ABSTRACT

We present general guidelines to help us with the treatment of diabetic retinopathy (DR) at a time when numerous therapeutic alternatives have been developed although their role has not yet been adequately defined. This protocol is not directed at experienced retinologists but rather at general ophthalmologists who require a practical and up to date guide of a pathology as prevalent as RD.

The different therapeutic options available, and their most accepted indications depending on the degree of diabetic retinopathy that patients have, are reviewed. We propose what to do in cases of mild, moderate and severe non-proliferative diabetic retinopathy as well as in cases of proliferative diabetic retinopathy (panphotocoagulation/antiangiogenic drugs/vitreoretinal surgery). The treatment of diabetic macular edema depending on its angiographic and topographic characteristics is also discussed. The importance of metabolic control of the patient is stressed (tight glycemic control, control of arte-

RESUMEN

Se presentan unas directrices generales con el objetivo de proporcionar una orientación en el manejo de la retinopatía diabética (RD) en un momento en el que han aparecido numerosas alternativas terapéuticas cuyo papel aún no está suficientemente definido. Este protocolo está dirigido no a retinólogos expertos sino a oftalmólogos generales que precisan una guía práctica y actualizada de una patología tan prevalente como la RD.

En este documento se revisan las distintas opciones terapéuticas disponibles y su indicación más aceptada según el grado de retinopatía diabética que presente el paciente. Se plantea así que hacer con una retinopatía diabética no proliferativa (RDNP) leve, moderada (ambas control por su oftalmólogo de zona) y severa (en casos muy seleccionados puede considerarse la realización de una panfotocoagulación –PFC–). Los pacientes con retinopatía diabética proliferativa (RDP) serán tratados en los centros hospitalarios (PFC/fármacos antiangiogénicos/ciru-
rial hypertension and dyslipemia) in aiding the treatment of diabetic retinopathy.

This therapeutic proposal has been discussed widely by retinologists from the four largest hospitals in the Canary Islands, and is therefore an agreed text based on recent scientific literature (Arch Soc Esp Oftalmol 2009; 84: 65-74).

**Key words:** Diabetic retinopathy, Diabetic macular edema, optic coherence tomography, vitrectomy, intravitreal antiangiogenic drugs.

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**MANAGEMENT OF DIABETIC RETINOPATHY**

This protocol suggests action lines for several diabetic cases. It does not seek to set out mandatory criteria or to release ophthalmologists from their responsibility, i.e. from analyzing specific cases and acting based on their own professional judgment. Furthermore, it does not restrict the freedom of ophthalmologists in decision-making related to the treatment of specific patients. Thus, ophthalmologists may opt for different patterns among the conventional techniques required when, based on their experience, the desired results call for different types of therapy. The fact that the present paper does not recommend this treatment pattern (line of action) should under no circumstance be considered as professional malpractice.

Adapting this protocol to each particular healthcare system may require changes in certain aspects. For instance, if no laser devices are available at healthcare centers, the treatment of proliferative diabetic retinopathy and macular edema must necessarily be in-patient. Health communities where healthcare centers are equipped with this type of devices will refer patients mainly to hospital for surgery.

Treatment patterns were based on the following classifications.

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**INTERNATIONAL CLINICAL CLASSIFICATION OF DR (GRDPG)**

- No apparent diabetic retinopathy (DR): Absence of microaneurysms.
- Mild non-proliferative DR (NPDR): Only microaneurysms (fig. 1.)
- Mild NPDR: Microaneurysms associated to less than 20 intraretinal hemorrhages (H) in each of the four quadrants (Q), hard exudates (HE), cotton-wool spots (CS), venous beading (VB) only in one Q (fig. 2.)

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Fig. 1: Mild NPDR.
Severe NPDR: The 4 - 2 – 1 Rule.
- Microaneurysms + severe intraretinal H (>20) in each of the four Q or venous beading in ≥ two Q or intraretinal microvascular anomalies (AMIR) in ≥ one Q (fig. 3.)
- Replacing «or» with «and» would amount to extremely severe NPDR.

PDR: Neovessels (NV) and/or pre-retinal or vitreous hemorrhage (fig. 4.).

CLASSIFICATION OF MACULAR EDEMA (ETRDS) (1985)
- No macular edema.
- Macular edema (ME): retinal thickening within 1 disc diameter (DD) at the center of the macula (in the absence of thickening, fluorescein diffusion during FAG signifies no ME.) Under the ETRDS, the presence of hard exudates within 1 DD is also classified as ME.
- Clinically significant macular edema (CSDME) (figs. 5-7):
  • Retinal thickening at or within 500 µ of the center.
  • Hard exudates at or within 500 µ of the center whenever associated with adjacent retinal thickening.
  • Area of retinal thickening of at least 1 disc area, a part of which is at least 1 DD of the center.
- Bear in mind that visual acuity DOES NOT fall within the definition of macular edema and may range from 1.2 to light perception (LP) inclusive, and be associated with CSDME.

ANGIOGRAPHIC CLASSIFICATION OF ME
- Focal ME: well-defined diffusion areas linked to individual or associated microaneuerysms (fig. 5.)
- Multifocal ME (frequently mistaken with diffuse ME) (fig. 6.)
- Diffuse ME: frequently associated with cystoid macular edema (CME) It has been defined as a retinal thickening ≥ 2 papilla diameters involving some parts of the foveal avascular zone. It tends to be bilateral. Clinically this results in a poorly defined edema area; few microaneurysms and hard exudates; more or less ischemia under angiography (FAG); brightness; opacity of posterior
MANAGEMENT OF DIABETIC RETINOPATHY

Performing the first ophthalmic exploration

- Type 1 Diabetes: first check-up should be performed 3-5 years after diagnosis. If any signs of retinopathy are observed, eye controls are to be carried out at hospitals due to the high risk of complications and the aggressive nature of retinopathy.
- Type 2 Diabetes: first check-up should be performed at the time of diagnosis, carrying out subsequent controls every one to two years until the onset of any degree of retinopathy. Upon detection, the recommended criteria are provided according to the degree of involvement, based on the presence or absence of edema and that of complications secondary to advanced retinopathy.

Subsequent ophthalmic controls

In order to set out the frequency of subsequent check-ups, we should first refer to the different degrees of retinopathy and then to the condition of the macula. As for the frequency of check-ups, the prevailing criterion should be proximity, i.e. in patients suffering from mild NPDR (annual check-ups recommended) in addition to the associated CSDME, the latter shall determine the frequency of visits (for example, every 3 months.)

Endocrinological control at all stages of DR is essential, particularly in the case of: glycemia, arterial hypertension (HTN), overweight, lipids, cardiac and renal condition.

1. No apparent diabetic retinopathy

Ophthalmic control every one to two years.

2. Mild NPDR (fig. 1)

Annual ophthalmic controls.
Perform check-up in advance when: a large amount of microaneurysms may compromise the fovea…; first exploration of poorly checked patients; recent replacement of oral anti-diabetic drugs with insulin; pregnant patients (check-ups should be performed every three months; after delivery, controls should be carried out every 6 months during the first year).

3. Moderate NPDR (fig. 2)

Ophthalmic control every six months.

Does not require FAG.

Does not require pan-photocoagulation (PFC) since the risk of progression to PDR after one year ranges from 1-8%.

4. Severe NPDR (fig. 3)

Severe NPDRs should be considered as high-risk cases due to the probability of progression to PDR being approximately 50.2 percent one year later and to PDR with CAR around 14.6 percent (1.)

DM 2: ophthalmic control every 2-4 months.

DM 1: ophthalmic control every 2-4 months.

Consider early PPC in those patients at greater risk of progression: DM 2 with poor metabolic control and patients who do not undergo check-ups on a regular basis; PDR in the other eye; prior to cataract surgery, pregnancy or desired pregnancy; generalized FAG ischemia.

In such cases, the recommended photocoagulation sequence is one quadrant per session starting with the nasal or lower quadrant and ending with the temporal quadrant (fig. 9.) As for frequency, sessions shall take place every 2-3 weeks (whenever possible, sessions should be delayed 3 weeks) since the macula cannot recover in just one week (2.)

5. PDR and transparent media (fig. 4)

PPC one month or a month and a half later: 300-500 burns per session (whenever traction is present, perform 200-300 burns per session.) Check-ups every 3-6 months.

If unresponsive: options: 1. antiangiogenic drugs (*): every 4-6 weeks. 2. Retinal and vitreous surgery (RVS).

Special cases

– Extended vitreo-retinal adhesions: RVS with PPC – previous antiangiogenic drugs may be used (indication under study*) + RVS before day 3 + Antiangiogenic drugs (indication under study*)–.

– Diabetic tractional papillopathy: RVS.

Fig. 8: Vitreo-macular traction syndrome in OCT.

Fig. 9: Photocoagulation sequence in quadrants.
– Tractional maculopathy: RVS.
– Rubeosis iridis: Extensive PPC.

6. PDR with hemovitreous

Keep in mind that limiting the activity of diabetic patients with PDR is not an effective measure to prevent hemovitreous. In the presence of bleeding, prescribing rest will not prove effective either. Therefore, in both cases, patients may carry on with any activities unhindered by their limited vision.

– Rhegmatogenous or mixed RD: urgent RVS.
– No RD (patients with vitrectomized eyes and hemovitreous: risk of anterior proliferation): Wait 2 months. VA / echographic controls every 15 days.
– Surgery deferral (2-3 months) in the event of no improvement.
  Antiangiogenic drugs (*) in the event of: persistent or extremely severe hemorrhage. Injections will be administered every 4 weeks while closely monitoring the risk of tractional retinal detachment (TRD). In the event of no improvement: RVS after antiangiogenic drugs*: never beyond day 3.

8. PDR with premacular retro-hyaloid hemorrhage

Early RVS, preferably within a month.

9. PDR with recurrent hemovitreous after RVS

Immediate bleeding (3)

Results from dissection of fibrovascular tissue during vitrectomy or dispersion of residual blood. The large majority of cases resolve spontaneously in days or weeks (ask patients to keep their heads slightly propped up): wait 1-2 months, VA and echographic control. If it persists: vitrectomy aimed at restoring vision and eliminating any products that may promote proliferation.

RVS in 2-4 months [presurgical antiangiogenic agent (*)].
  Attempt blood-air exchange.
  Antiangiogenic option: Antiangiogenic drugs (*): every 4-6 weeks.
  Echographic control every 15 days.
  In the event of improvement: complete PPC/extreme peripheral cryotherapy.

Late bleeding

Appears in a significant number of cases (from 13% to 50%) and may be due to different causes, the two most frequent being
  – Bleeding of the peripheral proliferative tissue present in sclerectomy: the origin of these neovessels is not the anterior retina (as is the case of anterior fibrovascular proliferation) but the ciliary body. Due to proximity, this fibrovascular tissue can extend to the anterior vitreous. It is associated with the incarceration of vitreous in sclerotomy. Diagnosis can be reached via the scleral depression. Occasionally, there may be an episcleral sentinel vessel entering the sclerotomy (although its sole presence does not guarantee the existence of fibroproliferative tissue in the latter.)
  Treatment shall include new RVS and extraction of this tissue using gas buffer.
  – Anterior fibrovascular proliferation (4.) In such cases, the hemovitreous occurs between 1 and 7 months after vitreo-retinal surgery. This neovascular proliferation appears in the peripheral retina and extends through the anterior hyaloid towards the posterior side of the lens capsule. Examination with scleral depression and indirect biomicroscopy reveals neovascularization, appearing sometimes as rubeosis iridis. Echography may reveal strips of thickened tissue from the peripheral retina to the ciliary body and posterior surface of the iris, tractional detachments of the anterior retina and the ciliary body (frequently associated with hypotony.) As treatment is discouraging, prevention is essential, particularly in patients at high risk such as: young patients with type 1 DM; severe retinal ischemia; tractional and/or mixed RD, especially whenever extra-scleral cerclage has been placed; several surgical procedures; PDR untreated or unresponsive to PPC; PDR with extensive fibrovascular posterior proliferation; post-surgical rubeosis iridis; recurrent hemovitreous...

Such patients require aggressive PPC. If proliferation evolves in spite of the treatment, an RVS is recommended with careful extraction of the anterior vitreous (which may require a lensectomy) in addition to extensive anterior photocoagulation.

When fibrovascular proliferation is already present, early detection is encouraged before the occurrence of tractional RD of the retina and/or ciliary body and the formation of cyclitic membranes. Vitreoretinal surgery should be followed by lensec-
tomy; extraction of the posterior lens capsule; dissection of the base of the vitreous; endodiathermy of neovessels; and the most extensive endophotocoagulation possible (avoid cryotherapy, as it may cause contraction of fibrotic tissue and peripheral RD). In the presence of peripheral tractional RD of the retina and/or ciliary body, peripheral retinotomies and the use of silicone oil are frequently prescribed to preserve the ocular globe.

10. PDR with retinal detachment

Tractional detachment involving or threatening the fovea: RVS+TAIV (*) as elective intraoperative tool+buffer (gas/silicone oil.)
Rhegmatogenous/mixed: RVS <48hr + silicone oil.

11. PDR with neovascular glaucoma

1st stage: atropine eye drops, antiglaucoma agents: all except pilocarpine.
Sequence: Brimonidine, beta blockers, carbonic anhydrase inhibitors: topical or systemic. The use of prostaglandin analogues is disputed (access to the uveoscleral pathway is blocked by fibrovascular tissue at the angle and increases inflammation.) Antiangiogenic therapy (*). PPC: full completion.
2nd stage: unresponsive PIO. Trabeculectomy with antimetabolites / Valve implants / Cyclo-ablation. Phenolization (in the presence of amaurosis in the eye) / Evisceration / Enucleation.

12. Mature cataract

Diabetic patients <65 years of age are 3 and 4 times more susceptible of suffering from cataracts (particularly cortical and subcapsular posterior) than non-diabetic patients (in younger patients the risk increases up to 25 times.) Patients aged over 65 are at the same risk level.

As long as cataracts allow for visualization of the ocular fundus or laser treatment to halt the progression of retinopathy, an expectant stand should be adopted. Phacoemulsification is indicated whenever these limits are exceeded. After surgery, patients should undergo photocoagulation whenever applicable or be monitored if surgical trauma induces progression of retinopathy.

**DIABETIC MACULAR EDEMA**

I. Assessment prior to therapeutic action

If systemic control is undisputed in diabetic retinopathy, this is even more so in the case of macular edema. The importance of glycemia controls should be stressed, as well as those of HgbA1C, blood pressure, overweight and lipids. Refer to endocrinologist/internist/renal physiologist whenever necessary. The improvement of certain diabetic retinopathies is truly amazing when metabolic control is enhanced.

In the event of poor metabolic controls, the treatment of macular edema may be postponed until improved.
Assessment of the edema shall always include improved corrected visual acuity, biomicroscopy retinography and OCT. FAG may not be necessary in certain clear cases of circinate rings around hard exudates.

II. Therapy options

**Focal or multifocal clinically significant macular edema (CSDME) (figs. 5 and 6)**

Focal photocoagulation remains the preferred treatment for this type of edema.
In exceptional cases where central macular thickening hinders focal laser therapy, which usually corresponds to OCT values above 400 microns, local corticosteroid therapy 1/antiVegf may be prescribed instead. Once the edema is reduced, focal photocoagulation can be administered 3-4 weeks later.
RVS (6-9) (figs. 10 and 11) with or without ILM dissection (10-12) and TAIV (*) are prescribed for vitreous-macular traction. The efficacy of dissecting the internal limiting membrane is still under study and no conclusive data are available with respect to its impact on the evolution of ME.
In the event of stabilizing and improving patient condition, he/she shall be referred to his/her ophthalmologist for check-ups. If no improvement is attained, patients shall be treated for focal or multifocal macular edema without traction (Chart 1).

**Diffuse CSDME (fig. 7)**

The therapeutic indication for a vitreous-retinal syndrome is RVS with hyaloideectomy, dissection of
the internal limiting membrane and final use of TAIV (*) (13,14) being optional. In the event of stabilizing and improving patient condition, he/she shall be referred to his/her ophthalmologist for check-ups. If no improvement is attained, patients shall be treated for diffuse macular edema without traction.

In the absence of traction, the most widely accepted option is modified grid laser treatment. The latter uses burns of lesser intensity (soft gray) and smaller in size (50µ) while microaneurysms are treated directly without seeking to achieve a change in their coloring. Similarly, areas of retinal thickening and non-perfusion associated with the edema are treated. As the results of this treatment are not fully satisfactory, there are some therapeutic options which, in spite of abundant evidence of their efficacy, have not been sufficiently proven. Among these options it is worth mentioning the administration of an intravitreous injection of triamcinolone (*) followed 2-3 weeks later by modified grid laser therapy. Whenever the use of TAIV is not possible, intravitreous antiangiogenic drugs (15-21) or subtenon corticosteroid therapy (22) may be administered. Once the edema is reduced, attempts should be made at locating and applying laser on the more evident leaks.

In the event of stabilizing and improving patient condition, he/she shall be referred to his/her ophthalmologist for check-ups. If patient condition does not improve, antiangiogenic drugs (*) (23), either those used previously or others, shall be administered. If still unresponsive, the remaining therapeutic options are very limited and only in a few selected cases will vitreo-retinal surgery be

Fig. 10: Macular edema with vitreous-macular traction syndrome.

Fig. 11: The same case after vitreo-retinal surgery.

Chart 1: Treatment algorithm for focal and multifocal macular edema.

Fig. 12: Cystoid macular edema.

Fig. 13: The same CME after TAIV.
prescribed (24,25) (figs. 14 and 15), since certain studies found this surgical procedure to be ineffective (Figueroa MS, Contreras I, Noval S. Resultados y complicaciones de la vitrectomía vía pars plana en el macular edema diabético difuso no traccional. Madrid: XI Congreso de la Sociedad Española de Retina y Vítreo; 2007: 68.) (Chart 2).

Cystoid macular edema (fig. 12)

Cystoid diffuse macular edema (CME) with vitreous-macular traction may be treated with RVS without dissection of the internal limiting membrane (ILM) in those cases whose time of evolution is unknown or over 6 months long (due to the risk of inducing a macular hole.) When evolution is below 6 months, the ILM may be dissected.

In patients suffering from CME and exhibiting no signs of traction, the most suited treatment is TAIV (*) followed optionally by antiangiogenic drugs and/or modified grid laser (26) (chart 3) (figs. 12 and 13).

REFERENCES

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NOTA
* El empleo de triamcinolona intravitreal y de antiangiogénicos está en fase de ensayo clínico. Su uso precisa el consentimiento informado por escrito del paciente y la autorización de la Agencia Española del Medicamento.