Review Article

Capsula Eburnea

MACULAR EDEMA TREATMENT IN DIABETIC RETINOPATHY

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SUMMARY

Macular edema represents a common clinical complication in diabetic patients with retinopathy. The risk for a diabetic patient to develop macular edema is around 10%. Although the precise etiology of macular edema is not completely known, understanding its pathogenic mechanisms could help in developing new therapeutic procedures. Keeping the common risk factors under control is of crucial importance in the prevention and management of ocular complications. As regards the treatment of these complications, current literature recommends laser therapy as the gold-standard. The aim of this article is to examine all the therapeutic possibilities by describing the advantages and disadvantages of each methodology.

Introduction

Diabetic retinopathy (DR) is the main cause of legal blindness in people aged from 20 to 65 in industrialized countries. It is more frequent in type I (juvenile) diabetes (40%) than in type II diabetes (20%). The longer a person has diabetes, the higher the risk of developing ocular problems. Other risk factors are represented by a poor glycemic control, hypertension, nephropathy and obesity. Diabetic retinopathy is usually classified in two types: the nonproliferative diabetic retinopathy, characterized by microvascular anomalies typically confined in the retina, not extending beyond the inner limiting membrane, and the proliferative retinopathy, characterized by fibrovascular lesions extending beyond the inner limiting [1]. In subjects suffering from type I diabetes, it is often possible to observe a proliferative retinopathy, usually with peripheral involvement and macular sparing, whereas subjects suffering from type II diabetes show a macular involvement with peripheral area sparing. In DR, the macula can be involved in different ways: it is possible to have a severe capillary occlusion with important ischemia and widening of the central vascular area; pathologies due to epiretinal membranes can occur even without edema. The most frequent macular pathology during DR is without no doubt the macular edema, with its several levels of severity. Diabetic macular edema (DME), the most common cause of blindness in diabetic patients, is caused by an intraretinal fluid accumulation originating from microaneurysms and capillaries. Two types of edema can be distinguished: focal and diffuse; these can also occur concomitantly. Focal edema is caused by the diffusion, of single microaneurysms or small groups of microaneurysms; these can be associated with hard exudates which are lipoprotein deposits in the external retinal layers, or subretinal layers in the worst cases. Diffuse edema is the result of an abnormal permeability of entire capillary segments, microaneurysms and arterioles [2]. A macular edema, in order to be clinically significant (CSME), should be associated with one of these conditions: retinal tickening within 50mn from the foveal center; hard exudates within 50 nm from the foveal center if an adjacent retinal thickening is present;

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one of several areas of retinal thickening with a dimension of at least one papillary diameter (1500 nm), a part of which is located within one papillary diameter from the center of the macula.

Factors involved in the etiopathogenesis of DME

The pathogenesis of DME can involve different factors and is not well understood. The factors involved appear to be essentially three: hyperglycemia, tissue hypoxia and biochemical changes in the vitreous area. The high levels of glucose lead to an increase in polyol pathway activation, as well as in the production of advanced glycosylated end products (AGE) and Reactive oxygen species (ROS) [3]. These processes determine an increase in the production of diacylglycerol, with the consequent activation of Protein kinase C (PKC) [4, 5]. The increased activity of the PKC leads to a series of cellular modifications with the release of biochemical messages (histamine, ICAM-1, endothelin) by the retinal cells and the pigmented layer. These biochemical messages determine a rupture in the blood-retinal barrier, especially in the internal barrier, in the vicinity of the capillary endothelial cells, with a consequent increase in vascular permeability. PKC also activates the vascular endothelial growth factor (VEGF), a potent cytokine, leading to changes in the structure of the endothelial joints [6, 7]. Tissue hypoxia causes arteriole dilation and an obvious movement of fluids towards the extracellular area. The vitreous humour has an important role in the formation and maintaining of DME [8]. The biochemical changes in the posterior vitreous modify the structure of vitreous collagen and sustain its persistent adherence to the posterior pole [9]. These adherences create possible anterior-posterior and tangential tractions.

Diagnostic methods and treatment strategies

Three main types of analysis are used for diagnosing macular edema: biomicroscopy, fluorescein angiography and optical coherence tomography (OCT). Biomicroscopy involves direct observation with the use of a slit lamp and different types of lenses (contact lens, 60D, 78D, 90D). In general it is possible to observe a retinal thickening twice the diameter of a retinal vein, thicker in the side of the papilla. Fluorescein angiography is fundamental in order to determine the eligibility for photocoagulative treatment and to assess its efficacy. In fact, this analysis allows to interpret pathogenically the macular edema, and/or the neovessels, and to assess its diffusion into the nonperfused retina. OCT is a non invasive method which constitutes a useful addition to the aforementioned examinations and allows the identification of three types of DME patterns. In 88% of the cases, a diffuse thickening with subretinal hypo-reflective areas is observed, while in 47% of the cases hyporeflective cystic areas within the retinal tissue in the macular area can be identified, and in 15% of the cases it is possible to observe a detachment of the neuroepithelium that can be associated with the two types of edema [10, 11]. Several researches have underlined that the primary treatment consists in achieving the best possible glycemic control, maintaining constant levels of around 140-150 mg/day and avoiding wide oscillations towards higher levels or hypoglycemia [12]. The research of Lauritzen et al. [13] and the Oslo study [14] have shown some differences in the progression of diabetic retinopathy among groups of patients that were strictly controlled in regards to glycemia, as well as in patients who followed a conventional therapy protocol; the UKPOS study [15] has also highlighted the importance of effectively controlling hypertension and renal insufficiency, that are important risk factors in the development of DR. The DIRECT program [16, 17], made up of three clinical studies carried out on 5231 patients of 309 centers in 30 different countries, has shown that an the angiotensin II receptor antagonist, Candesartan, at a dosage of 32mg/day, is able to reduce by 35% the emergence of DR in patients with type I diabetes, as well as provoking a regression of moderate retinopathy in patients with type II diabetes. Even a poor control of the lipidic aspect contributes to an increase in the progression of macular edema; high levels of cholesterol are localized inside the external plexiform layer, forming the so called hard exudates, contributing to a higher risk of visual loss, since these can be associated with the development of subretinal fibrosis. Photocoagulation with Argon laser has been shown to be effective in the treatment of DME. It works through two mechanisms:

direct thrombosis of microvascular abnormalities, or transmission of heat into the pigment epithelium; causing an increase in oxygen tension that induces arterial vascularization or release of antiangiogenic factors such as PEDF [18, 19]. Argon -laser treatment can be carried out using two different kinds of techniques: "focal" or "grid". The focal technique includes the application of laser spots (sized 50-100 nm for 0.1 seconds) onto microaneurysms and microvascular lesions in the center of hard exudate rings located within 500-3000 nm from the center of the macula. It can be also considered the treatment of lesions up to 300 nm from the center of the macula if CSME persists despite previous treatment, and when the visual acuity is less than 6/12 (5/10). In these cases, an exposure time of less than 0.05 seconds is recommended. The grid technique consists in treating the whole area of retinal thickening by applying laser spots (sized 100 nm for 0.1 sec.) beyond 100 nm from the center of the macula and 500 nm from the temporal margin of the optic disc [20]. In addition to Argon -laser, it is possible to utilize lasers that use different wavelengths, such as Nd-Yag (better absorbed by hemoglobin), Krypton and Diode lasers (that cause less damage to the photoreceptors and penetrate the dioptric media better). Akduman et al. [21] found no significant differences in treatment with different types of lasers in terms of safety and efficacy. 70% of patients treated with laser photocoagulation remained stable, while 15% improved and the remaining 15% subsequently deteriorated. In patients who do not show an improvement, it is important to avoid taking hasty decisions on a second treatment, because for the resolution of edema it is necessary to wait 3-4 months. Besides an accidental coagulation of the foveal region, the complications of this type of treatment include iatrogenic choroidal neovascularization, subchoroidal fibrosis and paracentral scotomas. Recent studies have introduced new types of lasers, such as the subthreshold micropulse laser (810 nm) [22], or the light laser [23], which can help to avoid these complications. If there is a marked opacity of the dioptric media that does not allow the use of laser photocoagulation, peripheral retinal cryotherapy may be a valid alternative. However, in 25-38% of patients treated with cryotherapy, the development or progression of traditional retinal detachment occurs; for this reason its use should be limited to cases where laser treatment has not been effective. Other possible types of treatment include the use of drugs that reduce the biochemical changes caused by hyperglycemia in tissues. The use of vitamin E is important, for example, for the prevention of vascular damage caused by ROS [24]; PKC inhibitors, such as Ruboxistaurin or N-benzoyl- staurosporine have also shown a reduced risk of visual loss [25, 26]. Corticosteroids (Triamcinolone acetonide and dexamethasone), which are anti-inflammatory drugs for excellence, are able to reduce the production of VEGF and ICAM-1, with a consequent diminution of damage to the blood-retinal barrier and reduction of fibrovascular proliferation. In order to mitigate the systemic effects of the drug, but also to reach maximum concentration in the eye, it is injected inside the vitreous cavity [27]. But even this way of distribution is not risk free because can cause an increase in intraocular pressure, cataracts and endophthalmitis. In the last few years, great progress has been made with the anti-VEGF: these are drugs that inhibit the vascular endothelial growth factor. Two drugs currently in use, are Ranibizumab and Pegaptanib: Ranibizumab is a humanized monoclonal antibody fragment produced in Escherichia coli cells by recombinant DNA technology, targeted at the human vascular endothelial growth factor A (VEGF-A). It binds with high affinity to VEGF -A isoforms (VEGF 110, VEGF 121 and VGF 165), thus preventing the binding of VEGF-A with its receptors FLT-1 (VEGFR-1) and KDR (VEGFR-2). Several clinical studies, such as the retrospective study by Kotsolis and colleagues [28], have demonstrated the clinical efficacy of Ranibizumab; 16 eyes (of 10 patients), previously treated with laser, that would have been risky to treat with further laser therapy, were treated with Ranibizumab. The follow-up after 11 months evidenced stabilization and even improvement of visual acuity in most patients. The treatment protocol involves performing an intravitreal injection (0.5 mg) in the affected eye once per month until stable vision is reached for 3 consecutive months. If any improvement is noted, treatment should be ceased and the eyesight of the patient monitored each month. Pegaptanib is a pegylated modified

oligonucleotide that binds with high specificity and affinity to vascular endothelial growth factor (VEGF 165), inhibiting its activity. VEGF 165 is one of the isoforms, mainly involved in the pathological neovascularization. Many studies confirm the efficacy of Pegaptanib, but it seems to be slightly less effective than Rabimizumab [29]. Bevacizumab is a monoclonal antibody that by binding to VEGF prevents it to bind to its receptors, FLT-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells; it is used in the treatment of colorectal metastatic cancer, lung cancer, renal cell and breast carcinoma and it currently has no "official" ophthalmic indications; its use (off-label) is supported by extensive literature [30, 31], which documents the efficacy and tolerability, with AIFA also supporting its use. The side effects after intravitreal injection of Bevacizumab include vitritis, retinal detachment, alteration of the lens, increased intraocular pressure and corneal abrasions; however, there are no known systemic side effects.

Conclusions

Diabetic retinopathy is a common cause of severe visual impairment and blindness. Patients with diabetes who are not affected by retinopathy should undergo an eye examination every 12-24 months, while in the presence of lesions, the specialist should schedule periodic inspections. The gold standard in diagnosis is undoubtedly the FLAG that allows viewing of the retinal and choroidal circle, identifying any injuries. However, the fluorescein angiography may also be preceded by optical coherence tomography (OCT). In addition, the fluorescein angiography allows verifying the location of the lesion, essential for therapeutic decisions. The novel drugs, especially anti-VEGF, are very promising for the future, and others are still being tested. New types of laser treatments are also being tested, especially in an effort to reduce the side effects. However, despite its limitations, the classic laser treatment remains the first choice therapy in diabetic macular edema, at the moment.

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