GUIDELINES OF CLINICAL PRACTICE OF THE SERV: MANAGEMENT OF OCULAR COMPLICATIONS OF DIABETES. DIABETIC RETINOPATHY AND MACULAR OEDEMA

GUÍAS DE PRÁCTICA CLÍNICA DE LA SERV: MANEJO DE LAS COMPLICACIONES OCULARES DE LA DIABETES. RETINOPATÍA DIABÉTICA Y EDEMA MACULAR

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ABSTRACT

Objective: Diabetes mellitus is considered the most common cause of blindness in the working population of industrialized countries, with diabetic macular edema being the most common cause of decreased visual acuity and proliferative diabetic retinopathy (PDR) being responsible for the most severe visual deficits. We have therefore tried to establish a guide for clinical intervention whose purpose is to provide orientation on the treatment of diabetic retinopathy and its complications. This is necessary at

RESUMEN

Objetivo: La diabetes mellitus está considerada como la causa más frecuente de ceguera en la población activa en los países industrializados, siendo el edema macular diabético la causa más frecuente de disminución de la agudeza visual y la retinopatía diabética proliferante la responsable de los déficit visuales más severos. Por ello hemos intentado establecer una guía de actuación clínica cuyo propósito es proporcionar unas directrices que sirvan de orientación para el tratamiento de la reti-
1. OBJECTIVES

The purpose of this guide for managing the ocular complications of diabetes is to present general guidelines for treating diabetic retinopathy (DR) and/or macular edema (ME) at a time when we are witnessing the emergence of new therapeutic alternatives which as yet do not have well-defined roles.

To establish the differences we have carried out a large revision of literature and existing protocols. The task was entrusted to a committee set up for that purpose by the Spanish Retina and Vitreous Society, which has discussed the therapeutic options available at present and their most accepted indications according to the degree of DR exhibited by patients. Discussions focused on procedures to be applied with a slight or moderate non-proliferative DR (both controlled by the area ophthalmologist) or a severe DR (susceptible to photocoagulation on some occasions) or a proliferative DR (requiring hospital control). In addition, the committee suggested how to proceed with diabetic macular edema and discussed the role of various supplementary explorations.

The adaptation of these guidelines to different health systems could involve variations in some procedures. For instance, the autonomous communities of Spain where Specialized Care Centers are equipped with laser devices, the treatment of diabetic retinopathy and macular edema can be executed, referring only surgical cases to hospitals. In communities where said Centers do not have laser, the entire treatment must necessarily be done at hospitals.

2. INTRODUCTION

Diabetes Mellitus is regarded as the most frequent cause of blindness in the active population of
industrialized countries, while diabetic macular edema is the most frequent cause of visual acuity reduction in diabetics and proliferative diabetic retinopathy accounts for the most severe visual deficits (1).

Laser has been and continues to be the main treatment for the ocular complications brought about by diabetes.

Panretinophotocoagulation (PPC) avoids the progression towards blindness in a significant percentage of patients. However, the results of laser are much more disappointing in macular edema, where the progression is only diminished in 50% of patients.

The search for new alternatives has become a priority objective and even though the pathogenic mechanisms involved in the development of this process are not yet well known, the involvement of the endothelial vascular growth factor has opened a new line of research. A considerable number of publications discuss the usefulness of intra-vitreous triamcinolone and anti-angiogenics (anti-VEGF) for controlling diabetic macular edema, and at present several clinical trials are ongoing in Europe and the United States to assess the safety and efficacy thereof. Anti-VEGF drugs are repeatedly administered through the intravitreal pathway which, in a chronic diseases such as diabetes, involves an important difficulty. For this reason, research has a role to assessing the possibility of utilizing said drugs in combination with laser treatment to achieve a longer effect.

In this situation of change and uncertainty, it is necessary to establish a standard criteria to approach said complications while we await the conclusion of these studies which will allow us to design the new guidelines to improve the function of visual prognosis of these patients.

3. CLASSIFICATION OF DIABETIC RETINOPATHY (DR) AND MACULAR EDEMA (DME)

In accordance with the results of the large multi-centre studies, the prevention of blindness induced by DR involves regular ocular fundus assessments in order to treat in a timely manner the DR forms with the highest risk of severe vision loss or even blindness. This requires the application of standard criteria for classification and treatment of diabetic retinopathy. The classification proposed by the Early Treatment Diabetic Retinopathy Study (ETDRS) (2) pursued this goal and is considered as a reference to be followed in clinical trials. However, it is not routinely applied in clinical practice due to its complexity and the large amount of levels or stages and also because there must be a correlation with the stereoscopic photographs of the seven Basic fields.

In an attempt to achieve a universal means of communication, a group of experts (Global Diabetic Retinopathy Project Group –GDRPG–) (3) proposed in 2002 a new classification for diabetic retinopathy for improved management. This is the International Retinopathy Severity Scale which this group believes should be utilized in clinical practice. This new classification is based on the ETDRS results and therefore is based on scientific evidence. It does not aim to replace the original classification but to provide a simple management basis adequate for clinical practice.

3.1. International Clinical Classification of DR (GDRPG) (table I)

However, for approaching macular edema the classification proposed by ETDRS seems more adequate.

<table>
<thead>
<tr>
<th>Table I. DR classification by GDRPG</th>
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<tbody>
<tr>
<td>Without apparent DR</td>
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<tr>
<td>Slight nonproliferative DR (NPDR)</td>
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<tr>
<td>Moderate NPDR</td>
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<tr>
<td>Severe NPDR</td>
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<td>Very severe NPDR</td>
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<tr>
<td>PDR</td>
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<tr>
<td>Absence of microaneurysms (uA)</td>
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<tr>
<td>μA associated to less than 20 intra-retina hemorrhages (H) in each of the four quadrants (C), hard exudates (HE), cotton-like «exudates» (CE), venous circinate formations in only 1 C (fig. 9)</td>
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<tr>
<td>μA together with one of the following findings:</td>
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<td>– severe intraretinal hemorrhage (&gt;20) in each one of the four C</td>
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<tr>
<td>– Venous circinate formations in ≥ 2C</td>
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<tr>
<td>– intraretinal microvascular anomalies (IMA) in ≥ 1 C (fig. 11)</td>
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<tr>
<td>uA together with at least two of the previous findings</td>
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<td>Neovessels (NV) and/or pre-retinal or hemovitreous hemorrhage (fig. 12)</td>
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3.2. Classification of Macular Edema (ETDRS) (1985)

- Without macular edema.
- With macular edema (ME): retinal thickening within one disc diameter (DD) from the centre of the macula, determined in the stereoscopic exploration with a slit lamp or color stereoscopic photographs (30°) (ME is not the fluorescein diffusion in fluorescein angiography if there is no thickening). The ETDRS also defined ME with the presence of hard exudates within one DD from the centre.
- With Clinically Significant Macular Edema (CSME):
  - Retinal thickening within 500 µm from the centre (fig. 1).

Fig. 1: Retinal thickening within 500 µm from the centre.

Fig. 2: Hard exudates within 500 µm from the centre associated to an adjacent retinal thickening.

Fig. 3: Retinal thickening of at least 1 DD, part of which is less than 1 DD from the centre.

Fig. 4: Focal CSME.
• Hard exudates within 500 µm from the centre when associated to an adjacent retinal thickening (fig. 2).
• A retinal thickening area having the size of at least one disc area, part of which is at less than 1 DD from the centre (fig. 3).

The best corrected visual acuity (BCVA) is not part of the macular edema definition and it can range between 1.2 to perception of light (PL), both included, and exhibit CSME.

3.3. Angiographic Classification of ME

– Focal ME: a well defined diffusion area arising out of individual or associated microaneurysms. The focal ME definition also includes diffusion areas in which ≥ 67% is associated to microaneurysms (4,5). The characteristic funduscopic image is that of a circinate ring which threatens or compromises the centre of the macula (fig. 4).
– Multifocal ME: with several diffusion areas (frequently confused with diffuse ME) (fig. 5).
– Diffuse ME: defined as an area of hyperfluorescence with late diffusion ≥ 2 DD involving the fovea (6-11) or a hyperfluorescence in which ≤ 33% is associated to microaneurysms (3). Diffuse ME is usually bilateral and asymmetric. Clinically, it is a poorly defined edema area, with few microaneurysms and hard exudates. On some occasions, reflections and opacity of posterior hyaloids appear, with or without epiretinal membranes. It is frequently associated to cystic macular edema (CME) (fig. 6).
– Combined ME: both focal and diffuse edemas can coexist, giving rise to the combined macular edema.

3.4. Classification based on Optic Coherence Tomography (OCT)

The classification of ME based on OCT (12) is divided in:

Fig. 5: Multifocal CSME before and after laser treatment.

Fig. 6: Diffuse CSME.
1. **Morphology-based** (fig. 7a):

- **E1:** simple thickening (sponge-like, affecting the outermost layers of the retina and without observing cystoid spaces).

- **E2:** cystoid thickening. Retina thickening associated to cysts, ranging in severity from «a» (between two and four small cysts) to «c» (coalescence of several cysts).

2. **Based on the existence of epiretinal traction** (fig. 7b).

   - **T0:** absence of hyper-reflecting line.
   - **T1:** Presence of continuous hyper-reflecting line adhered to the retina but without distorting it.
   - **T2:** The continuous hyper-reflecting line has multiple points of union with the retina, causing its distortion.
   - **T3:** anteroposterior traction with the typical «gull wing» configuration.

3. **DIABETIC RETINOPATHY MANAGEMENT**

**Establishment of the first ophthalmic exploration**

- **Diabetes type 1:** the first ophthalmological assessment must be made within 3-5 years after the DM diagnosis. If any sign of retinopathy appears, it is advisable to maintain ocular control in hospitals due to the high degree of complications and their aggressive nature.

- **Diabetes type 2:** the first assessment must be made at the time of diagnosis, with annual or biannual assessments being advisable if there are no associated risk factors up to the appearance of some degree of retinopathy. When the latter is detected, the advisable criteria are based on the degree of involvement, the presence of edema and/or of complications secondary to advanced retinopathy. Special attention must be paid to diabetes Type 2 patients of early appearance, more specifically between 30 and 50 years of age, due to the higher life expectation and usually inadequate metabolic control, as well as those in treatment with insulin because they could behave as type 1 diabetics in what concerns complications (13).

**Follow up**

To establish the frequency of subsequent checkups we must take into account the degree of reti-
nopathy as well as the condition of the macula. As regards the periodicity of the assessments, the highest visual risk criterion must be followed. For example, if a patient with a slight NPDR with annual recommended assessment also exhibits CSME, the frequency of the visits will be determined by the latter condition (every three months).

In all DR stages, it is essential to maintain endocrinological control, mainly of glycemia, glycated hemoglobin, microalbuminuria in urine, high arterial blood pressure, overweight, lipids, condition of the heart and kidneys. This has a twofold consequence: On the one hand, if the patient has an important metabolic imbalance, the ocular control must be more frequent, and on the other hand we can postpone ocular treatments (for example, a macular edema) until the patient reaches acceptable levels of glycemia and/or blood pressure. In addition, the patient must be advised to quit smoking.

4.1. Without apparent Diabetic Retinopathy

Six-monthly ophthalmological assessment if the patient has good metabolic control (Hb A1c < 7%) and absence of associated risk factors (high blood pressure, dyslipemia, etc.). In these cases, an ophthalmological exploration twice a year (14) seems sufficient for a timely detection of macular edema as well as PDR. This would reduce 25% the number of first visits to the ophthalmological practice and thus allow a considerable saving in health costs as well as avoiding unnecessary explorations for the diabetic patient.

The ophthalmological explorations should be carried out annually in the presence of associated risk factors or doubtful or deficient metabolic control.

4.2. With Slight NPDR

Annual ophthalmological checkup.

Bring the check-up forward if µA appear in large amounts or threaten the fovea, first exploration of a poorly controlled patient, recent step from oral anti-diabetics to insulin, pregnant patients (quarterly explorations and every six months the first year after labor).

In this stage it is crucial to inform the patient and make him aware about the importance of metabolic control. According to the DCCT (Diabetes Control and Complications Trial) (15-18) in type 1 diabetics who maintain a mean level of 7.2% of Hb A1c the prevalence of retinopathy is reduced 76% and the progression of diabetic retinopathy 54%.

The UKPDS (United Kingdom Prospective Diabetes Study) (19) verified similar findings in type 2 diabetics. In addition, it demonstrated that strict control of blood pressure reduces the progression of DR 34% and the deterioration of visual acuity in 47% (20) (fig. 8).

4.3. With Slight NPDR

Ophthalmological control every six months. Fluorescein angiography and panphotocoagulation (PPC) are not required as the yearly risk of pro-
gression to PDR ranges between 5.4% and 26.3%. It must be taken into account that a large variety of conditions are comprised here, from those that only exhibit μA with hard exudates up to cotton-like «exudates», intraretinal hemorrhage and even venous circinate patterns. Therefore, the precise follow up periodicity remains at the criterion of the ophthalmologist (fig. 9).

4.4. With Severe NPDR

Severe NPDR must be analyzed with caution due to the probability of progression to PDR which is of about 50.2% within one year [14.6% with high risk characteristics (21)].

– DM 2: Hospital control every 3-4 months.
– DM 1 with poor metabolic control: Hospital checkup every 2 months.

Consider early PPC in patients having a high risk of progression; DM 2 with poor metabolic control, patients who do not usually comply with the checkups, PDR in the other eye, patients with cataracts with obvious visual significance which could limit PPC in the near future, prior to cataract surgery, actual or intended pregnancy and generalized angiographic ischemia areas.

In the above cases, the recommended photocoagulation order is to carry out one quadrant in each session, beginning with the nasal or inferior and ending with the temporal (fig. 10). As regards frequency, one session every 2-3 weeks is recommended (if time is not of the essence, 3 weeks is better than two). This is because the macula does not recover in one week (22). Before beginning photocoagulation, we must take into account the different degrees of magnification of the available lenses (table II).

Some papers propose the use of anti-VEGF as a coadjuvant of PPC in an attempt to minimize the post-laser macular edema (23-25).

It is important to emphasize that in severe NPDR cases in which we have decided to perform PPC and which also exhibit clinically significant macular edema, we must treat the edema prior to carrying out the PPC (fig. 11).

4.5. PDR and transparent media

PPC in 1 or 1.5 months: 300-500 impact sessions (if traction exists, the sessions should be of 200-300 impacts) starting with the inferior quadrant. Reassessments every 3-6 months. When PPC is propo-
sed, it is advisable to explain the following points to the patient:

a. scientific evidence demonstrates that PPC can halt the progression of PDR but not in all cases.

b. the risk of hemorrhage persists after PPC because the regression of neovascularization is slow.

c. PPC can produce a moderate reduction of vision, of the visual field or adaptation to darkness, but the benefits considerably exceed the collateral effects.

It is convenient to insist with the patient about these points emphasizing that, if vitreous hemorrhage occurs, it is a consequence of the disease and not of the laser treatment.

If the treatment does not respond (proliferation progresses, bleeding occurs) the PPC level must be reassessed, considering if both the confluence and the extension towards the extreme periphery are adequate. After this verification we have two options: 1. Anti-VEGF (the use of triamcinolone (TAIV) and anti-VEGF in diabetic retinopathy is in the clinical trial stage. Therefore its use in a different context must have the informed consent of the patient, which must warn about the lack of long-term experience and the possible complications. It also must have the authorization of the Medication Agency of Spain (for compassionate use). The application must be submitted to the General Direction of Pharmacy and Health Products of the Health and Consumer Ministry): every 4-6 weeks. 2. Retinovitreous Surgery (CRV) (figs. 12 and 13).

Special Cases

- With extended non active vitreoretinal adhe-
  rences, without traction and without threatening the macular area and good visual acuity: Regular check-
  kups

- With extensive vitreoretinal adherences which
  compromise the macula: CRV with PPC. anti-
  VEGF + CRV can be utilized before the third day ±
  anti-VEGF at the end of the surgery.

- PDR with active traction but without severe hemovitreous: anti-VEGF prior to surgery: 1 or 2
days before to minimize bleeding during the sur-
  gery.

- Tractional diabetic papillopathy: CRV.

- Tractional maculopathy: CRV.

- PDR + rubeosis with medium transparency:
immediate PPC

- PDR + rubeosis + neovascular glaucoma: immediate PPC ± anti-VEGF + valve.

After the intravitreal injection of bevacizumab (IVB) a fast contraction of the neovascular mem-
brane has been described (26) which tractions the root of the iris, producing a permanent synechial
angular closure. This undesirable situation can be prevented avoiding the use of intravitreal anti-
VEGF in eyes exhibiting broad areas of peripheral anterior synechiae. Gonioscopic exploration is
essential because the involvement of the angle can proceed the involvement of the iris and this may go unnoticed in biomicroscopic exploration only. The ablation of an ischemic retina by means of laser
PPC, or cryo-ablation –when laser is not feasible– will achieve the same effect as anti-VEGF but it will be longer lasting.
4.6. PDR with Hemovitreous

If the ocular fundus cannot be explored, ocular echography is required.

Limiting the activity of PDR diabetic patients is not efficient to prevent hemovitreous. If bleeding exists, prescribing rest is not efficient either. Therefore, in both cases, the patient may carry out the activity allowed by the visual limitations.

- If DR is regmatogenous or combined (tractional/regmatogenous): urgent CRV.
- If there are no peripheral anterior synechiae (the presence of peripheral anterior synechiae at the angular level brings into question the use of anti-VEGF because of the severe contraction of the tissue in response to the intravitreous injection may induce acute angular closure and the development of neovascular glaucoma with very negative consequences. Therefore, in the case of patients with PDR where the anti-VEGF therapeutic option is considered, angular gonioscopy is a requirement): anti-VEGF + surgery to resolve the media opacity and treat PDR.
- If recurrence of hemovitreous after CRV
- CRV directly.

The surgery aims at restoring the vision and eliminating products which could stimulate proliferation. If recurring hemovitreous appears, echographic control every 15 days is recommended. We have two options:

- New CRV in 2-4 months. (anti-VEGF pre- or intra-op).
- Anti-VEGF every 4-6 weeks.

If there is improvement, complete PPC/ cryotherapy in extreme periphery. Late bleeding (after the first month).

Late bleeding appears in a significant percentage of cases (13%-50%), and can have different causes, the most frequent being the following.

- Bleeding of the peripheral proliferative tissue present in sclerotomies: the origin of these neovessels is not the anterior retina (as in anterior fibrovascular proliferation) but the ciliary body. This fibrovascular tissue can be extended towards the anterior vitreous because of its proximity. It is associated to incarceration of the vitreous in sclerotomies. The diagnostic can be made by means of scleral depression. Sometimes an epi-scleral sentinel vessel may exist when entering the sclerotomy (although its existence does not ensure the existence of fibroproliferative tissue therein).
The treatment will consist in a new CRV extracting this tissue. Gas can be left as a tampon. Recently the use of anti-VEGF has been proposed in late recurring vitreous hemorrhages (31).

- **Anterior fibrovascular proliferation** (32). In these cases, the hemovitreous occurs between the first and seventh month after retino-vitreous surgery in the form of neovascular proliferation originating in the peripheral retina and extends through the anterior hyaloids to the posterior face of the lens capsule. An exploration with scleral depression and indirect biomicroscopy reveals neovascularization. Rubeosis in the iris appears occasionally. The echography may show thickened tissue strips from the peripheral retina to the ciliary body and the posterior surface of the iris, tractional detachments of the anterior retina and ciliary body (frequently associated to hypotonia). As treatment is discouraging, prevention is more important, mainly in patients at risk such as young people with DM type 1, severe retinal ischemia, tractional and/or combined DR, above all if extra-scleral cerclage has been fitted, multiple surgeries, PDR which has not been treated or does not respond to PPC, PDR with extended fibrovascular posterior proliferation, post-op rubeosis iridis, recurring hemovitreous, etc. In these patients, aggressive PPC must be carried out. If even so they continue to evolve, the indication is CRV with careful removal of the anterior vitreous (for which a lensectomy may be necessary) followed by extensive anterior photocoagulation.

If the anterior fibrovascular proliferation is already present, it must be detected as early as possible before a tractional detachment of the retina and/or ciliary body and the formation of cyclitic membranes occur. CRV must be performed, followed by lensectomy, extracting the posterior lens capsule, dissecting the vitreous base, endodiathermia of neovessels and endophotocoagulation with the broadest possible extension (avoid cryotherapy because it could cause a contraction of the fibrotic tissue and peripheral DR). If peripheral tractional detachment of the retina and/or ciliary body exists, it is frequently necessary to perform peripheral retinotomies and use silicon oil to preserve the ocular globe.

4.9. PDR with retina detachment

*Tractional*, compromising or affecting the macula = CRV with or without the use of TAIV as a manipulator.

*Regmatogenous/combined:* CRV < 48 hr + long duration gas or silicon oil.

4.10. PDR with anterior ischemia

When faced with a condition comprising rubeosis and neovascular glaucoma it is important to study the chamber angle. As stated above, this is essential when considering the use of anti-VEGF.

4.11. PDR with rubeosis

- **Incipient:** complete PPC and check-up at month 2.
- **Evident:** complete PPC, anti-angiogenic therapy, check-up at month 1.

If the iris rubeosis is associated to vitreous hemorrhage which prevents photocoagulation: anti-VEGF followed by CRV (2-3 days after the injection), trying to broaden the PPC to the extreme periphery.

4.12. Neovascular glaucoma (NG)

NG is a type of secondary glaucoma arising from the obstruction of the trabecular mesh by fibrovascular and/or associated synechiae. It usually courses with ocular pain, severe visual acuity reduction, very high intra-ocular pressure, conjunctival hyperemia, corneal edema, tyndall, hyphema, iris rubeosis, choreotopia, uveal ectropion and significant goniosynechiae.

It is likely that in the immediate future we will witness changes in the prognosis of this disease due to the anti-VEGF. Even though the results seem highly encouraging in the short term, at present there are no prospective studies reporting the dosage of choice, secondary effects and long-term safety or the best combination with other therapeutic measures.

In all patients at risk, a complete ocular assessment must be performed, including exploration without miidriasis of the pupillary edge with large increase and gonioscopy.
Neovascular glaucoma treatment has three therapeutic approaches (33-35).

1. Medical treatment

- Topical ocular hypotensors: beta blockers, alpha-adrenergics, carbonic anhydrase inhibitors. Pilocarpine is contraindicated and prostaglandin equivalents are under debate (access to the uveoscleral pathway is blocked by the fibrovascular tissue in the angle and the inflammation increases).
- Systemic ocular hypotensor: osmotic diuretics and IV and oral carbonic anhydrase inhibitors.
- Controlling the inflammatory component (which is always present and is very intense) with miotics (Atropin or Cyclopegic) and topical corticoids (Dexametasone or methyl prednisolone/3 hours). The effect of this measure not only controls the inflammation, it also diminishes pain and intraocular pressure. If necessary, administer sub-conjunctival or subtenon corticoids.

2. Anti-vasoproliferative treatment

PPC is indicated (level A evidence): 1,200-1,600 impacts produce the regression of rubeosis in 70.4% of cases. The PPC destroys the ischemic retina responsible for the synthesis of vasoproliferative factors and also increases the availability of oxygen in the untreated retina. PPC must be performed urgently and always complete up to the extreme periphery. However, the regression of neovessels after PPC is slow (weeks). For this reason, we could consider the use of anti-VEGF as a supplementary measure (36) because it causes a nearly immediate regression of rubeosis (within 24-48 hours). These eyes must be closely followed up because, as mentioned above, the anti-VEGF could cause the contraction of existing fibrovascular tissue, generating an angular closure. In any case, the patient must be requested to maintain close control of glycemia because the Hb A1c number is the most important factor in the recurrence of PDR after PPC.

If the diagnostic was early, the application of the above measure could suffice to resolve the condition.

3. Surgical treatment

Whenever possible, we must try to postpone surgery until the disappearance of rubeosis.

- Trabeculectomy with antimetabolites.
- Valve implant.
- Cyclophotocoagulation (37) with diode laser.

There is no consensus about which of these techniques is more indicated. Filtrating surgery, with or without drainage valve, seems to be the best option if the retina is panphotocoagulated, rubeosis has regressed and there is angular blockage due to the peripheral synechiae. The use of anti-VEGF combined with filtrating surgery could help to diminish vitreous hemorrhage and scarring of filtration ampoule, above all in rubeosis which remain active. Bevacizumab has been used as adjuvant treatment tofiltrating surgery with good results (38,39).

In what concerns cyclo-destructive processes, the choice process is laser diode. Occasionally the effect can be transient but it usually suffices to complete the PPC. The procedure is quite safe in refractory glaucoma cases but neovascular glaucoma seems to have a higher prevalence of post-treatment hypotonia (15%).

Summarizing the above, the treatment guideline for NG we advise is in agreement with the guidelines recently published by the European Glaucoma Society (40) and comprises:

- Stage 1: Atropin eye drops + topical corticoids + antiglaucomatous: all except pilocarpine. Suggested sequence: Brimonidin, betablockers, carbonic anhydrase inhibitors: topical or systemic. PPC: complete it as much as possible. Anti-angiogenic therapy has proved to be useful but its use for this indication is not yet approved.
- Stage 2: without response in IOP. Trabeculectomy with anti-metabolites/valve implants/cycloablation. Phenolization (if eye painful with amaurosis)/evisceration /enucleation.

4. Cataracts

Diabetic patients under 65 have 3 or 4 times greater risk of developing cataracts than the non-diabetic population (in younger groups the risk increases up to 25 times). After age 65, the risk balances out.

Whenever the cataract allows to visualize the ocular fundus and laser treat the progression of retinopathy, the attitude should be of expectation. When said limits are overcome, phakoemulsification is indicated.

After surgery, the patient must be photocoagulated if applicable and placed in follow up for six
months in case the surgical trauma induces the retinopathy progression. It must be taken into account that diabetics without ME who submit to cataract surgery an increase of the central macular thickness may appear in the first three months post surgery although some resolve spontaneously (41).

In diabetics with ME, it must be treated before cataract surgery if possible. If the cataract prevents the treatment of ME, we can consider the use of peri-op anti-VEGF/TAIV. At present there are clinical trials assessing its efficiency (42,43).

In summary, in the presence of diabetic retinopathy without macular edema, regular controls must be established after cataract surgery. If ME appears, we must maintain an expectant attitude trying to discard a pseudophakic ME, which usually has a favorable spontaneous evolution. Sometimes, due to the clinic as well as angiographic aspect, it could be very difficult to differentiate between a diabetic ME or an Irvine-Gass syndrome. However, if the edema persists through time, we should treat it according to the scheme proposed in this guide.

Due to the risk of progression of DR, simultaneous cataract surgery in both eyes is not advised, as well as within a short interval.

It is important to emphasize that, just like any patient with macular pathology, in DME it is not advisable to implant multifocal or diffractive intraocular lenses (Graph 1).

### 5. MANAGEMENT OF DIABETIC MACULAR OEDEMA

As pointed out above, we use the EDTRS classification and will consider treatment whenever there is CSME. Similarly, the OCT result will be critical to decide the treatment.

#### 5.1. Assessment prior to the therapeutic action

If in diabetic retinopathy systemic control is paramount, in macular edema it is even more obvious. The approach of this complication should be multidisciplinary. It is necessary to insist in glycemia control (HbA1C), arterial blood pressure, overweight and lipids, referring the patient to the endocrinologist/internist/nephrologist whenever necessary due to the important influence of these risk factors. Deficient metabolic control could justify postponing the macular edema treatment awaiting for improvement. It is desirable that HbA1C numbers should be below 7.5%.

The edema assessment must always include the best corrected visual acuity, biomicroscopic assessment, retinography and OCT. Fluorescein angiography can be considered in some clear cases of circinates where the origin of exudation can be seen. In addition, it is a very useful test to determine the condition of the perifoveal vascular network.

The tractional diabetic macular edema (TDME) is characterized in OCT by a macular thickening with loss of foveal depression and edema of the external retinal layers. In addition, the posterior hyaloid is thick and hyper-reflected, tense and partially detached from the posterior pole but remaining applied to the papilla and the cusp of the elevated macular surface. The tense and thickened posterior hyaloid exerts a vitreomacular tangential traction which induces or exacerbates DME.

In contrast with OCT, biomicroscopy lacks sufficient precision to determine the condition of the posterior hyaloid when it is only slightly detached from the macular surface. For this reason, OCT is more sensitive to identify vitreo-macular adhesion and therefore allows an earlier diagnostic of a partial posterior vitreous detachment. In addition, it allows for a precise assessment of the macular thickness and is highly reproducible.

#### 5.2. Therapeutic options

##### 5.2.1. Focal or multifocal CSME

The treatment of choice for this type of edema continues to be focal photocoagulation. It provides good results in the long-term and is considered to be the reference treatment (figs. 4 and 5).

The treatment will be carried out over the microaneurysms which fugue and are located in the centre of the circinated crowns, between 500 and 3,000 microns from the centre of ZAF, with 50-100 micron spots and sufficient power to achieve a soft whitening thereof.

For the edemas which are generally of the combined type and not purely focal in which the central macular thickening makes laser therapy difficult (usually corresponding to OCT values above 400µ) (44) we could consider anti-angiogenic therapy or
Endocrinological control: it is particularly important to control glycemia (HbA1c<7%), HTA (<130/80), lipids (TG<150 mg/dl), LDL cholesterol <100 mg/dl except in high cardiovascular risk patients which should have <70 mg/dl. Heart and kidney condition. Avoid overweight. Physical exercise.

A patient who does not fulfill these values must be referred to endocrinologist/internist/general practitioner.

1. **Without apparent DR**
   Annual or bi-annual ophthalmological control.

2. **Slight NPDR**
   Annual ophthalmological checkup.
   Consider early PPC in case of: DM 2 with poor metabolic control and patients who do not usually comply with the checkups, PDR in the other eye, patients with cataracts with obvious visual significance which could limit PPC in the near future, prior to cataract surgery, actual or intended pregnancy and generalized angiographic ischemia areas.

3. **Moderate NPDR**
   Ophthalmological control every six months.

4. **Severe NPDR (1)**
   Check-up every 2-4 months.
   Consider early PPC in case of: DM 2 with poor metabolic control and patients who do not usually comply with the checkups, PDR in the other eye, patients with cataracts with obvious visual significance which could limit PPC in the near future, prior to cataract surgery, actual or intended pregnancy and generalized angiographic ischemia areas.

5. **PDR and transparent media**
   PPC in 1 or 1.5 months: 300-500 impact sessions (if traction exists, the sessions should be of 200-300 impacts). Check-ups every 3-6 months.
   Photocoagulation order as per the graph. Frequency: every 2-3 weeks (if possible, 3 weeks is better). The macula does not recover in 1 week.

   - If lack of response: Options:
     1. Anti-VEGF every 4-6 weeks
     2. If lack of response: CRV

6. **PDR with Hemovitreous**
   - If DR is regmatogenous or combined (tractional/regmatogenous): urgent CRV.
   - If no DR: wait two months with VA/echography controls every 2-4 weeks. Defer surgery (2-3 months) if no improvement is shown.

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*Graph 1. Diabetic retinopathy management.*
intravitreous corticoid therapy followed by laser (45-49). This subject is discussed in greater detail in the diffuse CSME section.

If a vitreo-macular traction with functional repercussion is evidenced, we would proceed to CRV (50-52) (figs. 7a and 7b) with or without this section of the internal limiting membrane (ILM) (53-55) and/or TAIV/anti-VEGF (44-48). If the patient exhibits a stable improvement, we can refer him to the ophthalmologist for control.

<table>
<thead>
<tr>
<th>Levels of Evidence</th>
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<tbody>
<tr>
<td>Grade A Evidence: high quality</td>
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<tr>
<td>Grade B Evidence: moderate quality</td>
</tr>
<tr>
<td>Grade C Evidence: low quality</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Degrees of recommendation</th>
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</thead>
<tbody>
<tr>
<td>1 Strong recommendation as benefits clearly outweigh risks</td>
</tr>
<tr>
<td>2 Suggested treatments where risks and benefits are more balanced or are uncertain</td>
</tr>
</tbody>
</table>

Special Cases

With extensive vitreoretinal adherences: CRV with PFC, prior anti-VEGF + CRV can be utilized after the third day ± anti-VEGF.

Tractional diabetic papillopathy: CRV

Tractional maculopathy: CRV

Iridian rubeosis: extensive PFC ± anti-VEGF

Anti-VEGF (⁎) in case of persistent or very severe hemorrhage.

To be injected at 4-week intervals with close follow-up due to DRT. If no improvement, CRV after anti-VEGF, not after the third day.

7. PDR with Premacular-Retrohyaloid hemorrhage

CRV before one month.

8. PDR with recurring hemovitreous after CRV

Immediate bleeding: echographic controls. If not spontaneously reabsorbed:

Retinovitreous surgery within 2-4 months.

Pre-op anti-VEGF.

Anti-angiogenic option: anti-VEGF every 4-6 weeks. Echographic control every 15 days.

If improvement is shown: complete PPC/ cryotherapy in extreme periphery.

Late bleeding:

CRV + cryotherapy in sclerotomies + anti-VEGF + elective gas.

Anti-angiogenic option.

9. PDR with retina detachment

Tractional, compromising or affecting the macula: CRV + elective tampon (gas/silicone oil).

Regmatogenous/combined: CRV < 48 hr + silicon oil.

Graph 1 (cont.). Diabetic retinopathy management.
5.2.2. Diffuse CSME

In case of diffuse CSME with vitreoretinal traction, the therapeutic indication is CRV with hyaloidectomy (56-57), with the dissection of ILM being under debate (58-63) as well as the use of TAIV surgery at the end (64, 65) (figs. 6, 14 and 15).

If there is no traction, the most widely used option which forms part of established protocols is the application of modified grid laser. This option utilizes less intense (mild grey) and smaller burns (50µm), treating microaneurysms directly but without trying to change their color. The OCT map is useful for identifying the retinal thickening areas. According to the ETDRS criteria, the treatment must be repeated at 3-4 months if the edema has not been resolved (3 treatments maximum).

The results obtained with said technique are inferior to those of focal macular edema. Only a moderate loss of visual acuity is avoided (equal to or greater than 15 ETDRS letters) in 50% of patients, while 26% continues to lose vision in the long term and only 3% experience a slight improvement of their visual acuity. For these reasons, new therapeutic alternatives are being considered of which we only have preliminary data as they are at present in the clinical research stage.

The pharmacological alternatives proposed for controlling diffuse macular edema include intravitreal triamcinolone and the new anti-VEGF drugs. These therapies aim at reducing the diffusion, selectively carrying out laser therapy in specific areas. Both options require the submission of a compassionate use application to the health Ministry.

The complications described with the use of TAIV (65-68) (glaucoma, DR, cataracts, endophthalmitis, etc) and the legal problems which may be derived from their use leads to an increasing screening of patients. In diffuse CSME with large central macular thickening (fig. 16), its efficiency makes it the most recommendable drug. The most extended option is the use of 4 mg TAIV in non-vitrectomized patients and 8 mg in in a vitrectomized patients (69). In cases where the central macular thickening is not so large, we would suggest the use of anti-VEGF (bevacizumab, ranimizumab, pegaptanib) as their secondary effects appear to be less important. As it has been seen that the effect of TAIV is temporary (70-73), the possibility of beginning treatment with a TAIV injection followed by an anti-VEGF and/or laser therapy has been considered (74-76).

If improvements are not obvious after the above recommended therapy, there are not many therapeutic options available. Only in a few selected cases a CRV can be performed (77,78) because some studies did not find improvements (79,80).

5.2.3. Cystic Macular edema

In the case of a cystic macular edema (CME) with vitreomacular traction, the proposal is to utilize CRV without dissection of MLI when the evolution time is unknown or exceeds 6 months (due to the risk of inducing a macular hole). When under 6 months the MLI dissection can be performed.

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Fig. 14: Macular edema with vitreo-macular traction syndrome.

Fig. 15: The same case after retinal-vitreous surgery.

Fig. 16: OCT E3 of a patient with diffuse CSME and large central macular thickening.
For CME patients who do not exhibit evidence of traction the option is the use of TAIV optionally followed by anti-VEGF and/or modified grid (81,83) (figs. 17-19).

Graph 2: Treatment algorithms for focal and multifocal macular edema.

By way of summary, we would like to emphasize that in the presence of a tractional component with functional repercussion in any type of diabetic macular edema we must assess the CRV indication.
5.2.4. Ischemic macular edema

Ischemic macular edema is defined by clinical signs such as:
- Increase of avascular foveal zone (ZAF) ≥ 1.000 µm.
- Rupture of the perifoveal capillary ring in the ZAF edge.
- Non-perfusion area within a disc diameter from the centre of the fovea.

In DME with ischemic tractional predominance, the possibility of CRV is to be considered. The use of anti-VEGF is initially contraindicated because, even though the edema is reduced, visual acuity worsens due to the increase of ischemia (84).

5.2.5. Massive lipid deposit

In some patients with chronic macular edema, lipid deposits concentrate in the macular area, causing irreversible damage to photoreceptors, and thus rendering any treatment inefficient.
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