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André Gomes de Sena

The treatment of diabetic macular edema: current status and future perspectives

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The Treatment of Diabetic Macular Edema: Current Status and Future Perspectives

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Área: Oftalmologia

Trabalho efetuado sob a Orientação de:
Dra. Susana Costa Nunes Penas

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Resumo

O Edema macular diabético é a principal causa de perda de visão moderada entre a população diabética. Fotocoagulação a laser e controlo intensivo da glicémia e da pressão arterial têm sido a abordagem terapêutica padrão por mais de 20 anos. No entanto, na maioria dos casos de edema macular diabético difuso e grave, o controlo da doença não é satisfatório. A crescente compreensão da patofisiologia multifactorial do edema macular incentivou a investigação de novas terapias na última década. Tanto os corticosteroides e como os inibidores do fator de crescimento endotelial vascular (bevacizumab, ranibizumab, pegaptanib e aflibercept) foram amplamente estudados e mostraram melhorias anatómicas e funcionais satisfatórias, com perfis de segurança aceitáveis. Infelizmente, alguns dos principais efeitos adversos dos corticosteroides e a necessidade de múltiplas injeções intravítreas permanecem grandes preocupações. Sistemas intravitreos de libertação sustentada de drogas foram desenvolvidos para reduzir estes e outros eventos adversos relacionados com as drogas e as injeções. A vitrectomia mostra ser valiosa apenas em alguns casos selecionados, geralmente associados a anomalias da interface vítreo-retiniana. Novos sistemas de aplicação de laser têm sido desenvolvidos para reduzir os eventos adversos relacionados com o laser. Algumas novas drogas experimentais estão também em investigação. A maioria dos estudos publicados têm interesse limitado devido ao pequeno número de participantes e ao curto período de acompanhamento. Além disso, os seus resultados são de difícil comparação, devido a desenhos de estudo e características diferentes. O número crescente de publicações e terapias em desenvolvimento revela o crescente interesse neste assunto. Uma abordagem multimodalidade pode tornar-se o padrão de tratamento para uma doença multifatorial como o edema macular diabético.

Palavras-chave: Edema Macular Diabético, Tratamento, Fotocoagulação a Laser, Corticosteroide, Inibidor do Fator de Crescimento Endotelial Vascular, Vitrectomia

The treatment of diabetic macular edema: current status and future perspectives

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Abstract

Diabetic macular edema is the main cause of moderate vision loss among diabetic population. Laser photocoagulation and intensive glycemic and blood pressure control have been the standard treatment approach for more than 20 years. However, in the majority of cases of diffuse and severe diabetic macular edema, the control of the disease is not satisfactory. The growing understanding of the multifactorial pathophysiology of macular edema encouraged the investigation of new therapies in the last decade. Both corticosteroids and vascular endothelial growth factor inhibitors (bevacizumab, ranibizumab, pegaptanib, and aflibercept) were widely studied and showed satisfactory anatomical and functional improvements with acceptable safety profiles. Unfortunately, some of corticosteroids' main adverse effects and the need for multiple intravitreal injections remain major concerns. Intravitreal sustained drug delivery systems were developed to reduce these and other drug- and injection-related adverse events. Vitrectomy proves to be valuable only in a few selected cases, usually associated with vitreoretinal interface abnormalities. New laser delivery systems have been developed to reduce laser-related adverse events. Some experimental new drugs are also under investigation. The majority of reported studies have limited interest due to a short number of participants and a short follow-up. Also, their results are difficult to compare, due to different study designs and characteristics. The increasing number of reports and developing therapies shows the growing interest in this subject. A multi-modality approach may become the standard of care for a multifactorial disease as diabetic macular edema.

Keywords: Diabetic Macular Oedema, Treatment**,** Laser Photocoagulation**,** Corticosteroid**,** Vascular endothelial growth factor inhibitor**,** Vitrectomy

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1 Introduction

Diabetic retinopathy (DR) is an important cause of severe and moderate vision loss in the working-age population. In 10 years, nearly 90% of patients with type 1 diabetes and more than 65% of patients with type 2 diabetes develop some form of retinopathy (Williams et al., 2004).

Diabetic macular edema (DME), a form of DR defined as the retinal thickening involving the macula, is the main cause of moderate vision loss (≥15 letters lost on the Early Treatment Diabetic Retinopathy Study [ETDRS] visual acuity [VA] chart or a doubling of the visual angle) among diabetic population (Klein et al., 2009b; Williams et al., 2004).

DME can occur at any stage of the disease progression, but incidence and prevalence tends to rise with the increase in duration and severity of diabetes (Williams et al., 2004). In type 1 diabetes patients, the annual incidence of DME ranges from 0.9% to 2.3% and there is a cumulative incidence of 26% within 14 years of diagnosis. In 25 years, 29% of these will be presenting DME and 17 % will show a clinically significant macular edema (CSME) (Klein et al., 1998; Klein et al., 2009a). In type 2 diabetes patients, the annual incidence of DME ranges from 1.25% to 1.40% and there is an increase in prevalence from 3% within 5 years of diagnosis to 28% after 20 years (Klein et al., 1995).

DME tends to be a chronic disease, however, about 1/3 of the patients can have a spontaneous recovery in 6 months, without any treatment except the adequate control of glycemic levels (Ferris and Patz, 1984; Hikichi et al., 1997).

Since the incidence and prevalence of diabetes are estimated to significantly increase during the next years (Narayan et al., 2006), the incidence of DR and consequently DME is also expected to rise. Therefore, in the future, it is likely that DME may be responsible for a substantial vision loss unless adequately treated. Aside from intensive glycemic and blood pressure control, for more than 20 years the standard of care has been laser photocoagulation. Laser proved to prevent further vision loss but unfortunately visual improvement is rare. This problem encouraged the search for other treatment modalities, and alternative therapies, such as intravitreal triamcinolone acetonide (IVTA) and vascular endothelial growth factor (VEGF) inhibitors, have been recently investigated in numerous clinical trials.

Thereby, this review aims to evaluate where we stand in terms of effectiveness and safety of these new treatment modalities and predict how treatment guidelines may change in the next years.

2 Definitions and classifications

The ETDRS defined DME as the thickening of the retina and／or presence of hard exudates within one disc diameter of the center of the macula (ETDRS, 1985, 1987). The study also proposed the term clinically significant macular edema to characterize the severity of macular edema for treatment guidelines proposes. Macular edema is said to be clinically significant when presenting: retinal thickening at or within 500 μm of the macular center; and/or hard exudates at or within 500 μm of the macular center if associated with adjacent retinal thickening; and/or a zone or

zones of retinal thickening greater than 1 disc diameter in size, at least part of which is within 1 disc diameter of the macular center.

Classically, DME is classified into focal or diffuse, according to the leakage pattern seen on the fluorescein angiogram (Kang et al., 2004). In focal DME, there are points of retinal hyperfluorescence due to focal leakage from microaneurysms, usually found within areas of focal retinal edema and commonly surrounded by rings of hard exudates. In diffuse DME, the fluorescein angiogram shows areas of diffuse leakage due to intraretinal outflow from a dilated retinal capillary bed and/or intraretinal microvascular abnormalities and/or (in severe cases) from arterioles and venules without foci of leaking microaneurysms. In addition, cystoid macular edema, which results from a generalized breakdown of the inner blood retinal barrier, with fluid accumulation in the outer plexiform layer, can also be present and associated to the diffuse type.

With the appearance of new imaging techniques, such as the optical coherence tomography, a quantitative classification of the edema was possible. Measurements of retinal thickness and retinal volume have revolutionized the classification. In the initial classification, there were 3 basic structural changes of the retina: retinal swelling, cystoid edema and serous retinal detachment (Otani et al., 1999). Posteriorly, it was modified into: type 1 with foveal thickening with homogenous optical reflectivity in the entire layer of the retina; type 2 with foveal thickening and a distinct decrease in the optical reflectivity of the outer retinal layer; type 3 with foveal thickening with subretinal fluid accumulation; type 3 is further divided into type 3A if no vitreofoveal traction is present and type 3B if vitreofoveal traction is present (Kang et al., 2004). Further investigation brought a new classification with five different morphologic patterns: diffuse retinal thickening; cystoid macular edema; serous retinal detachment without posterior hyaloidal traction; posterior hyaloidal traction without tractional retinal detachment; and posterior hyaloidal traction with tractional retinal detachment. In addition, mix patterns can arise from co-existence of at least two of these basic patterns in the same eye (Kim et al., 2006).

3 Pathophysiology

Much is already known about the pathophysiology of DME, but we are still far from fully understanding it. It is clear that the mechanism is multifactorial and very complex. Several angiogenic, inflammatory and oxidative stress overlapping and inter-relating pathways have been implicated. It is also clear that they are directly or indirectly triggered by chronic hyperglycemia, recognized as the primary insult, and converge into a final common pathway that results in macular edema. This last step is the disruption of the blood-retinal barrier.

The blood-retinal barrier has two components: the outer barrier is formed by retinal pigment epithelium (RPE) cells tightly connected by tight junctions (zonula occludens and desmosomes); the inner barrier is formed by retinal vascular endothelial cells tightly connected by tight junctional complexes (occludins and claudins) and glial cells, such as Müller cells. The disruption of the blood-retinal barrier occurs due to the compromise of at least one barrier component, leading to an increase of vascular leakage into the neurosensory retina that exceeds the removal of fluid from the retinal tissue into the systemic circulation (a process that can also be impaired), causing an accumulation of fluid in the intraretinal layers of the macula. This increase of

permeability is due to leakage between retinal vascular endothelium or RPE (allowed by junction proteins disruption and cell loss), up-regulation of vesicular transport, or/and increase of surface membranes fenestrations of retinal vascular endothelium and RPE (Bhagat et al., 2009; Ehrlich et al., 2010; Singh and Stewart, 2009).

Multiple factors have been implicated in the network of processes that lead to blood-retinal barrier disruption: free radicals, advanced glycation endproducts, protein kinase C beta, hepatocyte growth factor, fibroblast growth factor, insulin-like growth factor-1, metalloproteases, histamine, tumor necrosis factor, intercellular adhesion molecule-1, interleukins (1, 6, and 8), prostaglandins, renin, angiotensin II, and VEGF-A. They are produced mainly by and act on the cellular elements that form and support the blood-retinal barrier. Microaneurysms (resulting from vascular wall weakening, usually due to pericyte loss), altered blood flow, retinal leukostasis, retinal ischemia, retinal hypoxia, and vitreoretinal interface abnormalities also play a role (Bhagat et al., 2009; Ehrlich et al., 2010; Elbendary and Shahin, 2011; Singh and Stewart, 2009).

The findings of glucose-mediated enhanced leukocyte-endothelial cell interaction and leukocyte activation, mainly through the increase of intercellular adhesion molecule-1 expression induced by inflammatory and pro-inflammatory mediators (such as transforming growth factor-b, tumor necrosis factor α, interleukin 6, protein kinase C beta, monocyte chemotactic protein-1, VEGF, and nuclear factor-kappa-B), has led to the recognition of DME and DR as a state of low-grade inflammation (Bhagat et al., 2009; Ehrlich et al., 2010; Funatsu et al., 2009; Singh and Stewart, 2009). For this reason, anti-inflammatory agents have been tried as a treatment option.

VEGF has proven to be a very important mediator in the pathophysiology of DME, especially the VEGF-A165 isoform. It is a powerful angiogenic factor produced by cellular elements that form and support the blood-retinal barrier such as Müller cells, RPE cells and endothelial cells, and is up-regulated by hypoxia, hyperglycemia and several mediators (such as insulin-like growth factor 1, interleukin-6, and protein kinase C beta). VEGF increases vascular permeability by both up-regulation of vesicular transport and direct and indirect disruption of tight junctions. In addition, it also has pro-inflammatory properties through the induction of intercellular adhesion molecule-1expression. Due to its major role, VEGF has become an important therapeutic target (Bhagat et al., 2009; Ehrlich et al., 2010; Singh and Stewart, 2009).

On the other hand, structural changes of the vitreous gel, particularly the posterior cortical vitreous, of the posterior hyaloid, and of the internal limiting membrane (ILM) are likely to play a role in the pathogenesis of DME, since their presence is associated with DME exacerbation and persistence. These vitreoretinal interface abnormalities are thought to induce vitreomacular traction, exacerbating the macular edema or interfering with its resolution when treating. Accumulation of advanced glycation endproducts has been implicated in posterior cortical vitreous and ILM structural changes. A thick taut posterior hyaloid seems to occur due to the infiltration of the membrane with glial and inflammatory cells (Bhagat et al., 2009).

4 Glycemic and blood pressure control

Hyperglycemia and hypertension are well known as major systemic risk factors for DME. The strict control of blood pressure and glycaemia reduces the incidence and progression of DR and DME.

With an intensive treatment of diabetes, the risk of developing retinopathy is reduced in 76% (reducing 31% for each 1% decrement in HbA1c). In the same manner, CSME is reduced by more than 50%. The progression of retinopathy is also decelerated, by at least a half, and the frequency of photocoagulation treatments also decreases in 9 years (DCCT, 1993; Stratton et al., 2000; White et al., 2008).

Tightly controlled blood pressure reduces in at least 50% the moderate vision loss in 9 years. Also, a decrease of 10 mmHg in systolic blood pressure leads to an 11% reduction in photocoagulation or vitreous hemorrhage. Apparently, there is no lower level of blood pressure below which no benefit can be obtain (Adler et al., 2000).

Simultaneous tight control of blood pressure and blood glucose is very likely to have an addictive effect. The glycemic levels should be controlled to get and maintain an HbA1c of 6% or less and the blood pressure control should aim for a systolic pressure of 130 mmHg or less. (Stratton et al., 2006).

5 Laser photocoagulation

5.1 Mechanism of action

The specific mechanisms by which photocoagulation reduces DME are still unknown, but several hypotheses have been proposed over the years. The general idea is that laser destroys RPE cells and the adjacent blood–retina barrier; in response, the adjacent RPE cells release trophic factors and cytokines, and both these cells and endothelial cells in retinal capillaries proliferate and replace the destroyed ones, allowing the recovery of the blood–retina barrier within a few weeks (Matsumoto et al., 1994; Wilson et al., 2003). At the same time, the oxygenation of the inner retina improves (Stefansson, 2001) and, in combination with anti-angiogenic factors released by the RPE cells (Ogata et al., 2001; Yoshimura et al., 1995), leads to retinal vasoconstriction and VEGF reduction, with a consequent leakage decrease (Wilson et al., 2003). This improvement in oxygen may, in part, be due to the destruction of a few highly oxygen-dependent optical cells (Stefansson, 2001).

5.2 Techniques

Several types of laser wavelengths are available for photocoagulation. For the treatment of DME, the wavelengths mainly used are the green wavelengths (Argon [514 μm] and doubled frequency Nd: YAG [532 μm]) and the red/infrared wavelengths (Krypton [647 μm] and Diode [810 μm]). Of them all, the most used and studied is the argon green laser. Compared with the "green" lasers, the "red" lasers are less absorbed by the hemoglobin, which can useful in the presence of an intraocular hemorrhage, and produce less damage to the inner retina.

Laser treatments can be applied in different patterns and in pulses with different characteristics. The standard treatment guidelines were provided by the ETDRS (ETDRS, 1987). Patients with mild to moderate nonproliferative DR are treated with laser therapy, as soon as CSME is detected. The focal pattern is preferred for leaking microaneurysms, while the grid pattern is preferred for diffuse areas of macular edema more than 500 μm from the central macula or optic nerve and for nonperfused thickened retina. For proliferative DR, and selected cases of severe nonproliferative DR, once CSME is detected, the option is combination of scatter laser photocoagulation and focal laser photocoagulation. It is recommended that, whenever possible, laser treatment of DME should precede panretinal photocoagulation by at least 6 weeks, once macular exudation can increase after pan-photocoagulation. Patients should be scheduled every 3-4 months and retreatment is based on the persistence or recurrence of thickening and leakage. In patients with no visual symptoms that meet treatment guidelines, laser therapy should be considered to prevent an eventual vision loss. However, the decision should be based on several factors, such as the proximity of the exudates to the fovea, the status of the fellow eye, anticipated cataract surgery, and retinopathy approaching high-risk proliferative DR. In cases of treatment delay, a close follow-up is required for early progression detection and treatment.

The technique commonly used in clinical practice is the modified ETDRS treatment, a modification of the original technique used in the ETDRS, which basically consists of both focal closure of aneurysms and applications of light grid photocoagulation.

The development of subthreshold micropulse diode laser system allows the delivery of multiple pulses of very short duration (0.1 ms), in either a focal or grid pattern (Berger, 1997; Bhagat et al., 2009). The energy provided by each pulse is much lower than the one provided by the conventional laser photocoagulation. This lower energy is less dispersed to the surrounding structures, thus limiting most of the thermal damage to the target site (the RPE), minimizing the thermal damage on the photoreceptors and choriocapillaris. Therefore, most of the adverse effects of the conventional laser photocoagulation, such as scotomas, are avoided. Also, there are some economic advantages: it requires no cooling system, is more compact and cheaper to maintain, and has a longer operating time (Brancato et al., 1988). However, it presents some practical difficulties: as it leaves no visible scars, it is difficult to identify prior burns, making the placement of a grid or a retreatment potentially inaccurate. Therefore, a careful planning is required and fundus autofluorescence can be a useful tool when doing it.

Automated photocoagulation systems so far proved to be not very practical. In contrast, a semiautomated patterned scanning laser photocoagulator, commonly known as PASCAL®, has gained the interest of physicians, since it gives control over the treatment, unlike the fully automated systems. It usually uses Argon or DF-Nd: YAG wavelengths and can deliver one or multiple spots in a predetermined pattern in a single burst, with a pulse duration as fast as 10 ms. The advantages over conventional system are increased uniformity and precision of spot placement, reduction of treatment duration, and potential increase in safety due to reduced thermal diffusion (Blumenkranz et al., 2006). Due to shorter pulses, and therefore lower energy, lesions are usually barely visible, but they can be assessed by fourier-domain optical coherence tomography and fundus autofluorescence (Muqit et al., 2010).

5.3 Efficacy

Laser photocoagulation is mostly associated with vision stabilization, preventing further vision loss. The first major study demonstrating the efficacy of laser photocoagulation was the ETDRS study. This study concluded that focal argon laser photocoagulation could reduce the risk of moderate visual loss in eyes with CSME and mild to moderate nonproliferative DR, by at least 50%, for as long as 3 years. However, a visual improvement equal or superior to 15 letters was rare (ETDRS, 1985, 1987). In addition, no evidence has been found regarding any efficacy difference between the different wavelengths, in term of visual improvement and macular edema reduction (Akduman and Olk, 1997; Bandello et al., 2005; Casswell et al., 1990; Gupta et al., 2001; Khairallah et al., 1996; Olk, 1990; Tewari et al., 1998).

Unlike focal DME, diffuse DME tend to be more refractory to laser photocoagulation. A few studies suggested that the modified ETDRS treatment could effectively improve VA in diffuse DME eyes, although the effect persisted only for about 2 years (Ladas and Theodossiadis, 1993; Olk, 1986). When compared with the modified ETDRS treatment, a mild macular grid laser technique revealed a trend to worse outcomes after 1 year (Fong et al., 2007).

The subthreshold micropulse diode laser is as effective as the modified ETDRS treatment and the Nd:YAG laser photocoagulation in both vision improvement and macular edema reduction, at least for the first year (Figueira et al., 2009; Kumar et al., 2010; Laursen et al., 2004; Venkatesh et al., 2011; Vujosevic et al., 2010). According to a nonrandomized study, the treatment of diffuse CSME with subthreshold micropulse diode laser can resolve the macular edema in 92% in 2 years and stabilize VA in about 80% of the patients for at least 3 years (Sivaprasad et al., 2007). One recent study suggests that in 1 year, a high-density micropulse diode laser technique can provide superior anatomic and functional outcomes than the modified ETDRS treatment (Lavinsky et al., 2011). These results suggest that patients are probably overtreated with the conventional laser therapy.

A retrospective study shows promising results for DME with PASCAL®, demonstrating comparable outcomes to the standard focal laser treatment in a 4 months follow-up period (Jain et al., 2010).

Several clinical features have been shown to predict visual outcomes after photocoagulation. The ones that predict a poorer visual outcome are diffuse macular edema with central-involvement, diffuse fluorescein leakage, macular ischemia, hard exudate deposits in the fovea, marked cystoid macular edema, and greater baseline retinal volume. In contrast, a worse baseline VA is associated with more frequent VA improvement. Prior macular or panretinal photocoagulation, demographic factors, diabetes-related factors (type, duration, HbA1c, systolic or mean arterial blood pressure), anomalies detected by optical coherence tomography (cystoid abnormalities, subretinal fluid, vitreoretinal abnormalities), and fundus photograph findings (retinopathy severity, hemorrhage, microaneurysms, exudates, surface wrinkling) were not associated with the VA outcome (Aiello et al., 2010).

5.4 Safety

The adverse events that occur are, directly or indirectly, caused by thermal damage to the retina and/or choroid and can compromise quality of vision, and thus cause symptomatic visual loss, especially with repeated treatments. The main adverse events reported are scars. Its progressive enlargement may lead to decreased color vision and contrast sensitivity and/or loss of central vision, central and paracentral scotomas, choroidal neovascularization, and subretinal and macular fibrosis. In addition, accidental burns of the macular center and RPE metaplasia have also been reported (Bhagat et al., 2009; Thompson and Ip, 2004). Very short duration laser pulses minimize the risk for these complications.

6 Corticosteroids

6.1 Mechanism of action

The exact mechanism of action of corticosteroids in the treatment of macular edema is unknown. It seems that corticosteroids reduce vascular leakage in several ways: increasing tight-junction proteins (Antonetti et al., 2002); reducing the expression of VEGF (Edelman et al., 2005; Sears and Hoppe, 2005), interleukins and other cytokines (Sohn et al., 2011), and prostaglandins (by inhibition of the cyclooxygenase) (Martidis et al., 2002); and suppressing the influx of leukocytes into the retina, reducing leukostasis (Tamura et al., 2005).

6.2 Techniques of delivery

Treating DME with systemic corticosteroids is not practical because its prolonged systemic use is harmful to the metabolic control. Local ocular delivery is therefore the best option. Corticosteroids have been tested in different doses and administration routes (periocular and intravitreal injections and intravitreal slow drug release devices).

Intravitreal injections provide an excellent delivery to the retina and choroid with low systemic exposure, but the levels tend to decrease fairly quickly, requiring frequent injections, which is not convenient.

A less invasive and consequently thought to be safer alternative to intravitreal injections are peribulbar injection, which can be performed using anterior subtenon/subconjunctival, posterior subtenon, and retrobulbar approaches. Some authors consider this administration route not ideal to obtain a therapeutic dosage in the retina, while others demonstrate that a correct application of the injection allows therapeutic quantities in the macular area (Freeman et al., 1987; Thomas et al., 2006). There are some evidences that a superotemporal placement technique may lead to a more accurate placement of drugs near the macula (Freeman et al., 1987).

Intravitreal sustained drug delivery systems are another alternative that has gained some interest in recent years. These allow the continuum delivery of low doses of corticosteroids over long periods of time, thereby avoiding the need for repeated injections and the wide fluctuations in drug concentrations.

6.3 Intravitreal injections (triamcinolone acetonide)

The magnitude of the effect of IVTA is dose related: higher doses lead to a more pronounced and prolonged treatment response. However, among lower doses (from 2 to 6 mg) the therapeutic differences are not significant (Audren et al., 2006b; Beck et al., 2009; Kim et al., 2008; Lam et al., 2007b; Network, 2008; Spandau et al., 2005). Despite the optimal dose for the DME treatment is not yet defined, the 4 mg dose has been empirically chosen in the majority of the studies.

The therapeutic effects provided by a single IVTA (4 mg) injection are transient, not lasting more than 6 months. Therefore, additional injections are required to maintain the improvements over time. Visual improvement can occur in 3-4 weeks, but after a maximum gain, it gradually deteriorates (Kang et al., 2006; Lam et al., 2007a). Unfortunately, the VA continues to deteriorate with additional injections, and, eventually, around the 16^{th} month after the first injection it can become worse than at baseline (Beck et al., 2009; Kang et al., 2006; Lam et al., 2007a; Network, 2008). Some evidences suggest that this drop of efficacy may not be only the result of corticosteroid-induced cataract progression (Beck et al., 2009; Network, 2008). On the other hand, the anatomical performance is much better. Although a single injection can only sustain a significant reduction for little more than 3 months (Kang et al., 2006), additional injections, performed as needed every 4 months, can maintain the reduction for at least 3 years (Beck et al., 2009; Lam et al., 2007a; Network, 2008).

In cases of persistent or recurrent DME after laser treatments, short term results are promising (Audren et al., 2006a; Dehghan et al., 2008; Jonas et al., 2006; Larsson et al., 2009) and with a retreatment regimen as needed with IVT and laser, the therapeutic effect can be extended for at least 5 years (Gillies et al., 2009; Gillies et al., 2006; Sutter et al., 2004). However, by itself, IVTA may not be enough to provide sustained benefits at long-term, at least not better than laser (Ockrim et al., 2008). Refractory DME with cystic changes also responds to IVTA (Dehghan et al., 2008), even with lower dosages (1 or 2 mg) (Hauser et al., 2008); cystoid DME might beneficiate from a greater benefit with IVTA than the diffuse type (Kim et al., 2008).

IVTA also shows promising results as a primary treatment (Norlaili et al., 2011).

A few factors have been associated with the therapeutic response to IVTA. Greater anatomical and functional outcomes occur in eyes with worse baseline thickening and VA levels, respectively (Mohamed et al., 2009). Presence of macular ischemia is associated with poorer visual outcome (Jonas et al., 2005). The type/pattern of macular edema may also be important (Gibran et al., 2007).

A nonrandomized study suggests that IVTA could be a valuable tool in DME eyes with serous macular detachment; although recurrence does occur, re-injections results are tend to be as good as the ones obtained with the initial injection (Ozdemir et al., 2005).

Compared with laser, a regimen of multiple IVTA injections, in 4-month intervals, can provide superior anatomical and functional outcomes for the first 4 months. However, due to the progressive improvement with laser therapy and the decrease of the IVTA effect, the differences

dissolve after the first year. Around the 16th month of treatment, laser becomes significantly superior, remaining that way for at least another year (Beck et al., 2009; Lam et al., 2007a; Network, 2008). Like IVTA in monotherapy, a combined treatment sequence of an IVTA injection 3 to 6 weeks before the laser session, with retreatment as needed, shows better anatomical than functional results over time (Aydin et al., 2009; Gillies et al., 2010, 2011; Kang et al., 2006; Lam et al., 2007a). It also does not seem to provide significant advantages over laser monotherapy at long-term (2 years) (Gillies et al., 2010, 2011; Lam et al., 2007a). But, some benefits can be found; the combined treatment allows an earlier visual recovery (Aydin et al., 2009), a more sustained visual improvement (Kang et al., 2006), a slower recurrence of the macular edema (Kang et al., 2006; Lam et al., 2007a), and a lesser need for additional injections and laser treatments (Mohamed et al., 2009). In contrast, a concomitant association (laser immediately followed by IVTA) should be avoided, since it may lead to a worsening of the VA (Aydin et al., 2009).

In cases of DME with moderate to high-risk proliferative DR, the combination of IVTA with standard treatment (pan-retinal photocoagulation plus macular photocoagulation) or simply with pan-retinal photocoagulation shows superior results over the standard treatment alone. However, while in moderate risk cases the therapeutic effect can be maintained for 1 year (Maia et al., 2009), in high risk cases the superiority can only be maintained for a much more shorter period (Choi et al., 2007; Mirshahi et al., 2010). In addition, IVTA can also reduce the risk of short-term exacerbation of macular edema (and consequent associated VA loss) after pan-retinal photocoagulation, at least in short-term (Googe et al., 2011).

A small nonrandomized prospective study suggests that the adjunctive use of IVTA after vitrectomy should be avoided, because 1 year later the recurrence may be worse than with vitrectomy alone (Shimonagano et al., 2007a).

6.4 Peribulbar injections (triamcinolone acetonide)

Peribulbar route (by both posterior subtenon's triamcinolone acetonide injection [40 mg] and anterior subtenon's triamcinolone acetonide injection [20 mg]) was thought to be a good initial approach in eyes with mild DME and good VA. However, the results were disappointing, and further studies were not recommended (Chew et al., 2007).

In more severe diffuse DME, a single posterior subtenon's triamcinolone acetonide injection, combined with grid laser or not, can provide anatomical and functional improvements in some cases, with the effects lasting little more than 3 months. However, these improvements are not as good and sustained as the ones provided by a single IVTA (4mg) injection (Chung et al., 2008a; Yalcinbayir et al., 2011). On the other hand, in eyes with cystoid DME, the posterior subtenon injection approach seems to provide a longer effect than the intravitreal approach (Cellini et al., 2008) and combined with laser may provide a better chance of stabilizing vision loss than photocoagulation alone (Kuo et al., 2009).

As primary treatment for diffuse DME, posterior subtenon's triamcinolone acetonide injection can also provide an additive effect to laser. The improvement appears more prominent when the baseline ETDRS score is superior to 40 letters (Tunc et al., 2005). In contrast, it presents

no value in refractory to laser DME eyes (Bonini-Filho et al., 2005; Cardillo et al., 2005), even with additional injections (Entezari et al., 2005), and also as an adjuvant treatment to phacoemulsification (Takata et al., 2010).

Nonrandomized studies suggest that posterior subtenon's triamcinolone acetonide injection may perform better in vitrectomized eyes, even if they are refractory to vitrectomy (Koga et al., 2005; Sato et al., 2008; Wada et al., 2005).

As for factors that influence peribulbar injections' performance, the local of injection is one of the most important. It was shown that a precise placement of corticosteroids in the subtenon's capsule space, in direct proximity to the macula, might influence both the effectiveness and the side effects of the drug. (Freeman et al., 1987; Mueller et al., 1998). Drug reflux at the time of the injection is also a risk factor for treatment failure (Shimura et al., 2009).

6.5 Intravitreal delivery systems

Retisert® (Bausch & Lomb) is a non-biodegradable delivery platform implant providing fluocinolone acetonide. Its implantation and removal, once drug depletion, requires a surgical procedure in an operating room. It is sutured to the anterior eye wall and provides a highly reliable and stable long-term drug delivery (Driot et al., 2004). The initial release rate is 0.60 µg/day, decreasing in 1 month to a stable rate of 0.3-0.4 µg/day, and its life span is about 30 months (Jaffe et al., 2000). This implant is currently approved for the treatment of chronic noninfectious posterior uveitis. **Iluvien**® (Alimera Sciences) consists in very small non-biodegradable cylindrical tubes that have a polymer matrix loaded with fluocinolone acetonide (Campochiaro et al., 2011; Campochiaro et al., 2010). The device is inserted into the vitreous cavity through a 25-gauge needle, not needing a surgical procedure or an operating room. It can deliver the drug at a rate of 0.5 or 0.2 µg/day. When the drug supply is depleted, another one can be administered; the limit number of inserts that can be tolerated is unknown.

In eyes with persistent or recurrent DME, both Retisert® (Pearson et al., 2011) and Iluvien® (Campochiaro et al., 2011; Campochiaro et al., 2010) can provide significant macular edema reduction and VA improvement for about 2 years, reflecting the drug lifespan. They also decrease the need of additional laser treatment. However, there are some VA fluctuations, thought to be related to cataract formation and extraction.

Ozurdex® (Allergan Inc.) is a biodegradable drug delivery system that allows sustained-release of dexamethasone. Inserted into the vitreous cavity through a 22-gauge needle, it can deliver the drug at a rate of 350 or 700 µg/day and its life span is about 6 months. It is approved for the treatment of macular edema caused by retinal vein occlusion (Haller et al., 2010). In eyes with persistent or recurrent DME, the significant therapeutic improvement lasts for little more than 3 months and a release of 700 µg/day shows better efficacy than 350 µg/day (Haller et al., 2010). Vitrectomized patients with persistent or recurrent DME may also benefit from Ozurdex®, according to a nonrandomized study (Boyer et al., 2011).

6.6 Safety of corticosteroids

Despite the majority of the randomized studies are limited by the short follow-up and participant numbers, their combined evidences reveal that, in general, and regardless of the application route, the most common corticosteroid-related vision-threatening complications are the intraocular pressure (IOP) increase and the development and progression of cataract.

With IVTA and fluocinolone acetonide intravitreal delivery systems (Audren et al., 2006a; Audren et al., 2006b; Aydin et al., 2009; Beck et al., 2009; Campochiaro et al., 2011; Campochiaro et al., 2010; Choi et al., 2007; Dehghan et al., 2008; Gillies et al., 2011; Gillies et al., 2009; Jonas et al., 2006; Kang et al., 2006; Lam et al., 2007a; Lam et al., 2007b; Larsson et al., 2009; Lee et al., 2009; Maia et al., 2009; Ockrim et al., 2008; Pearson et al., 2011; Spandau et al., 2005) the elevation of IOP is usually mild to moderate, transient and controllable with topical antiglaucomatous medication, without future sequels. However, in some cases it can lead to secondary glaucoma and surgery might be required. The risk can reach 80% or more in 5 years and the first episode can occur in the first months (usually in the 2nd). Higher doses tend to increase the probability of IOP elevation and glaucoma; this might be the reason for the higher risk associated to Retisert® compared with Iluvien®. As for the progression of cataracts, it is progressive and, in most cases, only evident after 1 year and/or multiple doses. At least 2/3 end up requiring cataract surgery in 5 years, which can, in a few patients, exacerbate macular edema, leading to poorer outcomes. Unlike the elevation of IOP, cataract development seems less dose-dependent. Regarding the dexamethasone delivery system, the incidence of increased IOP seems lower than with IVTA, however, study follow-up was too short to allow long-term conclusions regarding incidence of both IOP increase and cataract progression (Haller et al., 2010).

Other adverse effects reported with intravitreal approaches are: vitreous hemorrhage, pruritus, vitreous floaters, subconjunctival hemorrhage, retinal detachment, corneal epithelial defect, abnormal sensation in the eye, eye pain, and endophthalmitis. They are generally transient and thought to be related to the implantation and injection procedures.

High-dosage IVTA may not necessarily have a higher side effects profile than low-dosage IVTA (Jonas et al., 2006). In contrast, multiple injections predispose to the cumulative risk of injection-related and drug-related (Gillies et al., 2009; Jonas et al., 2003) complications.

No systemic drug-related adverse events have been reported. In fact, triamcinolone acetonide is barely detected in the serum after an intravitreal injection of 20 mg (Degenring and Jonas, 2004).

The peribulbar approach is clearly less invasive than the intravitreal approaches and shows fewer vision-threatening complications (Cellini et al., 2008; Chung et al., 2008a). In short-term, the elevation of IOP seems lower than with IVTA, although the association of posterior approach with IOP elevation is less certain (Chew et al., 2011). Short follow-up period unable cataract discussion, with the exception of the anterior approach, which has been associated with an increased risk of cataract development, compared with laser and posterior peribulbar approach. Other potential injection- or infusion-related complications are: ptosis, accidental injection directly into the

choroidal or retinal circulation, perforation of the ocular bulb, occlusion of the central retinal artery, blepharoptosis, orbital fat atrophy, strabismus, conjunctival necrosis and ulceration, and endophthalmitis (Agrawal et al., 2003; Cellini et al., 2008; Chew et al., 2007; Chew et al., 2011). These complications are rare when the injection is properly given.

7 Anti-VEFG Therapy

7.1 Mechanism of action

VEGF plays a key role in the pathophysiology of DME. Thereby, VEGF blockage became an attractive therapeutic approach. After the first evidences that VEGF inhibition could effectively prevent experimental diabetic blood–retina barrier breakdown and also revert DME once it has occurred, VEGF inhibitors have been studied, in the last decade, as a therapeutic option for DME.

Bevacizumab, ranibizumab, pegaptanib and aflibercept bind to VEGF, preventing interaction with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells, thereby, nullifying its biological effect.

7.2 Intravitreal bevacizumab

Bevacizumab (Avastin®, Genentech Inc.) is a full-length recombinant humanized monoclonal IgG1 antibody directed at all isoforms of VEGF-A. Originally used in the treatment of various cancers, it is being used off-label as a treatment for DME.

The optimal dosage and algorithm for DME treatment are still not defined, but the majority of studies use a 1.25 mg dose. There is no evidence that a higher dose of 2.5 mg provides a significantly superior efficacy (at least in the first 6 months), so the lower dose is recommended (Lam et al., 2009; Scott et al., 2007). A single intravitreal bevacizumab (IVB) (1.25 mg) injection can reduce the macular edema in 24h, but the VA needs about 1 week to significantly improve (Sonoda et al., 2011). The effect lasts for little more than 12 weeks (Isaac et al., 2012; Wang et al., 2011), therefore, multiple injections are needed to sustain the effects for longer periods (Michaelides et al., 2010; Soheilian et al., 2009).

When compared with standard laser treatment, IVB demonstrates a significantly greater macular edema reduction (Scott et al., 2007). When in combination, focal laser applied 3 weeks after IVB does not seem to provide any additional short-term benefit over IVB monotherapy (Scott et al., 2007), but grid laser, also applied 3 weeks after IVB, is able to maintain the functional and anatomical improvements of a single IVB injection for a longer period of time in eyes with diffuse CSME (Solaiman et al., 2010).

In short-term, both IVTA (2 and 4 mg) and combination of IVB (1.25 mg) and IVTA (2mg) are anatomically and functionally more efficient than IVB (1.25 mg) alone (Isaac et al., 2012; Lim et al., 2012). However, after 1 year of treatment no significant differences can be seen between them, so IVB/IVTA association provides no significant additional benefit over IVB monotherapy (Lim et al., 2012; Wang et al., 2011). In contrast, the improvements may persist

longer with IVB alone than with IVB/IVTA association (36 weeks vs. 12 weeks), with or without additional injections (Soheilian et al., 2009).

Similar performance for IVB (compared to and/or associated to IVTA or laser) is found in treatment naïve eyes (Faghihi et al., 2008; Marey and Ellakwa, 2011; Shahin and El-Lakkany, 2010; Soheilian et al., 2007) and in eyes with refractory/persistent DME, even when center-involving (Ahmadieh et al., 2008; Michaelides et al., 2010; Paccola et al., 2008; Synek and Vesely, 2011). However, there are some evidences that in treatment naïve eyes it can be more effective than in eyes that had any prior treatment (Lam et al., 2009; Scott et al., 2007).

A prospective nonrandomized study (Kook et al., 2008) suggests that IVB can even be benefic in cases of chronic diffuse ischemic DME, but the preexisting macular ischemia limits the potential treatment benefits (Chung et al., 2008b).

IVB can also be useful in preventing the exacerbation of macular edema in diabetic patients undergoing cataract surgery. A single IVB injection has the potential not only to prevent the increase, but also reduce the macular edema and improve the VA, for at least 6 months (Cheema et al., 2009; Lanzagorta-Aresti et al., 2009; Takamura et al., 2009), although, in some cases, the positive effect lasts for a shorter period of time (Fard et al., 2011).

7.3 Intravitreal ranibizumab

Ranibizumab (Lucentis®, Novartis Pharma AG and Genentech Inc.) is a Fab fragment of a full-length recombinant humanized monoclonal IgG1 antibody that binds to the receptor-binding site of active forms of VEGF-A. As the Fab derivate of bevacizumab, its molecular weight is a fraction of the bevacizumab's weight (~48 kilodaltons vs. ~149 kilodaltons, respectively), which may explain its shorter intravitreal half-live in animal studies (3.2 vs. 5.6 days) (Stewart et al., 2012).

Already approved for the treatment of macular edema associated with retinal vein occlusion and age-related macular degeneration, it was recently also approved by the European Medicines Agency for the treatment of DME, based on evidence from the RESOLVE (Massin et al., 2010) and RESTORE (Mitchell et al., 2011) trials.

A single intravitreal ranibizumab (IVR) (0.5mg) injection is capable of reduce macular edema in about 1 hour and significantly improve the VA in 24 hours, although the maximum effect is only achieved after approximately 14 days (Querques et al., 2009b). After 1 month the effect starts to decrease, so additional injections are required to maintain the therapeutic levels. In general, a regimen of multiple injections of IVR, in a minimal interval of 4 weeks, can provide significant VA increase and macular edema reduction for at least 2 years (Massin et al., 2010; Mitchell et al., 2011). These results are also observed in patients with recurrent or persistent DME (Nguyen et al., 2009; Nguyen et al., 2010).

A small retrospective study suggests that despite no significant difference between one injection of IVB and IVR in terms of visual improvement (4.5 vs. 6 ETDRS letters, p=0.58,

respectively), a difference might exist in the degree of macular edema reduction, being greater with IVR (41 vs. 100 μm, p=0.005) (Ozturk et al., 2011).

The combination with laser photocoagulation does not seem to provide any functional or anatomical advantage over IVR monotherapy (Mitchell et al., 2011; Nguyen et al., 2009; Nguyen et al., 2010). In fact, in some cases, it can lead to a slower visual improvement rate compare with IVR alone (Nguyen et al., 2009; Nguyen et al., 2010). On the other hand, additional laser allows a decrease in the need for additional injections to control the edema. Delaying in 6 months the beginning of the laser sessions, instead of starting it closer to the IVR treatment, also does not seem to result in any difference (Elman et al., 2010; Elman et al., 2011). Compared with laser alone, IVR, associated or not with laser, demonstrates therapeutic superiority (Elman et al., 2010; Elman et al., 2011; Mitchell et al., 2011; Nguyen et al., 2009; Nguyen et al., 2010).

In addition, IVR may provide some short-term benefits in eyes receiving pan-retinal photocoagulation for DR and laser for DME by reduce the risk of short-term exacerbation of macular edema (Googe et al., 2011).

The approval of ranibizumab by the European Medicines Agency led a panel of experts to elaborate the first guidelines for its clinical use. Their recommendation is to use ranibizumab in monotherapy when visual impairment due to center-involving DME. Center-involving DME with no vision loss and no center-involving DME cases should follow the ETDRS guidelines. Injections are given on a monthly basis until normal VA or VA stability is achieved. If VA deteriorates again after treatment interruption, monthly injections should be reinitiated until a new stabilization is achieved. Addition of laser is neither recommended nor rejected; for now it is up to the physician's discretion. Non-responders to the therapy should discontinue it and try other treatment options (Bandello et al., 2012). Updates to these guidelines may occur as more results from longer-term studies become available.

7.4 Intravitreal pegaptanib sodium

Pegaptanib (Macugen®, Pfizer Inc. and OSI Pharmaceuticals Inc.) is a VEGF aptamer that binds to the VEGF-165 isomer inhibiting the interaction with its receptors. It is an approved treatment for age-related macular degeneration and an off-label treatment for DME.

In terms of dosage, there are some indications that a 0.3 mg can be more effective than 1 and 3 mg, although differences between 0.3 and 1 mg are very small (Cunningham et al., 2005).

In patients with DME, center-involving or not, a regiment of multiple injections of pegaptanib (0.3 mg), 6 or more weeks apart, with the possibility of focal/grid photocoagulation after the 18th week, demonstrates significantly better outcomes than sham (Loftus et al., 2011; Sultan et al., 2011), even as primary therapy (Cunningham et al., 2005). The visual benefits appear to be more outstanding than the anatomical ones. This beneficial visual effect can be observed in 6 weeks after the first injection and persists for at least 2 years, although slightly better during the 1st year of treatment (Sultan et al., 2011). Also, pegaptanib decreases the need for additional laser therapy (Sultan et al., 2011).

A retrospective study suggests that, as primary therapy, pegaptanib, in 6 month, may be significantly superior to both laser and combination of pegaptanib with laser (Querques et al., 2009a).

7.5 Intravitreal aflibercept

Aflibercept (VEGF Trap-Eye®, Regeneron Pharmaceuticals Inc. and Bayer Healthcare Pharmaceuticals) is a fully human recombinant fusion protein composed by the VEGF receptors domains and the Fc region of human IgG1, which binds to all VEGF-A isoforms and also to placental growth factor (Holash et al., 2002). Animal studies suggest that it has theoretical advantages over ranibizumab and bevacizumab, including a longer life span and a higher binding affinity to VEGF-A.

The DA VINCI phase 2 Study has recently shown some primary good results using aflibercept in DME patients. VEGF Trap-Eye (0.5 and 2 mg), in various retreatment schedules, shows significant and clinically relevant VA improvement, as well as macular edema reduction, which are superior to laser, for at least 6 months (Do et al., 2011).

7.6 Safety of anti-VEFG Therapies

The overall safety profile is similar between bevacizumab, ranibizumab and pegaptanib sodium and consistent with that observed in patients with neovascular age-related macular degeneration treated with these VEGF inhibitors (Brown et al., 2006; Singerman et al., 2008).

The incidence of drug-related ocular adverse effects is low, even with multiple injections. The great majority of reported ocular adverse is transient, mild to moderate in severity and considered injection-related (Ahmadieh et al., 2008; Cunningham et al., 2005; Do et al., 2011; Elman et al., 2010; Elman et al., 2011; Faghihi et al., 2008; Googe et al., 2011; Lam et al., 2009; Massin et al., 2010; Michaelides et al., 2010; Mitchell et al., 2011; Paccola et al., 2008; Scott et al., 2007; Shahin and El-Lakkany, 2010; Soheilian et al., 2009; Sultan et al., 2011; Wang et al., 2011). The most frequent are eye pain (up to 31% reported), conjunctival hemorrhage (up to 22%), and punctate keratitis (up to 18%). Other adverse effects also reported, are endophthalmitis (0.08-0,4%/injection), retinal detachment (<1%), vitreous hemorrhage (up to 5%), cataract formation and progression (up to 14%), IOP elevation (up to 17%), and transient mild anterior chamber reaction (up to 20%).

Regarding systemic side effects, the use of systemic VEGF inhibitors has been associated to cardiovascular events, cerebrovascular accidents, hypertension, and thromboembolic events. Because of the compromised blood–retinal barrier in diabetic patients, there is a potential higher risk of the passage of these drugs into the systemic circulation (Bhisitkul, 2006; Simo and Hernandez, 2008).

8 Vitrectomy

8.1 Techniques

There are reports in the literature of lower risk of macular edema development in diabetic patients with a posterior vitreous detachment (PVD) (Nasrallah et al., 1988), cases of reabsorption of macular edema after a spontaneous PVD (Hikichi et al., 1997) and a successful first trial with vitrectomy in 10 patients with DME and thickened taut posterior hyaloid (Lewis et al., 1992). Consequently, intraocular interventions through pars plana vitrectomy have been proposed as an alternative approach for DME treatment.

Induction of PVD by removal or detachment of posterior hyaloid is the main intervention. Triamcinolone acetonide can be used to facilitate the identification of vitreous remnants. Another technique, usually used after PVD induction, is the ILM peeling, a process that can be facilitated by the use of dyes (such as indocyanine green, trypan blue and, more recently, brilliant blue).

8.2 Mechanism of action

The mechanism by which vitrectomy may work is not fully understood. It is speculated that PVD removes local exacerbation factors, such as vitreous traction, and improves oxygen concentration on retinal cells. Also, the absence of the vitreous gel is thought to increase the transport of cytokines (such as VEGF) from the retina into the vitreous cavity (Stefansson, 2001, 2009).

It is speculated that normal ILM acts as a selective membrane. In DME it gets thicker, thus reducing its permeability (Saravia, 2011). With its removal, this disturbance could be resolved, therefore helping the resolution of the macular edema, for example, by further speeding up the clearance of cytokines from the retina. Also, absence of ILM may activate the repair mechanisms of Müller cells and can eliminate a reservoir of growth factors in residual vitreous cortex that remains adherent to the ILM after surgical vitreous separation (Hoerauf et al., 2011; Sonoda et al., 2004).

8.3 Efficacy

In general, the vitrectomy results in DME eyes are not satisfactory. It has been suggested that benefits may be limited to patients with vitreomacular traction and/or taut thickened posterior hyaloid (Laidlaw, 2008).

In diffuse DME cases with no evidence of macular traction, regardless the technique, the benefits are limited and appear slowly (Bardak et al., 2006; Doi et al., 2012; Kumar et al., 2007). In cases of persistent DME after laser therapy, vitrectomy, with or without ILM peeling, can provide some benefits, mainly in younger patients. However, the improvement, eventually superior to laser, persists for no longer than 1 year (Bahadir et al., 2005; Stolba et al., 2005; Yanyali et al., 2006), after which laser seems to provide better results (Patel et al., 2006a; Thomas et al., 2005).

Curiously, some retrospective studies, unlike randomized studies, suggest better visual outcomes with vitrectomy in eyes with diffuse DME with no macular traction, with the effectiveness maintained for years (Kumagai et al., 2009; Shimonagano et al., 2007b).

It is not clear if ILM peeling is necessary. Several studies report no significant benefit over PVD induction alone (Bahadir et al., 2005; Bardak et al., 2006; Figueroa et al., 2008; Mochizuki et al., 2006; Patel et al., 2006b; Shiba et al., 2009). However, in cystoid-type DME cases, while PVD induction alone seems to provide no benefit, adding ILM peeling may lead to a reduction of the macular edema and a better VA stabilization; in eyes with preexisting PVD, ILM peeling may actually increase the VA (Hoerauf et al., 2011).

According to a nonrandomized study, a few factors may predict the therapeutic response to vitrectomy. Greater VA improvement was associated with worse baseline VA and epiretinal membrane removal. Greater reduction in macular thickness was associated with worse baseline VA, greater preoperative retinal thickness, removal of ILM, and vitreoretinal abnormalities (Flaxel et al., 2010).

8.4 Safety

In surgery there is always a potential risk of complications. The most frequently reported complications related to vitrectomy, with or without ILM removal, are cataract formation (usually not evident before the 1st year), retinal tears, (rhegmatogenous) retinal detachments, epiretinal membrane formation, vitreous hemorrhage, cell flare in the anterior chamber, lamellar macular hole formation, hard exudates deposits in the center of the macula, glaucoma, choroidal detachment, fibrinoid syndrome, and macular ischemia (Bhagat et al., 2009; Stolba et al., 2005; Yanyali et al., 2005). The incidence of intra and postoperative complications does not seem to differ among the different techniques, except when triamcinolone acetonide is used, leading to an IOP increase (Shiba et al., 2009). As for the long term effects of mechanical injury of ILM peeling, surgical skills are very important, but the ILM staining long-term effects are still unknown. Indocyanine green dye is potentially toxic to the retina (Gandorfer et al., 2001; Haritoglou et al., 2001). Despite no toxicity reports with a 0.5 mg/ml dose in a minimum contact time, due to concerns, indocyanine green is no longer recommended to assist the ILM peeling.

9 Other potential pharmacological therapeutics

Ruboxistaurin is a specific protein kinase C beta inhibitor and therefore leads to VEGF-induced leakage reduction. In an oral 32-mg/day dosage, it reduces the retinal vascular leakage, the progression to sight-threatening CSME and consequent rate of VA loss in eyes with severe DME. The clinical benefit may be more prominent in cases of severe macular edema (Aiello et al., 2007; Aiello et al., 2006; Davis et al., 2009; Strom et al., 2005). It is well tolerated, unlike multitarget kinase inhibitors, which are associated with more frequent adverse events (Campochiaro, 2004)

Infliximab is a chimeric monoclonal antibody specific for human anti–tumor necrosis factor. The short-term outcomes of intravenous infliximab (5 mg/kg) in laser-refractory DME eyes, with severe VA impairment, are promising (Sfikakis et al., 2010). The safety is unknown; however,

postmarketing surveillance data in thousands of patients treated with infliximab for other conditions show an excellent safety profile (Sfikakis, 2010). There are some evidences that the intravitreal approach may not provide the same performance and may actually lead to more serious ocular adverse effects (Wu et al., 2011).

Sirolimus, also known as rapamycin, is a macrolide that, in complex with the immunophilin FK binding protein 12, inhibits the mammalian target of rapamycin, which is a key point of convergence for multiple intracellular regulatory pathways. This results, among others, in the inhibition of the expression and signaling of VEGF, inhibition of the activity of protein kinase C, and down regulation of the hypoxia-inducible factor 1α. The first randomized, dose-escalation study of sirolimus in DME patients suggests that both intraocular and subconjunctival injections (220 to 1760 μg) can provide therapeutic effects and are well-tolerated (Dugel et al., 2012).

Due to potential surgical complications of vitrectomy, a few intravitreal drugs (such as autologous plasmin and tissue plasminogen activator) have been used to induce PVD without the need for vitrectomy. In diffuse DME, intravitreal **autologous plasmin** is able to reduce the macular thickening and improve VA, either as a primary treatment or in laser-refractory cases (Diaz-Llopis et al., 2009; Diaz-Llopis et al., 2008). The efficacy and toxicity is dose-dependent and a 0.4 IU dosage was demonstrated to be sufficient to separate the posterior vitreous cortex from the ILM without retinal toxicity (Azzolini et al., 2004; Wang et al., 2004). Intravitreal **tissue plasminogen activator** (25 μg) is able to induce PVD in patients with refractory DME, but without therapeutic benefit (Abrishami et al., 2011). However, the benefits from PVD induction are known to appear slowly and the study has a very short follow-up period, so it is expected that therapeutic responses may occur over time.

Diclofenac, a nonsteroidal anti-inflammatory drug, inhibits the cyclooxygenase and lipooxygenase pathways. A recent report shows that short-term outcomes of intravenous diclofenac (500 μg) in diffuse DME eyes are promising, with comparable anatomical results to IVTA and no IOP increase. In 12 weeks, the functional improvement is lower compared with IVTA, but it is possible that with longer follow-up it may be at least identical (Elbendary and Shahin, 2011).

Other drugs that also have shown interesting results are topical difluprednate eye drops (0.05%) (Nakano Goto et al., 2011; Nakano et al., 2010) and topical dexamethasone-cyclodextrin eye drops (Tanito et al., 2011). In addition, oral fenofibrate (200 mg/day) may be an adjuvant to photocoagulation, since it can reduce the need for laser treatment (Keech et al., 2007).

10 Conclusions and future directions

This review tried to gather as much evidence as possible concerning the treatment of DME in an attempt to analyze the results of recently used therapies and, if possible, predict the future trends in the following years.

The literature search method for this review was based on online Medline Pubmed database searches, the last one in January 2012. Randomized studies results, as the most reliable source of scientific evidence, were privileged. A meta-analysis is very difficult to perform, due to several limitations. Besides limitations inherent to short sample sizes and follow-up periods, there

is also great variability when assessing results. The effectiveness of a specific treatment for DME is assessed mainly by anatomical (macular edema) and functional (vision acuity) parameters and there is a lack of uniformity among the studies while measuring these parameters: some measure the general macular thickness while others just the foveal thickness; for visual assessment some use the ETDRS charts (considered the most accurate and therefore the one required by FDA) and others the Snellen charts (considered faster and easier to use in clinical practice). Also, there are differences in the participants' baseline characteristics between studies. For all these reasons, the comparison of results between studies for different therapies or even for the same therapy may be quite challenging. Nonetheless, despite obvious limitations, and assuming that future studies will confirm the trends exposed in this review, a prediction for the near future treatment of DME can be made. However with the increasing number of drugs under investigation and the growing interest in this subject, as confirmed by the exponential rise in the number of published articles in this area, treatment guidance may drastically change in the next few years.

There is no cure for DME. Perhaps a cure will be possible once a cure for diabetes itself is accomplished. For now, the best way to deal with DME seems to be prevention, maintaining a tight blood sugar and pressure control in every diabetic patient, regardless of the presence of DME or any other diabetic-related retinopathy, as well as a regular monitoring to detect it as soon as possible.

Once DME is establish, only limited management options can be offered to patients. To date, the best-studied treatments are laser photocoagulation, corticosteroids, VEFG inhibitors, and vitrectomy. The choice between them can be complicated, but, taking into account the effectiveness and safety, some orientations were suggested. The treatment must be dynamic, applied and changed according to the disease stage and response to therapies. Tight blood sugar and pressure control must be a priority regardless of the severity of the disease, since it influences the response to other treatments.

In early CSME with no or little vision loss, laser photocoagulation should remain the first-line treatment to delay the progression as much as possible, because it is a very effective treatment and no advantages would be obtain from other therapies. Due to long-term safety advantages and equal effectiveness, subthreshold micropulse diode laser or PASCAL® should be preferred, when available. Greater vision loss and more advanced stages of DME tend to be more refractory to laser treatment and, even when there is a response, visual improvement is rarely satisfactory. This is when other treatment modalities must be employed, perhaps as primary treatment in an attempt to recover some VA; afterwards, laser can be applied to help stabilize the improvements. Among these alternatives, VEFG inhibitors should be the first option, corticosteroids should be reserved for more difficult cases, and vitrectomy should be considered only if evidences of vitreoretinal interface abnormalities are found. The reason for preference of VEFG inhibitors is based on the observation that, in general, they seem to provide similar long-term responses to IVTA with much less adverse effects. Intravitreal delivery systems of corticosteroids show better safety profile than intravitreal injections, since they work in lower doses, but even so, VEFG inhibitors seem safer. If the initial promising results are confirmed by future studies, ruboxistaurin, infliximab, sirolimus and diclofenac are very likely to become VEFG inhibitors' sidekicks and intravitreal PVD inducer

drugs, such as autologous plasmin, may become the substitute for vitrectomy in macular traction cases. Combination of therapies, preferably in sequence, can be tried, because different therapies may, in some cases, potentiate the effect of each other, due to the differing modes of action.

In the day-to-day practice, choice of therapies is based not only in effectiveness and safety but also in treatment costs. A tight monitoring of the adverse effects (mainly the IOP increase), an absence of history of ocular hypertension or glaucoma, and the fact that most diabetic patients will eventually need cataract surgery despite corticosteroids treatment, provides a risk–benefit ratio for intravitreal delivery systems of corticosteroids that justify their use over VEFG inhibitors. Ranibizumab was recently approved in some countries as treatment for DME. Other countries refuse ranibizumab considering it too expensive for the benefits it provides, preferring to wait for more bevacizumab studies, since it seems to provide similar clinical outcomes and is a cheaper alternative. After all, in the end, therapy decisions need to be discussed and made with patients, taking into account several patient-, treatment-, and cost-related factors.

The network-like character of the pathophysiology and the different responses to the same treatment by different patients and in the same patient over time suggest that some pathways contribute more than others and they may differ between patients and over time. Therefore, the optimal therapy needs to be multi-targeted. A substance with multiple targets might not be the solution, since it might lead to more frequent adverse effects, as seen with corticosteroids. A combination of selective drugs with different molecular targets might be a better answer. Because these drugs do not affect the underlying cause of DME and the condition tends to be chronic, once they are cleared from the vitreous the macular edema tends to reappear. Thus, intravitreal delivery systems with a long half-life are better than repeated injections, since they provide a long, continuous and stable drug delivery. Consequently, these also allow the use of lower and safer doses. So, the logical ideal therapy would be a long-duration intravitreal delivery system that provides several selective inhibitory drugs simultaneously. Perhaps, in the future, technical improvements will allow the creation of such a product, and it may, hypothetically, revolutionize DME treatment. On the other hand, several studies have shown that susceptibility to the development of DR may have a heritable component, independent of glycemic control and duration of diabetes; sequence variation in the VEGF-A gene is one example (Abhary et al., 2009). Therefore, the identification of specific genetic risk factors for diabetic retinopathy might improve not only the screening algorithms but also the treatment approach.

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