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EXPERT OPINION

Challenges in Diabetic Macular Edema Management: An Expert Consensus Report

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Purpose: This paper aimed to present daily-practice recommendations for the management of diabetic macular edema (DME) patients based on available scientific evidence and the clinical experience of the consensus panel.

Methods: A group of Spanish retina experts agreed to discuss different aspects related with the clinical management of DME patients.

Results: Panel was mainly focused on therapeutic objectives in DME management; definition terms; and role of biomarkers as prognostic and predictive factors to intravitreal treatment response. The panel recommends to start DME treatment as soon as possible in those eyes with a visual acuity less than 20/25 (always according to the retina unit capacity). Naïve patient was defined, in a strict manner, as a patient who, up to that moment, had never received any treatment. A refractory DME patient may be defined as the one who did not achieve a complete resolution of the disease, regardless of the treatment administered. Different optical coherence tomography biomarkers, such as disorganization of the retinal inner layers, hyperreflective dots, and cysts, have been identified as prognostic factors.

Conclusion: This document has sought to lay down a set of recommendations and to identify key issues that may be useful for the daily management of DME patients.

Keywords: diabetes, diabetic macular edema, optical coherence tomography, inflammation, biomarkers, consensus

Introduction

As the prevalence of diabetes mellitus is rising up, the importance of diabetic eye disorders increases.[1,2] In Europe, it was estimated that approximately 6.4 million people are currently affected by any diabetic eye disease and 8.6 million people will be affected in 2050.[3] In the year 2020, moderate-to-severe visual impairment due to diabetic retinopathy has been estimated in 4.06% (Western Europe); 4.77% (Asia-Pacific, high income); and 4.99% (United States, high income).[2]

Diabetic macular edema (DME) is a prevalent condition that impacts central visual acuity (VA), and, therefore, critically influence on patient's quality of life.[4,5]

The prevalence of DME in Europe was estimated in 3.7% and its pooled mean annual incidence in type-2-diabetes patients was 0.4%.[3]

The changes in the paradigm of DME treatment[6–11] as well as the development of technological advances for diagnosis[12–15] makes, from our point of view, necessary to reconsider the approach to the daily practice management of these patients.

The aim of this manuscript is to evaluate and respond to different issues related to the management of DME patients and to establish consensus-based recommendations to provide the ophthalmologists responsible for the management of diabetic

patients with a frame of reference based on available scientific evidence and the clinical experience of the group.

Methods

A group of ophthalmologists in charge of Retina Units from 11 Spanish hospitals, working in collaboration, has developed a consensus report about different issues related to clinical management of patients with DME.

In the first meeting, performed on 13 February 2019, the panel of retina experts selected and agreed a first list of topics related to the clinical management of DME patients. The different subjects that focused the panel's attention were as follows: 1) Therapeutic objectives in DME management; 2) Definition of naïve, refractory, and chronic DME; and 3) Role of biomarkers as prognostic and predictive factors to intravitreal treatment response.

Attending to these subjects, the expert panel developed a list of questions. These questions were discussed, updated literature was reviewed and responses were agreed in different meetings held from February to October 2019 (six meetings in total).

A PubMed literature search for English, French, and Spanish language articles published to date was performed using the terms "Diabetic macular edema" AND "Treatment" OR "Diagnosis" OR "Biomarkers" OR "Management" OR "Outcomes". References cited in selected articles were also reviewed to identify additional relevant reports. Likewise, published national and international guidelines were also scrutinized.

An initial document was drafted and it was reviewed by all members of the panel of experts, who had the opportunity to make all the changes/suggestions/comments deemed necessary. Finally, after making the required revisions based on the panel feedback and reached a consensus, the final text was then validated.

Results

Basic Concepts

Therapeutic Objectives in DME

Functional and anatomic outcomes are usually selected as therapeutic objectives.[16–34] While therapeutic objectives have been clearly defined in clinical trials, the identical criteria may not be applicable to routine clinical practice. Sometimes the objective of DME treatment is reduced to maintain VA. However, our treatment goals with DME patients should be more ambitious than that with neovascular age-related macular degeneration patients. There is some evidence suggesting that functional response critically depends on baseline VA, because patients with good visual acuity have a ceiling effect with limited visual improvement, and the status of retina as there are patients with retinal damage without any possibility of functional improvement and the stabilization of vision avoid the vision loss is an achievement.[20,21,35] Thus, our therapeutic objective in terms of vision should be:

- In patients with VA 20/25 or better: observation and start to treat if vision worsens.
- In patients with high baseline VA (20/40 to 20/32): To maintain the VA.
  - Although many clinicians initiate vascular endothelial growth factor inhibitors (anti-VEGF) treatment in DME patients when visual acuity is minimally affected or unaffected, Protocol V[35] found that, in eyes with central involved DME and good vision, visual acuity remained stable, at least, during 2 years. That is why, our main goal is maintaining VA and, as a secondary objective, to improve it, if possible.
- In patients with low baseline VA (20/50 to 20/320): To improve the VA.

On the other hand, and since functional response depends on the status of the retina,[36–41] the efficacy of a treatment cannot be measured just attending to functional response. It has been suggested that in eyes with DME, VA depends on retinal thickness[42] and integrity of retinal structure (including inner and outer retina layer), especially the photoreceptor layer.[43–45] Because the functional response depends on the anatomic status of the retina, from a daily practice perspective, the main therapeutic objective in DME patients should be to achieve the best anatomic response as fast as possible, and at that point we must check the maximum functional response the patient can get.

It should be taken into consideration that an early anatomic response may predict mid-to-long-term anatomic outcomes and, therefore, the functional ones.[46]

When Patients Should Be Treated?

The results of Protocol V, a prospective and randomized clinical trial that compared three different strategies, namely intravitreal aflibercept, focal/grid laser

photocoagulation, or observation, suggested that in eyes with DME and good VA, aflibercept or laser photocoagulation appeared to be no superior to observation at 2 years.[35]

Moreover, the OBTAIN study, was as a 12-month, retrospective, multicenter, and observational cohort study conducted in a real-world setting, which included DME patients with baseline visual acuity ≥20/25 Snellen and central subfield thickness (CST) >250 µm.[47] Among the 249 eyes included in the study, 94 eyes (37.7%) did not receive any treatment during 12 months of follow-up, and 155 eyes (62.2%) received treatment over the course of the study. Mean change in VA at the end of the study was −1.8 ± 5.6 letters and −3.4 ± 5.8 letters in non-treated and in treated eyes, respectively.[47] The results of this study suggested that most of the DME eyes with very good VA maintained that VA during the 12-month of follow up, whether the DME was treated or not.[47]

Although according to the results of the Protocol V[35] observation until vision deterioration occurs seems to be a feasible approach in DME with good baseline VA, these findings may not be applicable to all eyes with DME with good VA.[48] For example, mean CST was very low (311 µm) as compared with previous DME clinical trials. This is clinically relevant, since eyes with CST ≥400µm may have a different treatment response than eyes with a thinner CST.[49]

Real-life treatment patterns in newly diagnosed DME patients were evaluated by means of an analysis of the American Academy of Ophthalmology Intelligent Research in Sight (IRIS®) Registry.[50] A total of 13,410 treatment-naive DME patients were included in the analysis. The results of this study have found that the treatment patterns within 28 days of initial DME diagnosis were as follows: observation in 9990 (74.5%) patients; anti-VEGF in 2086 (15.6%); laser photocoagulation in 1133 (8.4%); corticosteroids in 133 (1.0%); and combined therapy in 68 (0.5%) patients.[50]

In daily practice, DME treatment does not represent an emergency. Nevertheless, because the presence of subretinal/intraretinal fluid may negatively impact on functional outcomes, early treatment would be highly recommended.[51]

Panel recommendation:

- When visual acuity is less than 20/25 DME treatment should begin as soon as possible, according to the capacity of the Retina Unit. The best scenario is one where patients are treated on the same day of diagnosis. However, the best scenario is rarely the most frequent. Therefore, in those cases in which patients cannot be treated on the same day, treatment should be administered within 10–15 days.

Definitions

What is DME?

DME can be defined as a retinal thickening (≥250 µm) within one disk diameter of the center of the macula or definite hard exudates in this region.[16]

If fovea is involved, we speak about "Center-involved DME".[16]

Eyes with central macular thickness (CMT) ≥500 µm, hard exudates within 500 µm of the center of the macula with adjacent retinal thickening, or one disk area of retinal thickening any part of which is within one disk diameter of the center of the macula are defined as "Clinically relevant DME".[52]

What is a Naïve Patient?

In the strictest agreement with the term, the panel defined a naïve patient as

- A patient who, up to that moment, had never received any treatment (pharmacological, laser, and/or surgical).

However, sometimes, it might be considered a naïve patient when he/she has received non-macula involved laser photocoagulation. In other words, would be a naïve patient for either intravitreal therapy with anti-VEGF and/or steroids or grid macular laser.

Have Patients Treated with Anti-VEGF a Different Profile Than Those Treated with Sustained Released Corticosteroid Devices?

The panel agreed that there are not different types of naïve patients, but rather different kinds of patients. Having said that, it is important to take into consideration that there are different profiles of naïve patients according to their disease evolution; metabolic control; retinal thickness, and/or visual acuity. Therefore, the therapeutic response will critically depend on the clinical and demographic patient characteristics.[6–11]

What is a Refractory Patient?

A DME refractory patient may be defined as the one who did not achieve a complete resolution of the disease, regardless of the treatment administered.[52–56]

Nevertheless, since anti-VEGF agents are broadly used as first-line therapy, the panel focused on the definition of DME patient's refractory to anti-VEGF or DME patients who do not adequately respond to anti-VEGF therapy.

- Patient refractory to anti-VEGF: A patient that after loading dose (three consecutive monthly injections), shows no improvement in visual acuity (>5 ETDRS letters) and a ≤10% reduction of the central foveal thickness measured by optical coherence tomography (OCT).[56] In a strict manner, the anatomical non-improvement could be defined as a thickness reduction <20% of CST.

Although we have defined a patient refractory to anti-VEGF as a patient that after three consecutive monthly injections of anti-VEGF showed no functional and anatomic improvement, according to data from Protocol T it seemed that maintaining anti-VEGF treatment for 24 weeks might have positive outcomes on DME resolution.[56] Therefore, extending the loading dose to five injections of intravitreal anti-VEGF, particularly with aflibercept, may be recommended.

What is a Chronic DME Patient?

To establish the definition of chronic DME is anything but easy.

We agreed to define chronic DME according to Bressler et al[56] as

- Those eyes who did not achieve a CST < 250 μm and/or >10% reduction on at least two consecutive visits subsequent to the last follow-up visit.

Do the Different Patients' Profiles Require Different Therapeutic Goals?

The panel members fully agreed that, in order to obtain the best results, it is necessary to individualize the therapeutic objectives according to the patient profile.

How Can We Define a Refractory ME? Does It Depend on the Patient Profile?

According to the Diabetic Retinopathy Clinical Research Network (DRCR.net)[56] and panel opinion, a refractory ME can be defined as:

- A VA improvement (≤5 letters ETDRS) and a ≤10% reduction in CST (measured by OCT) . The anatomical non-improvement could be also defined as a thickness reduction <20% of CST.

Baseline patient profile may impact on treatment success: The better baseline characteristics (profile) the better treatment response. Better baseline conditions include good VA; younger age; absence of vitreous retinal alterations, like epiretinal membranes; status of the outer retina, and grade of diabetic retinopathy.[57]

How Can We Define Lack of Treatment Response?

According to the panel members, after administration of three anti-VEGF intravitreal injections, a non-response to an intravitreal treatment would be defined as:

- Persistence or worsening of DME.
- Non-improvement in functional or anatomic outcomes.

Definition of Predictive and Prognostic Factor

Although the terms "predictive" and "prognostic" factors have been commonly used in many studies, they are seldom defined and are often used interchangeably.[58]

About this subject, the definitions that reached a greater agreement among the panel members were:

- Prognostic factor: A characteristic that gives some information about the evolution of the patient. It can be helpful to guide the therapeutic approach. These factors are related to the evolution of the disease, and they are associated to the functional response that can be expected for the patient independently of the treatment administered.
- Predictive factor: A characteristic of the patient (clinical, diagnostic, genetic, etc.) that gives some information about the response (anatomical and/or functional) he/she will have to specific treatment. Predictive factors could be related to the probability of response to treatment.

OCT Biomarkers

Different OCT biomarkers, such as disorganization of the retinal inner layers (DRIL), hyperreflective dots (HRD), and epiretinal membranes may help clinicians to predict the effect of intravitreal therapy and may assist the choice of the pharmacological agent in the future.[59]

Which Parameters Should Be Evaluated at Baseline in a DME Patient?

OCT parameters that are important to analyze at baseline visit

- CMT.
- Cysts (number, localization, and size).
- HRD (number and localization).
- Inner and outer retinal layers.
- Outer nuclear layer.
- Serous retinal detachment (SRD).
- Vitreo-retinal interface.

Serous Retinal Detachment (SRD)

Based on OCT examinations, it is possible to define three different morphologic subtypes of DME, namely sponge-like diffuse retinal thickening (DRT), cystoid macular edema (CME), and serous retinal detachment (SRD)[60,61] (Figure 1).

It has been proposed an association between inflammation and the presence of SRD.[62–64] Panel members agree with it. However, they consider that it is not clear whether the higher concentration of intravitreal cytokines is the cause or the consequence of SRD. Some papers propose a relationship between systemic diseases, such as chronic kidney disease, or glycemic control and SRD.[65,66] Panel members do not consider SRD as a prognostic factor itself. However, long-term edemas usually present higher concentration of inflammatory cytokines and SRD is more frequent in this type of edemas. Therefore, SRD might be correlated with chronicity and worse type of edema.

Regarding the question of whether SRD is a predictive factor of response to intravitreal treatment, currently available scientific evidence provides conflicting results. While some studies have reported that the presence of SRD was associated with better functional and/or anatomic results to anti-VEGF treatments,[39,67,68] others have reported no better responsiveness with the same treatments.[69–71]

In addition, there is evidence suggesting that dexamethasone intravitreal (DEX) implants might provide better functional and/or anatomic outcomes in eyes with SRD.[38,40,72] In this sense, panel members recommend to use DEX implants rather than anti-VEGF for treating DME with SRD, especially the chronic ones. However, other factors, such as lens status, responsiveness to steroids (elevation of intraocular pressure), and glaucoma should be taken into consideration.

Cystoid Macular Edema

Cyst formation begins with intercellular fluid accumulation, although it is not clear if the cystoid spaces are intracellular or extracellular to the Müller cells.[60,61,73,74]

According to evidence and panel opinion, the presence of cysts is a marker of disease activity, chronicity of DME, and/or structural damage.[56,75,76]

Panel members agreed that, up to now, there is not enough scientific evidence to support the use of a specific treatment based on the number, size, or location of the cysts.

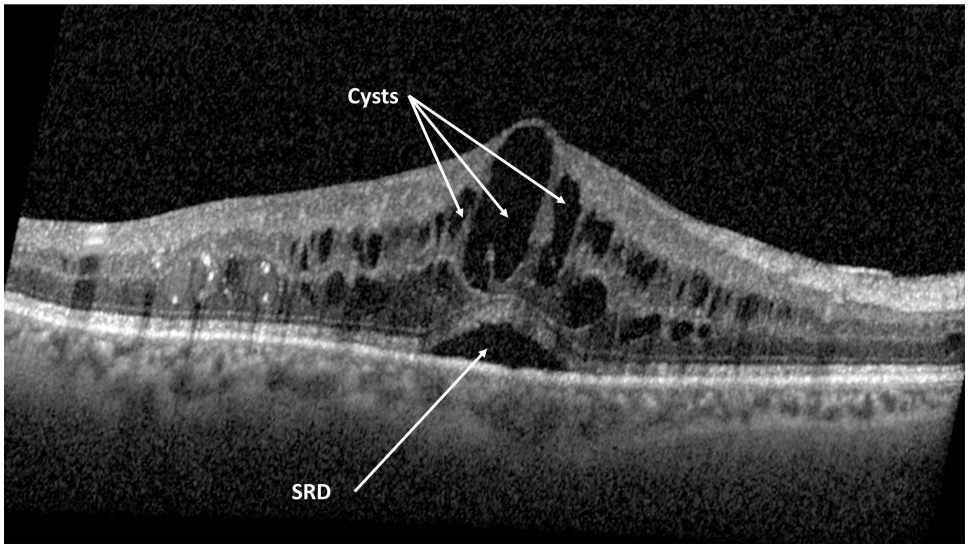

Figure 1 Spectral domain optical coherence tomography image of an eye with cystoid macular edema (CME) and serous retinal detachment (SRD).

Additionally, they all agreed that large empty cysts are usually related to more advanced stages of the disease and may be a sign of chronicity. Therefore, DEX implants might be an option as first-line therapy.

Hyperreflective Dots (HRD)

The presence of HRD as image biomarkers has been suggested in DME.[77] The role of the HRDs in predicting clinical outcomes in patients undergoing treatment for macular edema has shown controversial results. While some studies have shown that the presence of HRDs was associated with poorer visual outcome in patients with macular edema,[78,79] one study reported that a higher number of HRDs at baseline was associated with an adequate treatment response.[80]

Although the etiology of HRDs has not been fully elucidated, retinal inflammation seemed to be involved.[81] Panel members agreed with it and based on this assumption, DEX implant would be the treatment of choice.

However, they seem to be a marker of bad prognosis; therefore, the functional response might be limited.

Disorganization of the Retinal Inner Layers (DRIL) and Outer Retinal Layer (ORL)

DRIL

Disorganization of the retinal inner layers (DRIL) has been identified as a prognostic factor in DME patients.[82,83] In fact, there seems to be an association between DRIL resolution and best corrected VA (BCVA) improvement.[82–84]

Although the panel strongly recommended to assess the presence of DRIL at baseline, they are aware that it is not always easy to evaluate, that is why it is recommended to evaluate DRIL at follow up visits (Figure 2A).

Additionally, DRIL used to be associated with damage on other retinal layers like ellipsoid zone (EZ) and external limiting membrane (ELM).[83] Since the presence of DRIL indicates chronicity, panel members agree that treatment should be switched early if patient do not respond properly.

Recent scientific evidence has suggested that DEX implant may effectively ameliorate DRIL.[85]

Outer retinal layer (ORL)

ORL is the distance between ELM and retinal pigmented epithelium (RPE), which is the length of both inner and outer segment of the photoreceptor layer (Figure 2B and C). The main reason for delayed or incomplete visual recovery seems to be related to ultrastructural changes of the outer retinal layers.[86–89] Although DME may be treated effectively in many eyes, outer retinal structures may remain irreversibly damaged in some patients.[88]

ELM integrity was associated with a final BCVA improvement in DME patients.[88,89] This may suggest a significant relationship between ELM integrity and photoreceptor cell bodies' status, which may be a sign of advanced photoreceptor damage.[88,89] Moreover, ORL thickness correlates better with vision than the total retinal thickness.[90–92]

Additionally, in eyes with DME refractory to anti-VEGF therapy who received treatment with DEX implant, ORL disruptions might predict smaller VA gains if evaluated after an initial reduction of DME that DEX implant may effectively recover morphology of ORL in DME patients.[93,94]

Intercellular adhesion molecule-1 (ICAM-1) is an immunoglobulin that has been implicated in the development of leukostasis, a relevant feature of DR.[95] In fact, it has been suggested that both increased levels of VEGF and ICAM-1 are involved in DR development and are responsible of the ELM and of the inner segment and outer segment (IS/OS) junction disruption.[95]

Moreover, in patients with DME, intravitreal bevacizumab has been associated with a restoration of the ELM, which was followed by a restoration of the EZ.[96]

In patients with uveitic cystoid macular edema, DEX implant was able to reverse ORL alterations.[97] These findings were also observed in patients with macular edema associated with branch retinal vein occlusion.[98]

There is an increasing evidence suggesting that DEX implant may effectively recover the morphology of ORL in DME patients, which might be associated with better functional outcomes.[93,94,99,100]

Panel recommendation:

- ORL disruptions have a stronger prognostic value than DRIL in eyes with DME.
- Since ORL plays an important role as prognostic factor, it needs to be assessed at baseline. Despite the advances in OCT technology, in patients with "big DME", it could be difficult to properly evaluate all the layers, so it would be necessary to reassess at follow-up visit. If ORL does not improve at all after one DEX implant, panel members agree that functional prognosis is very poor.
- Despite the promising results obtained with DEX implants, more evidence would be needed determining the best treatment option in DME eyes with

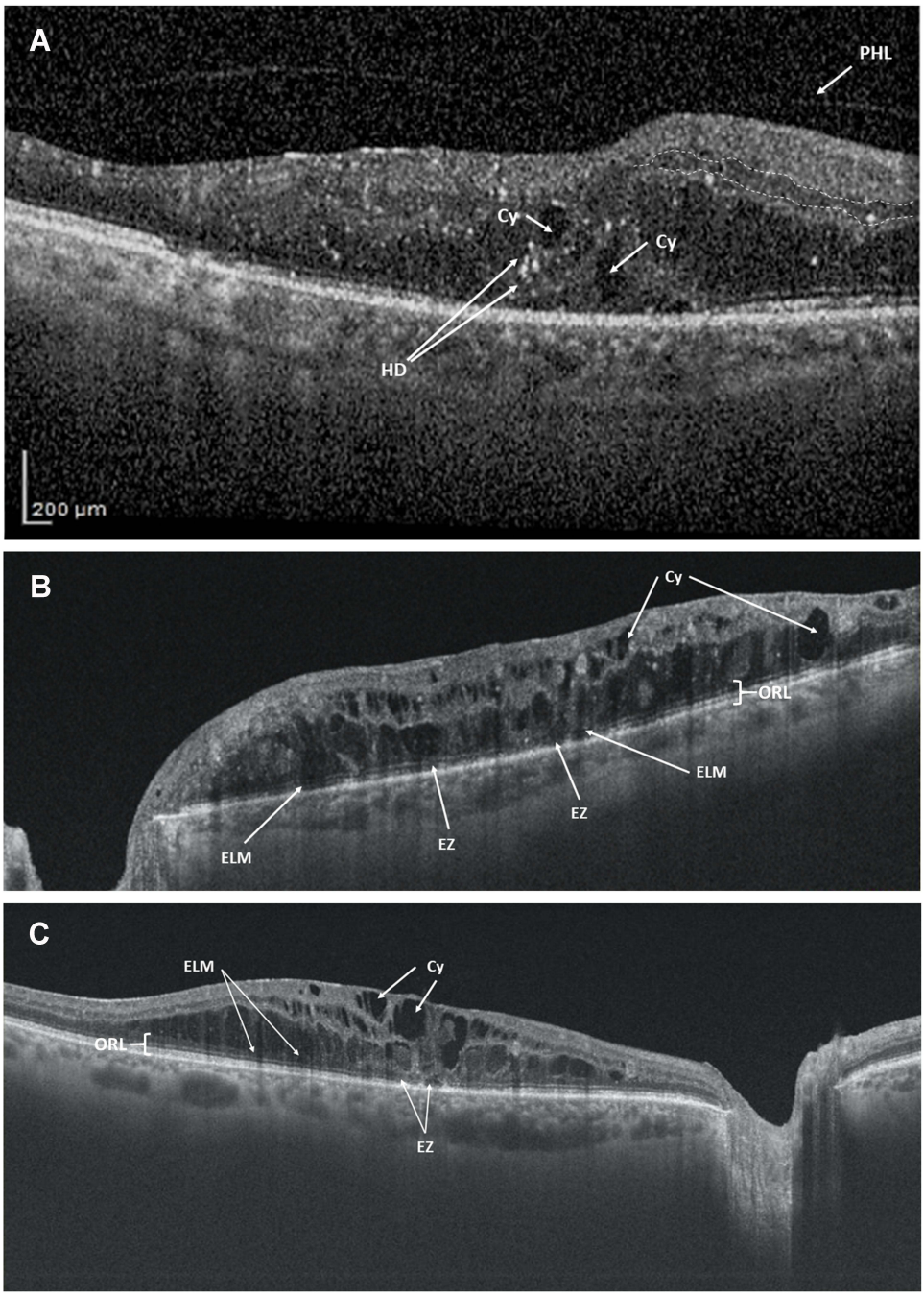

Figure 2 Spectral domain optical coherence tomography images. (**A**) Disorganization of the retinal inner layers (DRIL). It is not easy to identify the boundaries of the inner layers (white dotted line). Additionally, it is possible to see cysts (Cy) and hyperreflective dots (HD) in the outer layers, as well as the posterior hyaloid (PHL). (**B**) Spongiform edema with damage in the outer (ORL) and inner (INL) retinal layers. Besides the presence of cysts (Cy), it is possible to identify the external limiting membrane (ELM), and ellipsoid zone (EZ) disruptions. (**C**) Cystoid macular edema with external limiting membrane disruptions (ELMD). Additionally, it is possible to see some damage in the ellipsoid zone (EZ) and some cysts (Cy).
Abbreviation: ORL, outer retinal layers.

DRIL/ORL. Nevertheless, it should be taken into consideration that DEX implant provides a rapid anatomic response, which might facilitate an adequate assessment of ORL status.

Outer Nuclear Layer

The outer nuclear layer (ONL) contains the rod and cone cell bodies. ONL thickness is increased in diabetic patients.[101,102] ONL damage is a marker of bad visual

prognosis in DME patients and therefore the functional response is usually limited.[89,103,104]

It has been suggested that DEX implant may recover morphology of ONL in DME patients, which was associated with better functional outcomes.[104] However, further research is needed to confirm this finding.

Panel recommendation:

- Since functional response is usually limited in DME with ONL damage, intravitreal anti-VEGF injections or DEX implant could be indistinctly used as first-choice therapy. ONL alterations may be considered as a sign of bad prognosis. There is evidence suggesting that DEX implant might recover ONL damage, which, therefore, was associated with better functional outcomes.[104] However, further research is needed to confirm this finding.

Central Macular Thickness

Although CMT reduction, measured with OCT, is a very useful marker and is commonly used for monitoring treatment response in eyes with DME, there is not enough scientific evidence to support the relationship between CMT and chronicity or CMT and inflammation in DME.[6–15,40,41]

Panel recommendation:

- CMT has to be assessed at baseline. DEX implant may be a first choice in eyes with diffuse DME, since they may be associated with a greater inflammatory component.[105] Additionally, there is evidence suggesting a significant association between macular thickness and the concentration of inflammatory marker ICAM-1.[106] However, other factors need to be considered to decide the best treatment option.

Table 1 summarizes the main findings and comments of the panel regarding biomarkers.

Table 1 Overview of the Role of the Different Biomarkers Comments are based on the expert panel members experience as well as currently available scientific evidence [see references[60–106]]

	Inflammatory Marker	Prognosis*	Chronicity Marker	Predictor of Response to DEX	Candidate for First-Line Treatment with DEX
SRD	Yes	Good/bad prognosis (depends on time course and other biomarkers)	No	Yes	Yes
CYSTS	No (cysts with Hyperreflective material inside, have a greater inflammatory component)	Good/bad prognosis (depends on number, size, location and chronicity. Dense content is a sign of better prognosis)	Yes (if big cysts are present)	Yes (intraretinal inflammatory cysts)	Yes
HRD	Yes	Bad prognosis	Yes (in general terms)	Yes	Yes
DRIL	No	Bad prognosis	Yes	No	No
ORL	No	Bad prognosis	Yes	No	No
ONL	No	Bad prognosis	Yes	No	No (DEX and anti-VEFG indistinctively)
CMT^{+}	No	Bad prognosis	No	No (an exception in patients with SRD)	Yes (in cases with high TMV)

Notes: *Its presence is a sign of … + big volume.

Abbreviations: DEX, dexamethasone intravitreal implant; SRD, serous retinal detachment; HRD, hyperreflective dots; DRIL, disorganization of the retinal inner layers; ORL, outer retinal layer; ONL, outer nuclear layer; CMT, central macular thickness; anti-VEGF, vascular endothelial growth factor inhibitors; TMV, total macular volume.

Conclusions

As therapeutic objectives, the panel recommended in patients with good baseline VA to maintain it and improve it if possible, taking into account the ceiling effect, and in patients with low baseline VA to improve it as much as possible except in patients with severe retinal damage that could limit the functional improvement; in those cases, maintenance of vision should be the main objective. From a daily practice perspective, the panel recommended, as main therapeutic objective to achieve the best anatomic response as fast as possible, and at that point we have to check the maximum functional response the patient can get.

According to the panel, DME treatment should start at soon as possible, according to the Retina Unit capability.

According to the panel, after administration of three anti-VEGF intravitreal injections, no response to an intravitreal treatment would be defined as:

Persistence or worsening of DME and/or non-improvement in functional or anatomic outcomes.

Different biomarkers, including SRD, DRIL, cysts, HRD, ORL and ONL alterations, and CMT have been identified as prognostic and predictive factors in patients with DME. The panel recommended to assess these biomarkers and take them into consideration when selecting the therapeutic strategy.

As a limitation of the current consensus, it should be mentioned the lack of discussion about costs-effectiveness of the different treatment options or social impact of both disease impairment and treatment. It is well known that both DME and diabetic retinopathy have a significant economic impact due to their direct and indirect costs, including reduction in income or an increased need for social support as vision worsens.[107] Data about economic burden of DME in Spain suggested that the estimated direct annual cost per patient with DME was €6271 (excluding drug costs),[108] while the estimated annual cost of treatment with anti-VEGF was €7154.[106,109]

This consensus has highlighted different aspects related to the management of DME patients in daily clinical practice.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, agreed to the submitted journal, and agreed to be accountable for all aspects of the work.

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