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EDITORIAL

Current status in diabetic macular edema treatments

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Abstract

Diabetes is a serious chronic condition, which increase the risk of cardiovascular diseases, kidney failure and nerve damage leading to amputation. Furthermore the ocular complications include diabetic macular edema, is the leading cause of blindness among adults in the industrialized countries. Today, blindness from diabetic macular edema is largely preventable with timely detection and appropriate interventional therapy. The treatment should include an optimized control of glycemia, arterial tension, lipids and renal status. The photocoagulation laser is currently restricted to focal macular edema in some countries, but due the high cost of intravitreal drugs, the use of laser treatment for focal and diffuse diabetic macular edema (DME), can be valid as gold standard in many countries. The intravitreal anti vascular endothelial growth factor drugs (ranibizumab and bevacizumab), are indicated in the treatment of all types of DME, but the correct protocol for administration should be defined for the different Retina Scientific Societies. The corticosteroids for diffuse DME, has a place in pseudophakic patients, but its complications restricted the use of these drugs for some patients. Finally the intravitreal interface plays an important role and its exploration is mandatory in all DME patients.

Key words: Diabetic macular edema; Diabetic retinopathy; Laser, Anti-vascular endothelial growth factor drugs; Intravitreal dexamethasone; Triamcinolone; Vitrectomy

Core tip: Diabetic macular edema is the leading causes of decreased visual acuity in diabetic patients, being the most important blindness causes in young adult people. New treatments have been developed in the last years, intravitreal anti-vascular endothelial growth factor drugs, corticoid intravitreal implants or injections, but the laser photocoagulation being the gold standard of diabetic macular edema treatment. The following manuscript tries to clarify the current status of diabetic macular edema treatment.

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INTRODUCTION

There has been a dramatic increase in the incidence of diabetes mellitus (DM) worldwide, which has been exacerbated by the growing obesity problem across the globe. The World Health Organization (WHO, estimated 30 million people worldwide had some form of diabetes in 1985; by 2000, the number had increased to 177 million. The WHO projections suggest that the number of people suffering from the disease will increase to some 370 million by 2030[1].

Diabetes is a serious chronic condition, which increase the risk of cardiovascular diseases, kidney failure and nerve damage leading to amputation. Furthermore the ocular complications include diabetic retinopathy is a microvascular complication of diabetes that primarily affects capillaries, which is the leading cause of blindness among adults in the industrialized countries, affecting from 2% to 5% of the entire population[2,3]. The causes

of visual decrease include proliferative diabetic retinopathy and diabetic maculopathy; the last condition include ischemia of the macula due to retinal capillary occlusion around the macula, increasing the foveal avascular zone in fluorescein angiography, but the most frequent causes of visual acuity decease in diabetes is due to diabetic macular edema (DME), which is the leading cause of blindness in young adults in developed countries, affecting 12% of type 1 and 28% of type 2 diabetic patients[4]. Attending the increase of DME at 2030, the DME prevalence can increased to 100 million of patients. Despite of diabetic macular edema can have a spontaneous recovery (it is important to recognize that about 33% to 35% of patients resolve DME spontaneously after six months without treatment[3,5]), the treatment of patients who developed DME, has become the most important focus in the DM patient's treatment,

The medical DME treatment should be based on a good control of glycemia, arterial hypertension, lipids (it is important the role of low-density lipoprotein (LDL)-cholesterol in DME development, particularly in exudates macular deposits), and renal function[6,7]. However, despite the systemic metabolic control values being essential for patients with diabetic retinopathy, it has proven to be insufficient for DME if it appears, and we have to take additional measures, in order to avoid the subsequent loss of vision. While laser treatment of DME has been a valid treatment so far, in some cases it has been inadequate. The introduction of new treatments, such as intravitreal corticosteroids or anti-vascular endothelial growth factor (VEGF) drugs have recently shown their safety and efficacy, and together with laser photocoagulation are becoming the treatments of choice in the management of DME.

CONCEPT OF FOCAL VERSUS DIFFUSE DIABETIC MACULAR EDEMA

DME is further classified into focal or diffuse, depending on the leakage pattern seen on the fluorescein angiogram (FA). In focal DME, discrete points of retinal hyperfluorescence (leakage of intravascular liquid to interstitial space, due a vasopermeability) are present on the FA due to focal leakage of microaneurysms, which are the cause of retinal thickening. Commonly, these microaneurysms are surrounded by circular hard exudates. A variation of this form is the multifocal macular edema, which in some cases is confused with diffuse macular edema. This form appears under fluorescein angiography as multiple foci of leakage due to the presence of multiple foci of microaneurysms.

In diffuse DME, there are areas of diffuse leakage on the FA due to intraretinal leakage from dilated retinal capillary bed and/or intraretinal microvascular abnormalities (IRMA), and/or from arterioles and venules without foci of leaking microaneurysms[8]. To treat DME, it is important to use the classification by Bresnick *et al*[9] into focal or diffuse DME, modified by Browning *et al*[10].

LASER TREATMENT

Laser treatment was defined by the ETDRS study in its Reports number 3 and number 4; there are two different techniques[5,11]: (1) Focal laser. Focal treatment is required for focal lesions located between 500 and 3000 μm from the centre of the macula. The term "focal lesions" according to the ETDRS classification includes: microaneurysms, IRMA and short capillary segments that show focal fluorescein leakage. The treatment consists of burns of 50-100 μm of moderate intensity and 0.05-0.1 s duration, the end point of treatment is whitening or darkening of focal lesions. Microaneurysms below 40 μm in diameter had successful results with low laser intensity, but microaneurysms with more than 40 μm diameter need more intense laser burns (a more whitening result) and sometimes need a re-treatment. The clusters of microaneurysms, in particular those with in hard exudate rings, may be treated with larger spots (200-500 μm), with subsequent re-treatment of any large microaneurysms within the cluster with 50 μm spots to obtain darkening or whitening. The treatment of lesions of more than 3000 μm from the centre is recommended if prominent leaks are present and associated with retinal thickening or hard exudates that extend closer to the centre; and (2) Grid laser, in which mild power laser impacts were made with a spot size of 50-200 μm, for a duration of 0.05-0.5 s obtained a mild retinal pigment epithelium whitening, with power adjusted to prevent the burns from spreading to more than 200 μm in diameter. Grid treatment is not placed within 500 μm of the centre of the macula or within 500 μm of the disc margin, but may be placed in the papillomacular bundle. Grid can extend up to 2 disk diameters (3000 μm) from the centre of the macula or to border panretinal photocoagulation treatment, if present. Any focal leaks within the areas of the grid treatment are treated focally. The burns are placed approximately two visible burn widths apart in the areas of the macular edema (retinal thickening) that are thought to be related to diffuse leakage or capillary loss.

Laser photocoagulation is not a harmless technique, and side effects appear secondary to the burn induced in the retinal layers, in particular, the destruction of the retinal pigment epithelium might induce apoptosis of the surrounding retinal cells. In the macular area, some secondary effects might affect the visual acuity. One the most important effects that can decrease visual acuity is the enlargement of a laser scar, referred to as "atrophic creep", which might threaten the visual prognosis if the laser is applied too close to the fovea Schatz *et al*[12] reported that enlarged laser scars reached the central fovea in 11 of 203 eyes with diabetic macular edema after grid laser photocoagulation. Brancato *et al*[13] reported that the scars enlarged by an average of 103% after treatment of choroidal neovascularization in degenerative myopia. The Maeshima *et al*[14] study showed that the expansion rate of laser scarring was higher in the posterior pole (12.7%) than in the midperiphery (7.0%). The authors explain that because the density of the photoreceptors

is higher in the posterior pole, more photoreceptors are destroyed in the posterior pole than in the midperiphery when using the same spot size of laser photocoagulation. Furthermore, the photoreceptors interact with surrounding photoreceptors through horizontal or amacrine cells; thus, the authors hypothesized that necrosis of regional photoreceptors may lead to apoptosis of surrounding cells, which might explain why laser scars gradually expand at a higher rate in the posterior pole.

At present, despite the enthusiasm for evaluating several new treatments for DME including intravitreal therapies for DME (*e.g.*, corticosteroids, and anti-VEGF drugs), laser photocoagulation remains the gold standard of care and the only treatment with proven efficacy in a large-scale clinical trial for this condition. We can considered a best practice, use the focal laser photocoagulation for focal DME as the first choice treatment, and also in many countries, we can considered the use of grid laser for diffuse macular edema treatment.

INTRAVITREAL ANTI-VEGF DRUGS

The vascular endothelial growth factor belongs to a family of different growth factors (types: A, B, C and D). The type VEGF-A are present in ocular inflammatory pathologies, and it has become accepted as one of the most potent factors in the induction of angiogenesis. Six major isoforms of VEGF-A exist: 121, 145, 165, 183, 189 and 206. VEGF-A 165 is the most important factor in the pathophysiology of DME[15,16]. The VEGF is produced by endothelial cells, pericytes, and neuronal cells as: ganglion cells, Müller cells, and glial cells. The upregulation of VEGF is produced by hypoxia, hyperglycemia (which itself can enhance the response of retinal cells) and cytokines, such as insulin-like growth factor 1, interleukin-6, and protein kinase C-beta. The VEGF induce angiogenesis, vasculogenesis, inflammation, chemotaxis and increase of vascular permeability developing disruption of hemato-retinal barrier, and subsequent DME[17,18]. The use of anti-VEGF drugs in DME treatment has been corroborated by many studies, which demonstrate the validity of its use in DME[19-22]. In many countries the use of anti VEGF drugs (bevacizumab or ranibizumab) has been extended, and it's common practice as first choice in some patients. Despite the most important limitation of its use, is the high cost of intravitreal drugs[23].

INTRAVITREAL STEROID INJECTION

Role of the inflammation in DME

Inflammation is a nonspecific response to injury that includes a variety of functional and molecular mediators, including recruitment and activation of leukocytes. Many of the molecular and functional changes that are characteristic of inflammation have been detected in retinas from diabetic patients. The DME increases expression of intercellular adhesion molecule 1 in the retina, and produces an interaction between this adhesion molecule on retinal endothelia with the CD 18 adhesion molecule on monocytes and neutrophils, contributing to the diabetes-induced increase in leukostasis within retinal vessels. This attraction and adhesion of leukocytes to the vascular wall are important components of inflammatory processes. Furthermore, leukostasis can contribute to the development of capillary nonperfusion in retinal vessels, and it has been postulated that leukostasis is a factor in the death of retinal endothelial cells[18].

Place of intravitreal corticosteroids in DME treatment

The use of corticosteroids as a means to treat ocular DME has emerged as an increasingly common treatment for certain patients. The Diabetic retinopathy clinical research network (DRCRnet), reported 2-years' results of a multicentered, randomized, clinical trial comparing preservative free intravitreal triamcinolone (TA) and focal/grid laser for DME[24]. This randomized study indicates clearly that focal/grid laser is a better treatment than intravitreal TA in eyes with DME with VA between 20/40 and 20/30. The most frequent intravitreal TA complication is an increase in intraocular pressure (observed in 30% of patients) and cataract formation. From this study and other non-randomized studies, we suggest that intravitreal TA is a promising therapy method for DME that is unresponsive to laser photocoagulation and for patients previously submitted to cataract surgery.

Another corticosteroid currently used but without DME treatment indication for any international agency, is the dexamethasone intravitreal implant[25]. The most important difficulty in this type of study is the safety and drug release profiles of this injectable implant. Further studies are warranted to assess its long-term efficacy and safety.

TREATMENT OF REFRACTORY DME

As we said previously the DME is a chronic disease, that becomes difficult to treat in some patients, the refractory DME has become one of the biggest problems for the retina specialist. First we take into account the importance of systemic diabetes status control, we should control strictly the glycaemia, arterial tension, lipids and renal status[26], furthermore we should revise the diabetes treatment, because some drugs can induce DME as glitazone[27,28]. Despite of some patients seems that all is correct, in these cases which has all metabolic parameters correct and which has been treated by other therapies but the DME not decreased, is important to examine the vitreo-retinal surface.

Importance of vitreo-retinal interface

Clinical evidence indicates that the vitreo-retinal interface may play a role in the pathogenesis of DME, the persistent vitreo-macular traction by vitreous cortex before posterior vitreous detachment (PVD), or the persistence of residual cortical vitreous (vitreoschisis) after PVD, and thickened and taut posterior hyaloid that may be adherent

to internal limiting membrane (ILM), with a subsequent macular traction. In the macular area the vitreous and ILM have the strongest attachment and the ILM (which is the basement membrane of the Múller cells) is thinnest. A densely-packed collagen filament of posterior vitreous cortex penetrates the ILM in the macular area. Vitrectomy, removing all the posterior vitreous cortex and ILM peeling has been shown to improve visual acuity and decrease macular thickening[29].

Vitreous surgery

Laser photocoagulation has no place in cases of tractional or taut DME. In such cases there is clinical evidence that vitrectomy will resolve the DME. The beneficial mechanisms may be: to remove AGE ligand-induced mechanical traction between the posterior cortical vitreous and the ILM of macula and to remove AGE that may also inhibit the activation of the RAGE axis and its pro-inflammatory effects.

Currently the discussion is centered on ILM peeling and it usefulness. It is not clear that ILM peeling is necessary for tractional-DME treatment as it may hinder the formation of epiretinal membranes but may help to remove all the cortical vitreous that may otherwise be left behind even after the posterior hyaloid is removed[30]. The complications encountered after vitrectomy include cataract, retinal detachment, epiretinal membrane, glaucoma, and vitreous hemorrhage.

CONCLUSION

Today, blindness from diabetic macular edema is largely preventable with timely detection and appropriate interventional therapy. The treatment should include an optimized control of glycemia, arterial tension, lipids and renal status.

The photocoagulation laser is currently restricted to focal macular edema in some countries, but due the high cost of intravitreal drugs, the use of laser treatment for focal and diffuse DME, can be valid as gold standard in many countries. The intravitreal anti VEGF drugs (ranibizumab and bevacizumab), are indicated in the treatment of all types of DME, but the correct protocol for administration should be defined for the different Retina Scientific Societies. The corticosteroids for diffuse DME, has a place in pseudophakic patients, but its complications restricted the use of these drugs for some patients. Finally the intravitreal interface plays an important role and its exploration is mandatory in all DME patients.

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