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Biomarkers of risk of switching to dexamethasone implant for the treatment of diabetic macular oedema in real clinical practice: a multicentric study

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ABSTRACT

Objective To establish the influence of different optical coherence tomography (OCT) biomarkers at baseline treatment on the potential response to anti-vascular endothelial growth factor (VEGF) treatment for diabetic macular oedema (DME).

Methods Multicentric, retrospective, case-series study in patients with DME switched to dexamethasone implant injections (DEX-i) after anti-VEGF in real clinical practice. Biomarkers analysed on OCT images at baseline included intraretinal fluid (IRF), subretinal fluid (SRF), disorganisation of retinal inner layers (DRIL), disorganisation of retinal outer layers (DROL), hyperreflective foci (HRF), hyperreflective cystoid walls (HCW), dense intraretinal cyst (DIR) and vitreomacular interface (VMI) abnormalities. DME was classified according to the European School for Advanced Studies in Ophthalmology classification. Patients who were treated with anti-VEGF injections with an adequate response were selected as the control group.

Results 275 eyes were analysed in this study; 209 eyes (76.0%) switched from anti-VEGF to DEX-i were compared with 66 control eyes (24.0%). Patients who required switching were statistically older, showed worse initial BCVA and higher CRT. Logistic regression analyses showed that female gender, age, central retinal thickness, type of diabetes, SRF, HCW, DIR and VMI increase the likelihood of switching. The OR regarding the need to switch generated by the presence of two of these three factors (SRF, HCW, VMI) was 48.95. Having all three multiplies it by 4.56×10^{16}.

Conclusion If baseline OCT shows two of SRF, HCW and VMI biomarkers at baseline, the risk of failure of anti-VEGF therapy is close to 50%. In the presence at baseline of all three biomarkers, failure of anti-VEGF therapy is almost certain.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is a percentage of patients with diabetic macular oedema (DME) that do not show an adequate response to anti-vascular endothelial growth factor (anti-VEGF) treatments and need a treatment switch to manage their disease.

WHAT THIS STUDY ADDS

⇒ Biomarkers including subretinal fluid, hyperreflective cyst walls, dense intraretinal cysts and vitreomacular interface abnormalities statistically increase the likelihood of insufficient response to anti-VEGF drugs.

HOW THIS STUDY MIGHT AFFECT RESEARCH PRACTICE OR POLICY

⇒ The presence of such biomarkers at the moment of DME diagnosis may help identify potential non-responders who may benefit from an earlier switch or initial treatment with other drugs, such as intravitreal steroids.

INTRODUCTION

More than 90 million people in the world suffer from diabetic retinopathy (DR). This condition is derived from the microvascular changes that take place because of poorly controlled diabetes and can threaten our patients' quality of life through vision loss. The most common cause of such loss is diabetic macular oedema (DME), which affects more than 7% of patients with diabetes.[1–3]

Blood-retinal barrier disruption due to chronic capillary damage is one of the main causes of DR, and its status has been historically evaluated using fundus exploration and imaging techniques such as fluorescein angiography.[4] Nowadays, the use of optical coherence tomography (OCT) is the gold standard technique for the screening and follow-up of DME, providing in vivo cross-sectional images of the central retina[5] and providing valuable information about different parameters that could play a role in the response each patient shows to treatment.

Anti-vascular endothelial growth factor (anti-VEGF) and/or steroid injections are the most accepted therapies for DME, with anti-VEGF drugs being considered as first-line treatment by a large proportion of retina specialists.[6] It is important to take into account that a percentage of these patients will not respond adequately to anti-VEGF treatment.[7–12] Several OCT-based alterations of macular

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structure, ranging from subretinal fluid to vitreomacular interface changes, could potentially play a role in our patients' response to treatment and may contribute to a switch of drug or a different treatment strategy altogether. In fact, early anatomical response to ranibizumab can be considered as an indicator of long-term anatomical response to treatment.[10]

If, as believed, chronic DME can lead to permanent retinal damage, anti-VEGF non-responders could potentially benefit from steroid treatment.[13] Early switch to intravitreal dexamethasone implants (DEX-i) after three injections in suboptimal responders could better functional outcomes according to previous research.[14]

The objective of this study was to establish the influence of different OCT biomarkers at baseline of DME treatment in the potential response to anti-VEGF in patients suffering from DR.

MATERIAL AND METHODS

International multicentric, retrospective, case-series study conducted in consecutive patients with DME who underwent first-line anti-VEGF therapy and were switched to DEX-i in real clinical practice at the investigators' discretion for poor or insufficient response.[14]

The study was conducted in accordance with the principles of the Declaration of Helsinki for research involving human subjects.

Inclusion criteria were as follows: DM patients with DME treated with intravitreal injections of anti-VEGF inhibitors prior to the switch to intravitreal DEX-i (Ozurdex, Abbvie).

All patients underwent a complete ophthalmological examination that included: best-corrected visual acuity (BCVA), slit lamp anterior segment examination, intraocular pressure with Goldman tonometry, indirect fundus ophthalmoscopy and multimodal imaging (fundus colour photography and OCT). All examinations were performed in both eyes if they met the inclusion criteria.

The primary endpoint was the need for change of treatment from anti-VEGF to DEX-i. Secondary study variables analysed at baseline were age, duration of DM (years), duration of DME (months), initial BCVA, central retinal thickness (CRT), subfoveal choroidal thickness (SFCT), gender, type of DM, type of DR. Biomarkers analysed on OCT images at baseline were intraretinal fluid (IRF), subretinal fluid (SRF), disorganisation of retinal inner layers (DRIL), disorganisation of retinal outer layers (DROL) defined by the loss of integrity of either the ellipsoid zone or the external limiting membrane (ELM), hyperreflective foci (HRF), hyperreflective cystoid walls (HCW) defined as the presence of at least one intraretinal cyst with hyperreflective walls in absence of a microaneurysm in the corresponding infrared image; dense intraretinal cyst (DIR), defined as intraretinal cysts with hyperreflective internal material; and vitreomacular interface (VMI) abnormalities (figure 1). DME was classified according to the European School for Advanced Studies in Ophthalmology classification.[15] A failure to improve central retinal thickness by 20%, no improvement in BCVA and/or recurrence of DME despite monthly anti-VEGF injections were used as criteria for a patient to qualify as a non-responder.

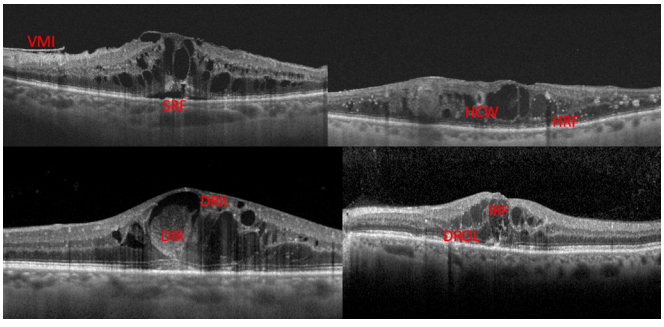

Figure 1 Biomarkers analysed on optical coherence tomography images at baseline were intraretinal fluid (IRF), subretinal fluid (SRF), disorganisation of retinal inner layers (DRIL), disorganisation of retinal outer layers (DROL), hyperreflective foci (HRF), hyperreflective cystoid walls (HCW), dense intraretinal cyst (DIR) and vitreomacular interface (VMI) abnormalities.

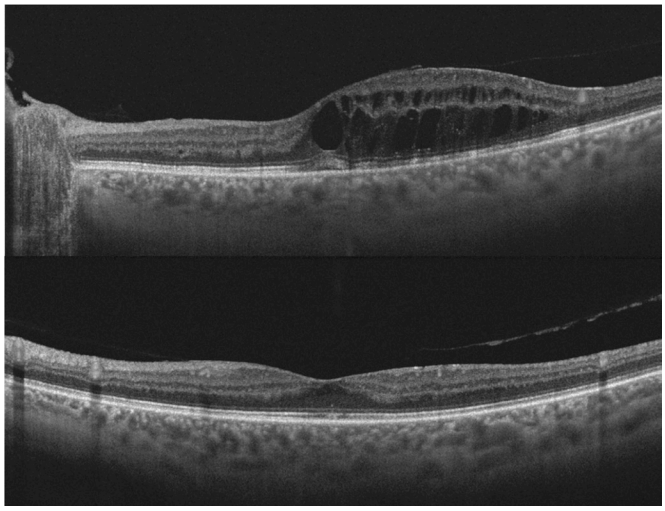

Figure 2 Optical coherence tomography of a patient with diabetes suffering from diabetic macular oedema (top panel). After a loading dose of anti-vascular endothelial growth factor intravitreal injections, the response was deemed adequate and the patient did not need a treatment switch (lower panel).

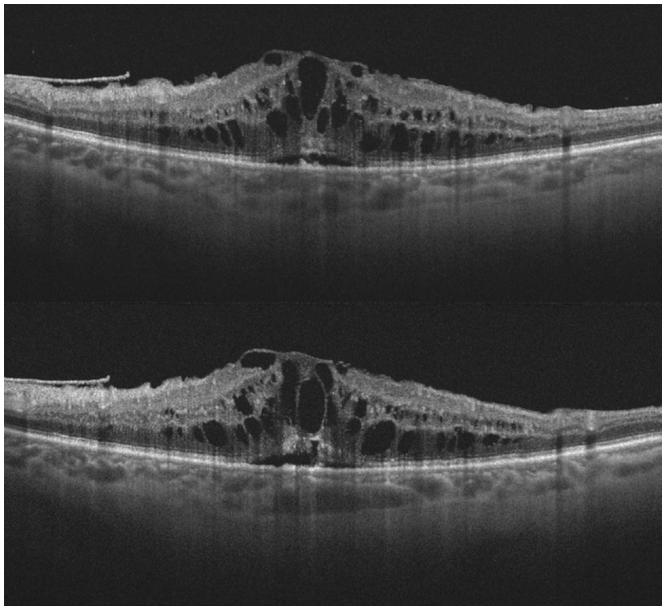

Figure 3 Optical coherence tomography of a patient with diabetes suffering from diabetic macular oedema (top panel). After a loading dose, the treatment response was deemed suboptimal and the patient underwent a treatment switch to intravitreal dexamethasone implant (lower panel).

Study patients were compared with a control group consisting of patients who were initially treated with anti-VEGF injections and showed an adequate response where a treatment switch was not deemed necessary (figures 2 and 3).

Statistical analysis

Statistical analysis was performed using MedCalc Statistical Software V.22.016 (MedCalc Software, Ostend, Belgium; https://www.medcalc.org; 2023). Differences between quantitative and qualitative variables were compared using the Mann-Whitney test and Fisher's exact test, respectively. χ^2 testing was used to study differences regarding the ESASO classification. A logistic regression model was used to estimate and test factors for their association with the need to switch treatments. A backward regression strategy was adopted, with a statistically significant cut-off point for the detection of variables of 0.05. Factors associated with progression in the univariate analysis at $p \leq 0.1$ were included in the multivariate analysis.

RESULTS

A total of 275 eyes were analysed in this study; 209 eyes (76.0%) were switched from anti-VEGF to intravitreal dexamethasone implantation for the treatment of DME in real clinical practice, compared with 66 eyes (24.0%) in which anti-VEGF therapy was maintained due to good response.

Comparing both groups, patients who required switching to Dex-i were older (69.0 vs 64.2 years), showed worse initial BCVA (0.3 vs 0.5), higher CRT (492.3 vs 351.4 µm) and a higher percentage of women (43.5% vs 18.2%). Biomarkers such as SRF (34.9% vs 3%), HCW (33% vs 1%), DIR (39.7% vs 19.7%) and VMI abnormalities (30.1% vs 3%) were more common among patients that underwent treatment switch; conversely, they showed a lower prevalence of DROL (38.8% vs 59.1%) and HRF (80.4% vs 98.5%). There were no differences regarding the duration of diabetes, duration of DME, SFCT, type of DR or presence of DRIL (see tables 1 and 2). Phakic patients in the control group were 76.11% vs 51.02% in the study group ($p<0.05$ χ^2 test).

Logistic regression analyses confirmed that the factors significantly associated with the need to switch from anti-VEGF to Dex-i in the univariate analysis that increase the relative likelihood of requiring switching are as follows (table 3):

- Age: 1.04-fold per year of age.
- CRT: 1.01-fold per µm.
- Type of diabetes: 5.15-fold for type 2.
- SRF: 17.18-fold.
- HCW: 32.04-fold.
- DIR: 2.69-fold.
- VMI: 13.80-fold if abnormal.

Conversely, the following reduce the relative likelihood of requiring a treatment switch:

- BCVA: Every 0.1 increase implies a 25-fold reduction of the risk of switch.
- Gender: Being male reduces the risk of switch by 3.45 times.

Table 1 Quantitative variables

Study group							
	N	Mean	SD	95% CI	Median	25–75 Percentile	Normal distribution
Age	209	69.08	10.69	67.62 to 70.54	70	62.75 to 77.00	0.008
Duration diabetes/years	199	14.15	8.92	12.90 to 15.39	12.00	7.00 to 20.00	<0.0001
Duration DME/months	204	13.56	19.96	10.80 to 16.32	8	0,32 to 0,40	<0.0001
Initial BCVA	209	0.35 (logMAR 0.48)	20	0.32 to 0.37	0.32	0.20 to 0.50	<0.0001
Injections (n)	209	5.84	4.68	5.20 to 6.48	4	3.00 to 7.00	<0.0001
CRT	209	492.31	133.78	474.07 to 510.55	469	392.50 to 572.00	0.0001
SFCT	209	249.59	91.91	237.06 to 262.12	240	194.25 to 287.00	<0.0001
Control group							
	N	Mean	SD	95% CI	Median	25–75 P	Normal distribution
Age	66	64.27	13.7	60.90 to 67.64	65.5	58.00 to 74.00	0.03
Duration diabetes/years	66	13.92	9.19	11.66 to 16.18	13	5.00 to 20.00	0.0002
Duration DME/months	66	11.18	12.31	8.15 to 14.20	6	4.00 to 14.00	<0.0001
Initial BCVA	66	0.53 (logMAR 0.29)	0.28	0.46 to 0.60	0.5	0.40 to 0.80	0.005
Injections (n)	66	3.51	0.79	3.32 to 3.71	3.36	2.98 to 3.90	0.002
CRT	66	267.77	115.91	239.27 to 296.26	266	179.00 to 336.00	0.02

Head to head									
	Control group			Study group			Difference		
Variable	n	Mean	SD	n	Mean	SD	Mean	95% CI	P value*
Age	66	64.27	13.7	209	69.08	10.69	4.81	1.62 to 8.00	0.009
Duration diabetes†	66	13.92	9.19	199	14.15	8.92	0.22	−2.28 to 2.74	0.64
Duration DME‡	66	11.18	12.31	204	13.56	19.96	2.38	−2.74 to 7.51	0.13
Initial BCVA	66	0.53 (logMAR 0.29)	0.28	209	0.34 (logMAR 0.48)	20	−19	−0.25 to −0.13	<0.0001
CRT	66	351.4	79.09	209	492.31	133.78	140.9	106.72 to 175.09	<0.0001
SFCT	66	267.77	115.91	209	249.5	91.91	−18.17	−45.46 to 9.10	0.3

*Mann-Whitney test.
†Years.
‡Months.
BCVA, best-corrected visual acuity; CRT, central retinal thickness; DME, diabetic macular oedema; SFCT, subfoveal choroidal thickness.

Table 2 Qualitative variables

Variables	Study group	Control group	P value
Gender (female)	91 (43.5%)	12 (18.2%)	0.0002*
Type DM (1/2)	7/202	10/56	0.001*
Type RD (RDNP/P)	175/34	50/16	0.1*
IRF	209 (100%)	66 (100%)	–
SRF	73 (34.9%)	2 (3%)	<0.0001*
DRIL	94 (45%)	27 (40.9%)	0.57*
DROL	81 (38.8%)	39 (59.1%)	0.004*
HRF	168 (80.4%)	65 (98.5%)	0.0001*
HCW	69 (33%)	1 (1.5%)	<0.0001
DIR	83 (39.7%)	13 (19.7%)	0.002*
VMI abnormalities	63 (30.1%)	2 (3%)	<0.0001*
ESASO	31/157/21/0	27/38/0/1	<0.0001†

*Fisher's exact test.
†χ^2 test.
DIR, dense intraretinal cyst; DM, diabetes mellitus; DR, diabetic retinopathy; DRIL, disorganisation retinal inner layers; DROL, disorganisation retinal outer layers; HCW, hyperreflective cystoid walls; HRF, hyperreflective foci; IRF, intraretinal fluid; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; SRF, subretinal fluid; VMI, vitreomacular interface.

- DROL: Its presence reduces the risk of switch by 4.17 times.
- HRF: Its presence reduces the risk of switch by 16.67 times.

The factors significantly associated with the need to switch anti-VEGF treatment in multivariate analysis were SRF (20.81-fold), HCW (40.78-fold), DIR (5.07-fold) and VMI (16.91-fold). Conversely, those that reduced the relative probability of requiring a switch were gender (0.27-fold if male), DROL presence (0.21-fold) and HRF presence (0.06-fold).

Table 3 Multivariate analysis

	Switch			
	Univariate		Multivariate	
Variable	OR (95% CI)	P value	OR (95% CI)	P value
Age, years	1.04 (1.01–1.06)	0.0041	1.05 (0.99–1.12)	114
Duration diabetes, years	1.00 (0.97–1.04)	0.8587		
Duration DME, months	1.01 (0.99–1.03)	0.3673		
BCVA, per 0.1	0.04 (001–0.11)	<0.0001	0.01 (0.00–202.90)	0.3714
CRT, µm	1.01 (1.01–1.02)	<0.0001	1.01 (0.99–1.03)	0.0732
SFCT, µm	0998 (0996–1001)	0.1929		
Gender	0.29 (0.15–0.57)	0.0004	0.27 (0.08–0.86)	0.0273
Type diabetes	5.15 (1.88–14.15)	0.0015	1.82 (0.14–23.89)	647
Type DR	0.61 (0.31–1.19)	0.1457		
SRF	17.18 (4.09–72.20)	0.0001	20.81 (2.07–208.96)	0.0099
DRIL	1.18 (0.67–2.07)	0.5619		
DROL	0.44 (0.25–0.77)	0.0041	0.21 (0.06–0.73)	0.0145
HRF	0.06 (0.01–0.47)	0.0069	0.06 (0001–0.65)	2
HCW	32.04 (4.35–235.76)	0.0007	40.78 (3.35–496.28)	0.0036
DIR	2.69 (1.38–5.23)	0.0037	5.07 (1.40–18.30)	0.0132
VMI	13.80 (3.28–58.17)	0.0003	16.91 (2.30–124.44)	5

BCVA, best-corrected visual acuity; DIR, dense intraretinal cyst; DME, diabetic macular oedema; DR, diabetic retinopathy; DRIL, disorganisation retinal inner layers; DROL, disorganisation retinal outer layers; HCW, hyperreflective cystoid walls; HRF, hyperreflective foci; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; SRF, subretinal fluid; VMI, vitreomacular interface.

The OR of having 'at least' two of the three factors mentioned (SRF, HCW, VMI) was 48.95 (95% CI 29.80 to 80.42; p<0.0001). In other words, having any two of the three factors mentioned above increases the risk of anti-VEGF failure by a factor of 49 (48.95-fold). Having all three multiplies it by 4.56 per 10^{16}, that is, almost absolute certainty; but the limited number of cases studied must be considered.

Out of 209 patients, 68 showed intraocular pressure (IOP) elevations that were controlled with topical treatments and did not require glaucoma surgery during the study. No cases of endophthalmitis were reported during the follow-up.

DISCUSSION

The first-line treatment for DME is anti-VEGF drugs such as aflibercept, ranibizumab or faricimab, while intravitreal steroids such as dexamethasone or fluocinolone acetonide implants will be used only as second-line treatment, mainly due to the higher relative risk of ocular side effects, particularly adverse events related to IOP and cataracts.[16] Anti-VEGF agents are clinically effective in most patients with DME; however, a significant proportion (>40%) of patients with DME may not respond fully to this treatment.[17–21]

Multiple studies have shown that in some patients with DME, VEGF levels may be normal, with elevated levels of inflammatory markers such as interleukin (IL)-8, IL-6, IL-1b and intercellular adhesion molecule 1 (ICAM-1) in serum or aqueous humour. It is these patients who do not respond adequately to standard anti-VEGF treatment.[22 23] On the other hand, chronic long-standing DME, in general, also appears to show a limited response to anti-angiogenic drugs.[24] Therefore, these patients who do not respond sufficiently to anti-VEGF drugs could benefit from steroid therapy that controls the important role of inflammation in DME. The problem is to be able to identify these patients before starting anti-VEGF treatment.

If macular thickening persists and functional response is limited, DME is considered refractory to treatment and the patient is classified as a poor or insufficient responder. However, the exact definition of limited response to treatment and poor response is heterogeneous. In a previous work, our group defined 'Not-adequately' responders to anti-VEGF when after three anti-VEGF injections (either ranibizumab, bevacizumab or aflibercept), there was no improvement in BCVA; and/or a CRT reduction <20%; and/or recurrence of DME despite monthly anti-VEGF injections; and/or similar BCVA but worsening of DME; and/or decreased in BCVA and a CRT thickening.[14] Other authors recommended defining patients who did not show a BCVA gain of >5 ETDRS letters and a CRT reduction <10% or a CRT decrease <20% after three consecutive anti-VEGF injections as anti-VEGF refractory therapy.[11]

A homogeneous definition of therapy-refractory DME and poor response to anti-VEGF treatment would be necessary to establish general guidelines on when and how to switch treatments in DME. But the main unsolved problem is to be able to know before starting treatment which DME will not respond adequately in order to avoid having to do three or six injections of anti-VEGF, with the cost that this entails,[25 26] and the loss of time without resolving the DME. In addition, there is sometimes a decrease in BCVA.[14 27 28]

Based on OCT examination, attempts have been made to identify biomarkers to predict responsiveness to treatment.[29–31] These biomarkers can be used to guide individual therapeutic

decisions and optimise outcomes. The reason why a patient may be a good responder to first-line therapy or a poor responder is based on the presence (or absence) and interaction of a large number and variety of parameters.

In some cases, initiation with steroids may be recommended as first-line therapy. According to the European Society of Retina Specialists guidelines, corticosteroids in DME are second-line options that should be restricted to patients who do not respond to anti-VEGF (after three to six injections, depending on the specific response of each patient). However, corticosteroids are considered first-line treatment in patients with a history of major cardiovascular events, in patients who are unwilling to attend monthly and frequent visits,[32] and in pregnant or breastfeeding women.[16]

In particular, dexamethasone implantation as first-line treatment is recommended in patients with high-risk cardiovascular disease, poor compliance, severe oedema (>500 µm), pseudophakic patients, patients scheduled for cataract surgery and patients with a history of vitrectomy,[33] and/or non-compliant patients.[34 35] Cost-benefit studies favour the use of dexamethasone or fluocinolone acetonide over other treatment options in these cases.[34 35]

The use of clinically available biomarkers will be crucial for the optimal choice of initial treatment. There are systemic inflammatory and glycaemic biomarkers, biomarkers in aqueous humour and morphological biomarkers in OCT.

OCT is non-invasive, easy to use, fast, reliable and has become the primary diagnostic technique for detecting and monitoring DME. The biomarkers identified in OCT so far are the following: increased retinal thickness,[36] intraretinal cystoid spaces,[37] hyperreflective retinal foci[38] which are strictly related to inflammation,[39] hyperreflective cystoid walls,[40] exudates,[41] DRIL,[29] DROL,[42] SRF,[30] central CT[31] and VMI (mechanical traction on the fovea correlates with worse prognosis and may suggest further surgical treatment).[43]

It has been suggested that large intraretinal cysts (≥250 µm), DRIL, HRF and SRF in chronic DME may be OCT biomarkers to select candidates for intravitreal steroids as first-line treatment.[44] DEX-i may also be the preferred option in phakic patients who are candidates for cataract surgery, protecting them from possible decompensation of previous DME[45–48] and in patients with DME with a high inflammatory component, as assessed by the presence of inflammatory biomarkers on OCT (large intraretinal cysts, DRIL, HRF and SRF).[45–49] But our results seem to indicate that biomarkers that were believed to be associated with a higher risk of suboptimal response, like DROL and HRF, may not act that way. Of course, further study will be necessary to corroborate these findings. In addition, in patients who do not respond to anti-VEGF injections, clinicians should consider switching to DEX implantation after the loading dose of three to six consecutive anti-VEGF injections.[45 46] If we review the literature, there is currently no absolute certainty as to when to use DEX-i as first line based on OCT biomarkers; for this reason, we have decided to carry out the study in reverse. That is to say, we selected patients with DME in whom in real clinical practice, following the recommendations of the literature, the switch to steroids had been made.

The main limitation of our study is the limited number of cases, which compels us to be cautious about claiming absolute certainty. The definition of recalcitrant macular oedema was variable given the multicentric nature of the study, although the general rules of no improvement in BCVA; and/or a CRT reduction <20%; and/or recurrence of DME despite monthly anti-VEGF injections were followed. For the same reasons, the switch criteria used were not completely uniform among different centres. The average number of injections received or the CRT prior to the switch was not registered. However, it was a multicentric study carried out in real clinical practice in hospitals from different regions of Spain and internationally. We are aware of the higher number of pseudophakic patients in the study group with a statistically significant difference compared with the control group. A higher prevalence of DME has been described in pseudophakic patients, but it has not been confirmed that this group responds worse to anti-VEGs, although a good response to steroids has been described.[50]

In conclusion, if the OCT shows 'at least' two of the following biomarkers at baseline: SRF, HCW and VMI alterations, the risk of failure of anti-VEGF therapy is close to 50%. If it shows all three biomarkers, failure of anti-VEGF therapy is almost certain. It would be desirable to be able to repeat this multicentric study with a larger number of cases that would allow us to reach a higher degree of certainty in our conclusions and avoid the waste of time and money involved in making three to six intravitreal injections to confirm the patient as an insufficient responder and make the switch to steroids.

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