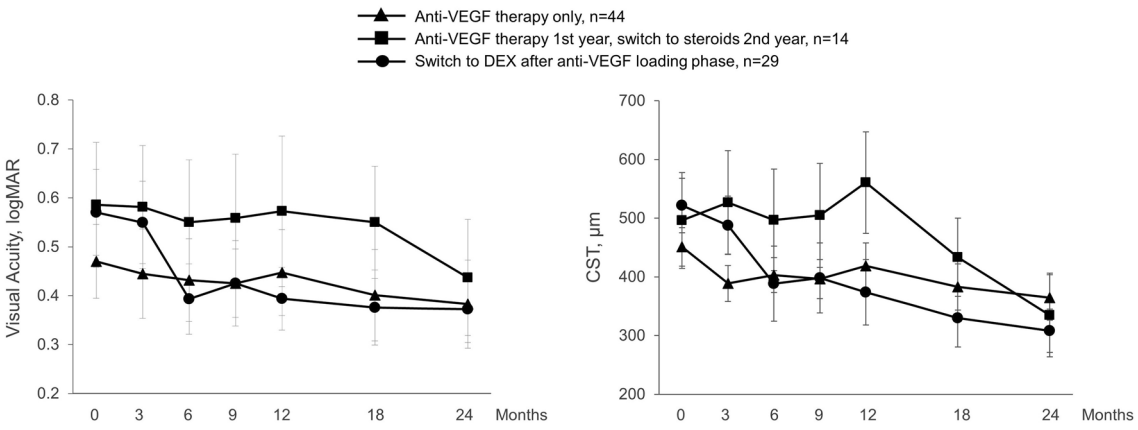

Fig. 1 Visual acuity (VA, **a**) and central subfield thickness (CST, **b**) over the 24-month follow-up. Data are mean ± 95% confidence interval. DEX—dexamethasone, VEGF—vascular endothelial growth factor

Table 3 Functional and anatomical study outcomes

	Anti-VEGF throughout 1st year			Early switch to DEX implant ($n=29$)	Univariable analysis, p value*	Multivariable analysis, p value*
	Only anti-VEGF during study ($n=44$)	Switch to steroids in 2nd year[a] ($n=14$)	Matched group[b] ($n=33$)			
Baseline VA, logMAR, mean (SD)	0.47 (0.25)	0.59 (0.22)	0.57 (0.21)	0.57 (0.23)	0.992	–
VA at M3, logMAR, mean (SD)	0.45 (0.30)	0.58 (0.22)	0.55 (0.27)	0.55 (0.22)	0.992	–
VA at M12, logMAR, mean (SD)	0.45 (0.29)	0.57 (0.27)	0.54 (0.28)	0.39 (0.17)	0.023	0.039
VA at M18, logMAR, mean (SD)	0.40 (0.31)	0.55 (0.20)	0.51 (0.28)	0.38 (0.20)	0.049	0.049
VA at M24, logMAR, mean (SD)	0.39 (0.29)	0.44 (0.21)	0.44 (0.28)	0.37 (0.18)	0.253	–
VA change M3–M12, letters, mean (SD)	−0.1 (9.1)	+0.4 (10.2)	+0.5 (9.7)	+7.8 (10.1)	0.005	0.003
VA change M3–M24, letters, mean (SD)	+2.8 (12.9)	+7.2 (8.3)	+5.4 (11.9)	+8.9 (13.2)	0.274	–
VA change M3–M12, AUC, letters, mean (SD)	+0.2 (15.9)	+2.9 (18.8)	+1.9 (17.6)	+17.9 (20.6)	0.004	0.004
VA change M12–M24, AUC, letters, mean (SD)	+25.7 (155.1)	+38.2 (102.2)	+38.8 (145.8)	+138.0 (156.1)	0.017	0.035
VA change M3–M24, AUC, letters, mean (SD)	+25.9 (167.4)	+41.1 (118.5)	+40.8 (158.2)	+155.9 (173.8)	0.012	0.027
VA gain ≥ 5 letters at M24[c], *n* (%)	19 (43.2)	8 (57.1)	18 (54.5)	20 (69.0)	0.247	–
VA gain ≥ 10 letters at M24[c], *n* (%)	11 (25.0)	7 (50.0)	13 (39.4)	17 (58.6)	0.133	–
VA loss ≥ 5 letters at M24[c], *n* (%)	13 (29.5)	1 (7.1)	7 (21.2)	5 (17.2)	0.693	–
VA change during anti-VEGF therapy[c], mean (SD)	+2.8 (12.9)	−1.5 (9.2)	+2.5 (12.3)	–	–	–
VA change during therapy with steroids, mean (SD)	–	+8.9 (7.4)	+9.5 (7.6) $n=10$	+8.3 (13.4)	–	–
Baseline CST, logMAR, mean (SD)	451 (108)	496 (141)	484 (115)	522 (121)	0.221	–
CST at M3, µm, mean (SD)	389 (101)	527 (153)	452 (123)	488 (131)	0.275	–
CST at M12, µm, mean (SD)	419 (128)	561 (150)	471 (157)	374 (147)	0.019	0.009
CST at M18, logMAR, mean (SD)	383 (129)	433 (116)	398 (135)	330 (130)	0.054	0.054
CST at M24, logMAR, mean (SD)	365 (128)	335 (123)	371 (140)	308 (97)	0.057	0.057
CST change M3–M12, AUC, µm, mean (SD)	+61 (278)	−35 (385)	−38 (269)	−246 (378)	0.023	0.020
CST change M12–M24, AUC, µm, mean (SD)	+133 (2011)	−1106 (2146)	−593 (2067)	−2318 (2664)	0.012	0.007

Table 3 (continued)

	Anti-VEGF throughout 1st year			Early switch to DEX implant ($n=29$)	Univariable analysis, p value*	Multivariable analysis, p value*
	Only anti-VEGF during study ($n=44$)	Switch to steroids in 2nd year[a] ($n=14$)	Matched group[b] ($n=33$)			
CST change M3–M24, AUC, µm, mean (SD)	+195 (2230)	−1141 (2446)	−630 (2264)	−2564 (3005)	0.012	0.012

Data were missing for VA at month 18 for 8 eyes (9%), for CST at month 18 for 10 eyes (11%), and for CST at month 24 for 5 eyes (6%). Last carried observation forward method was used to impute missing data

AUC, area under the curve; CST, central subfield thickness; M, month; SD, standard deviation; VA, visual acuity

[a]Includes DEX and fluocinolone acetonide implant

[b]Includes 23 eyes with anti-VEGF therapy only and 10 eyes with switch to steroids during 2nd year

[c]From M3—end of loading phase

*p values are for difference between matched anti-VEGF and DEX group tested by logistic regression model. Multivariable analyses included age, proliferative diabetic retinopathy at baseline, diabetes duration, damage to ellipsoid zone at baseline, lens status at baseline and after 24 months, status post-panretinal photocoagulation at baseline and after 24 months, and baseline VA (for VA outcomes) or baseline CST (for CST outcomes). A backward selection procedure was performed, and only those confounders with a p value ≤ 0.10 were kept in the model

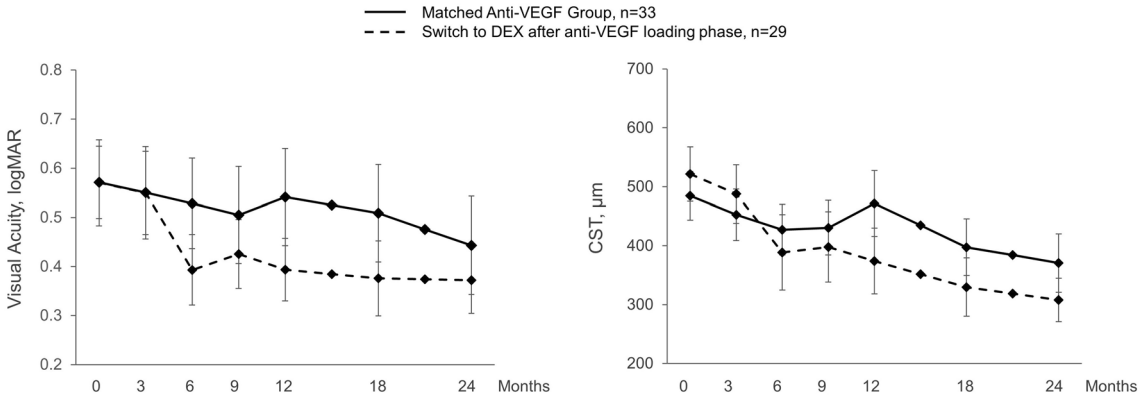

Fig. 2 Visual acuity (VA, **a**) and central subfield thickness (CST, **b**) over the 24-month follow-up. Data are mean ± 95% confidence interval. DEX—dexamethasone, VEGF—vascular endothelial growth factor

Table 4 Proportion of eyes with VA gain among non-responsive eyes with continued anti-VEGF therapy during the first year

Eyes being non-responsive[a] at	VA gain > 5 letters at the end of anti-VEGF therapy[b], n (%)	VA gain > 5 letters at month 24, n (%)
Month 3, $n=58$	18 (31.0)	23 (39.7)
Month 6, $n=50$	15 (30.0)	20 (40.0)
Month 9, $n=46$	12 (26.1)	17 (37.0)
Month 12, $n=42$	10 (23.8)	15 (35.7)

CST, central subfield thickness; VA, visual acuity

[a]Defined by VA gain ≤ 5 letters and/or CST reduction < 20% from baseline

[b]At month 24 in the case of continued anti-VEGF therapy or before switch to steroids in the case of switch to steroids during second year

[11]. This present study reports the two-year outcome of this same cohort.

The functional and anatomical benefits seen in eyes switched early to DEX at month 12 were maintained during the second year which supports results from previous studies [8–10]. Eyes which received anti-VEGF therapy alone did not significantly improve vision or reduce their central subfoveal thickness at 12 or 24 months compared to baseline. However, these eyes exhibited stable visual acuity, confirming results from Protocol I by DRCR.net [4]. The mean number of anti-VEGF injections in the second year was 4.3 ± 3.7, which is similar to the injection frequency in the second year reported in randomized controlled trials [14, 15]. Eyes continued on anti-VEGF alone for 24 months had a better baseline VA and thus less opportunity for VA gain due to a ceiling effect compared to those which were switched to steroids. Furthermore, the eyes which were switched early

to steroids were more likely to undergo cataract surgery during the study period compared to those which received anti-VEGF alone (46.2 vs. 22.2%), which might have had an impact on VA. However, the better anatomical results in eyes with early switch to DEX at 24 months are unlikely to be influenced by baseline VA, lens status, or cataract surgery.

Eyes switched from anti-VEGF therapy to steroids in the second year still experienced significant functional and anatomical benefits in our study. There was a similar improvement in vision in both steroid groups at 24 months (+8.9 letters [early switch] vs. +7.2 [late switch]); however, area-under-the-curve analysis showed better outcomes of patients switched early. Even though the timepoint of switching to steroids does not influence the outcome at 24 months, it needs to be considered that, by a later switch to steroids, patients experience a significantly longer time of reduced visual acuity, which is associated with a longer time of disability.

Our data showed that most eyes that were non-responsive after 3 months were still non-responsive at month 12 (72%) when continued on anti-VEGF therapy alone. It is questionable whether it is worthwhile continuing therapy in eyes shown to be non-responsive to treatment. However, a significant proportion (24%) of eyes being non-responsive at month 12 actually gained more than one line of vision when anti-VEGF was continued further. The proportion was even higher for those switched to steroids, with 36% gaining more than one line of vision at 24 months.

The predominant limitations of the present study are its retrospective design and the shortcomings of a real-world setting. There was no predefined treatment protocol, and treatment decisions could have differed between centers. Reasons for switching therapies were not assessed. Due to the diversity of treatment regimens in the second year, we are not able to draw conclusions on the appropriate treatment of non-responders within the second year. In the second year, treatment with fluocinolone acetonide was applied in 6 eyes, which is a steroid implant with an expected durability of up to 36 months. Thus, in these patients, the need for further intravitreal therapy might have been less compared to patients with anti-VEGF or DEX implant treatment. Due to variability of cataract grading among the study sites, the presence and progression of cataract were not included in our study, which might have impacted VA results. Similar to other real-world studies, 21% of patients in our study were lost to follow-up [7, 16, 17]. However, the lost to follow-up rate is significant even in randomized clinical controlled trials of treatment of DME. Protocol T reported that 15% of their enrolled patients did not complete their two-year visits [14]. Patients that were lost to follow-up in our study had better baseline VA, were more likely to have lost vision during the first year of treatment, and underwent less injections, which may indicate that they were undertreated (and less compliant) even in their first year.

In conclusion, we reported on the two-year outcomes of DME patients being non-responsive to anti-VEGF therapy during the loading phase who were either switched early to DEX implant or continued anti-VEGF therapy in a real-world setting. Eyes switched early to DEX implant had better outcomes at 12 months and were able to maintain those outcomes during the second year. Eyes that were switched from anti-VEGF therapy to steroids in the second year still experienced significant improvements. Eyes that were continued on anti-VEGF therapy over the 24-month study period did not improve vision or macular thickness but maintained their baseline VA. However, treatment should be continued even in eyes being non-responsive for 12 months since those eyes still have a significant chance to experience VA gains.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the individual institutional review board of the participating centers.

Informed consent None.

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Affiliations

Catharina Busch[1] · Samantha Fraser-Bell[2] · Matias Iglicki[3] · Marco Lupidi[4] · Aude Couturier[5] · Voraporn Chaikitmongkol[6] · Ermete Giancipoli[7,8] · Patricio J. Rodríguez-Valdés[9] · Pierre-Henry Gabrielle[10,11] · Inês Laíns[12,13,14] · Ana Rita Santos[13,15] · Zafer Cebeci[16] · Atchara Amphornphruet[17] · Valentin Degenhardt[1,18] · Jan-Darius Unterlauft[1] · Carlo Cagini[4] · Valérie Mané-Tauty[5] · Giuseppe D'Amico Ricci[7,8] · Isaac Hindi[19,20] · Kushal Agrawal[21] · Jay Chhablani[22,23] · Anat Loewenstein[19,20,24] · Dinah Zur[19,20] · Matus Rehak[1] · for the International Retina Group

✉ Catharina Busch
busch.catharina@gmail.com

[1] Department of Ophthalmology, University Hospital Leipzig, Liebigstr. 10-14, 04103 Leipzig, Germany

[2] Department of Ophthalmology, Sydney University, Sydney, Australia

[3] Private Retina Service, University of Buenos Aires, Buenos Aires, Argentina

[4] Department of Biomedical and Surgical Sciences, Section of Ophthalmology, University of Perugia, Perugia, Italy

[5] Department of Ophthalmology, Hôpital Lariboisière, AP-HP, Université Paris, 7 – Sorbonne Paris Cité, Paris, France

[6] Retina Division, Department of Ophthalmology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

[7] Department of Surgical, Microsurgical and Medical Sciences, Eye Clinic, University of Sassari, Sassari, Italy

[8] Department of Biomedical Sciences, University of Sassari, Sassari, Italy

[9] Instituto de Oftalmología y Ciencias Visuales, Escuela de Medicina, Tecnológico de Monterrey, Monterrey, Mexico

[10] Department of Ophthalmology, Dijon University Hospital, Dijon, France

[11] UMR1324, INRA, Center for Taste and Feeding Behaviour, Dijon, France

[12] Faculty of Medicine, University of Coimbra, Coimbra, Portugal

[13] Association for Innovation and Biomedical Research on Light and Image, Coimbra, Portugal

[14] Massachusetts Eye and Ear, Harvard Medical School, Boston, USA

[15] School of Allied Health Technologies, Polytechnic Institute of Porto, Porto, Portugal

[16] Department of Ophthalmology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

[17] Department of Ophthalmology, Faculty of Medicine, Rajavithi Hospital, Rangsit University, Bangkok, Thailand

[18] Department of Ophthalmology, University Hospital Heidelberg, Heidelberg, Germany

[19] Division of Ophthalmology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

[20] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[21] Jupiter Hospital, Thane, India

[22] UPMC Eye Center, University of Pittsburgh, Pittsburgh, USA

[23] L.V. Prasad Eye Institute, Banjara Hills, Hyderabad, India

[24] Incumbent, Sydney A. Fox Chair in Ophthalmology, Tel Aviv University, Tel Aviv, Israel