Macular edema in Branch Retinal Vein Occlusion: Novel Therapies.

A review study on safety and efficacy

Filipe Tiago Vilela de Sousa Neves

6th year medical student at the Faculty of Medicine, University of Coimbra, Portugal

ftvsneves@hotmail.com

ABSTRACT

Several treatment methods have been described for Macular Edema in Branch Retinal Vein Occlusion (BRVO). Grid laser photocoagulation has been the gold standard treatment for the past decades. The limited functional outcomes achievable by laser treatment and its induced cicatricial problems have prompted research on alternative therapies which included corticosteroid injections and implants, anti-vascular endothelial growth factor (VEGF) drugs and combined therapies.

The purpose of this study was to review the main types of treatment of this condition taking into consideration novel therapies and its safety and efficacy.

An extensive revision of literature has been made and the level of evidence was graded. Pubmed has been used as the main basis for research.

Focus has been directed into recent studies on the number and type of treatments needed to obtain a stabilized condition as it has an important economic impact, a better compliance by patients and an improved understanding by healthcare financial providers of services.

Results show new treatment options and suggest combined therapies as well as an option for methods that may result in fewer interventions.

RESUMO

Vários tratamentos têm sido descritos para o Edema Macular secundário a Oclusões Venosas Retinianas de Ramo. A fotocoagulação laser em grelha foi o tratamento de primeira linha nas últimas décadas. As suas limitações no resultado final associadas a alguns problemas cicatriciais catapultaram a investigação de terapias alternativas que incluíram injeções e implantes de corticosteroides, injeções de fatores anti-angiogénicos e tratamentos combinados.

O objetivo deste estudo foi a revisão dos principais tipos de tratamentos existentes para esta patologia tendo em devida conta terapias recentes e a sua respetiva segurança e eficácia.

Foi feita uma extensa revisão da literatura e foram anotados os respetivos níveis de evidência clínica. O Pubmed foi a principal base da pesquisa.

O principal interesse foi direcionado para o número e tipo de tratamentos necessários para a estabilização da doença publicados em estudos recentes. Estes fatores repercutem-se no impacto económico dos tratamentos, na melhor adesão por parte dos pacientes e numa melhor compreensão por parte dos financiadores dos cuidados de saúde.

Os resultados mostram novas opções terapêuticas e sugerem terapias combinadas assim como opções por métodos que possam resultar em menos intervenções.

KEYWORDS

Branch retinal vein occlusion, macular edema, laser treatment, corticosteroid injections, dexamethasone implant, anti-vascular endothelial growth factor, combined therapy, economic impact.

INTRODUCTION

BRVO is the second most common vascular disorder of the retina following diabetic retinopathy[1].

Loss of vision is caused by ischemia, retinal and/or vitreal hemorrhages and macular edema. Although the treatment of BRVO also involves looking into coexistent medical conditions, the aim of the present study was to analyze the existing several ways of treating outflow obstruction and improving vision by decreasing macular edema.

The Branch Retinal Vein Occlusion Study[1] published in 1984 has demonstrated some benefits of grid argon laser photocoagulation in patients with persistent macular edema and with a loss of vision equal or lower than 20/40 although some earlier studies like the one published by Shilling and Jones[2] had already cast doubts on the efficacy of photocoagulation specially in cases of perifoveal non perfusion. However it has become the mainstay treatment of this disorder and even in 2006 Battaglia et al presented a very small randomized study with similar results using subthreshold grid laser[3] presumably with no effects on laser scarring.

However the limited functional outcomes have prompted attempts on novel therapies: corticosteroid injections (triamcinolone acetonide) have been tried for their anti edematous and anti angiogenic properties and several small studies published[4-8] but only SCORE-BRVO

randomized studies[9,10] finally produced reliable results on reducing macular edema and side effects.

Dexamethasone implants, which may allow steroid delivery over a more sustained period, have been tried and the Ozurdex GENEVA study[11,12] produced interesting results not only because it diminishes macular edema over a longer period but also because it seems to produce less side effects and has been approved by official FDA in United States of America and EMA in Europe.

Anti-VEGF drugs have been introduced in the last few years to neutralize the effects of vascular endothelial growth factor which is key mediator not only of neovessels but also of macular edema. BRAVO trials[13], with even better visual results on the randomized study than its fellow trial based on central retinal vein occlusion (CRUISE)[14], have demonstrated the benefits of ranibizumab with consequent approval for treatment of macular edema by FDA and EMA. HORIZON[15] followed the previously mentioned studies in order to establish its efficacy and safety over a longer period. Bevacizumab, which has been widely used worldwide in several ocular pathologies as an *off label* product, has been the subject of several studies[16-20] and seem to present similar results to ranibizumab lacking nevertheless a well defined medium to long term randomized study to clear all doubts on efficacy and safety (clinical evidence level 3 of the US Agency for Health Research and Quality Scale) as it much cheaper than its approved counterpart. Pegaptanib has one of its best designed studies performed by Wroblewski JJ and colleagues in USA[21] which reached a clinical evidence 2 status on the benefits of treating macular edema following BRVO but it seemed to lack continuity. VEGF trap-eye is another product which has some promising perspectives as it presents a greater affinity to VEGF-A, B and PlGF (placental growth factor) than the actual medications but it lacks hard clinical evidence in the treatment of BRVO[22]. Copernicus and

Galileu are randomized studies undertaken in central retinal vein occlusion[23] with VEGF trap-eye monthly injections which may give an idea for its application in BRVO.

Taking into account efficacy, cost[24] and compliance by patients, we finally looked into different treatment schemes which could minimize the economic impact of these novel therapies as people demand for treatment is greatest and at the same time financial constraints are top priorities for health care and government decision makers.

EPIDEMIOLOGY AND PATHOGENESIS

The 4-year incidence of retinal vein occlusions has been estimated at 5.36/1000 in patients of age 64 years or older in 1996[25]. The most recently published study[26], dated 2010, and summarizing the prevalence of retinal vein occlusions as reported in studies from the United States, Europe, Asia and Australia has shown an age and sex standardized prevalence of 5.20 per 1000 (95% confidence interval [CI] 4.40–5.99) for any form of retinal vein occlusion. This study combined data regarding 68.751 individuals from 15 studies, with participants ages ranging from 30 to 101 years. The prevalence of BRVO was 4.42 per 1000 (95% CI 3.65–5.19). Prevalence varied by ethnicity and increased with age, but did not differ by gender. Prevalence of central retinal vein occlusion (CRVO) was lower than BRVO in all ethnic populations.

Hayreh et al.[27] showed that the probability of developing a second episode of occlusion in the other eye within 4 years is about 7%.

Therefore, BRVO occurs approximately three times more commonly than CRVO, and men and women are affected equally.

Most epidemiologic and histopathologic evidence implicates arteriolar disease as the underlying pathogenesis although its cause is generally multifactorial and still unclear. BRVO

almost always occurs at an arteriovenous crossing, where the artery and vein share a common adventitia sheath. This observation was first attributed to Leber, a German ophthalmologist over 100 years ago, who first suggested the vulnerability of arteriovenous crossing and the importance of arteriosclerosis in the pathogenesis of BRVO. The artery nearly always is anterior (innermost) to the vein[28]. It is postulated that that a rigid , arteriosclerotic artery compresses the retinal vein, which results in turbulent blood flow and endothelial damage, followed by thrombosis and obstruction of the vein. Most BRVO occur superotemporally, probably because this is where the highest concentration of arteriovenous crossings lie.

The classic general risk factors are age, smoke, diabetes, hypertension and hyperlipidemia and local predisposing factors include open-angle glaucoma and other conditions inducing increased intraocular pressure. However, there are other risk factors that are related to hemostasis such as hyperhomocysteinemia [29,30].

The close association of BRVO with systemic vascular disease emphasizes the need to investigate cardiovascular risk factors in these patients.

Evaluation of a new patient with BRVO must include a screen for hypertension, diabetes and lipid abnormalities because it may be the presentation of significant vascular morbidity. In younger patients, most of whom are otherwise healthy, the exact pathogenesis and risk factors of BRVO are still poorly understood. However, when tests for common cardiovascular risk factors are negative, evaluation for potential coagulation disorders may be indicated, particularly in young patients with bilateral BRVO, a history of previous thrombosis or a family history of thrombosis[31].

Rarely, local ocular diseases, especially of an inflammatory nature, can result in a secondary branch retinal vein obstruction. This has been reported in diseases such as toxoplasmosis, Eales's disease, Behçet's syndrome, and ocular sarcoidosis. Also, macroaneurysms, Coats'disease, retinal capillary hemangiomas, and optic disc drusen are linked to BRVO.

In the present study we preferentially look into Macular Edema (ME) as we will review the main treatments available for the resolution of ME in BRVO.

In hydrodynamic terms we may think of thrombosis within a retinal vein leading to a partial obstruction of blood flow within the vein and from the eye. The subsequent increased intraluminal pressure, if sufficiently high, will cause transudation of blood products into the retina according to Starling´s law. This will result in increased interstitial (retinal) fluid and protein. The latter will increase the interstitial oncotic pressure, perpetuating tissue edema, which will impede capillary perfusion and lead to ischemia.

Several studies have also mentioned the role of inflammatory mediators in causing macular edema and so its pathogenesis is rather complex: vascular dysfunction, a dysfunctional blood-retinal barrier and several inflammatory mediators like IL-23, IL-8, IL-6, IL-15, IL-12 and IL-17, including vascular endothelial growth factors (VEGF), are among the possible responsible mechanisms and factors leading to, or involved in the development of ME. Retinal hypoxia has also been implicated in the pathogenesis of BRVO as it causes an expression of VEGF which is a potent inducer of vascular permeability that has been shown to cause damage to vascular endothelial cells [32,33].

CLINICAL ASPECTS OF BRVO

Taking into account that BRVO has a lesser risk of ischemia than CRVO and therefore has a much more favorable clinical evolution, one can divide it into major BRVO and macular BRVO as in this latter form the ischemic process is always very small and unable to induce neovascularization (NV).

Major BRVO

It varies in accordance to the duration of the occlusive process[34]. In the early acute phases it presents with congestion and tortuosity of venous vessels in the involved quadrant, in association with superficial and deep retinal hemorrhages and possible cotton wool spots (Fig. 1). As a result of the distribution, the hemorrhages usually assume a triangular configuration with the apex at the site of blockage – flame hemorrhages predominate. Mild obstructions are associated with a relatively small amount of hemorrhage. Complete obstructions result in multiple intraretinal hemorrhages, cotton-wool spot formation, and widespread capillary nonperfusion. Occasionally, BRVO is an incidental finding without symptoms, noted on routine examination.

Major BRVO comprises a nonischemic form and an ischemic form detectable in one third and two thirds of cases, respectively[35]. NV can only develop in the ischemic form.

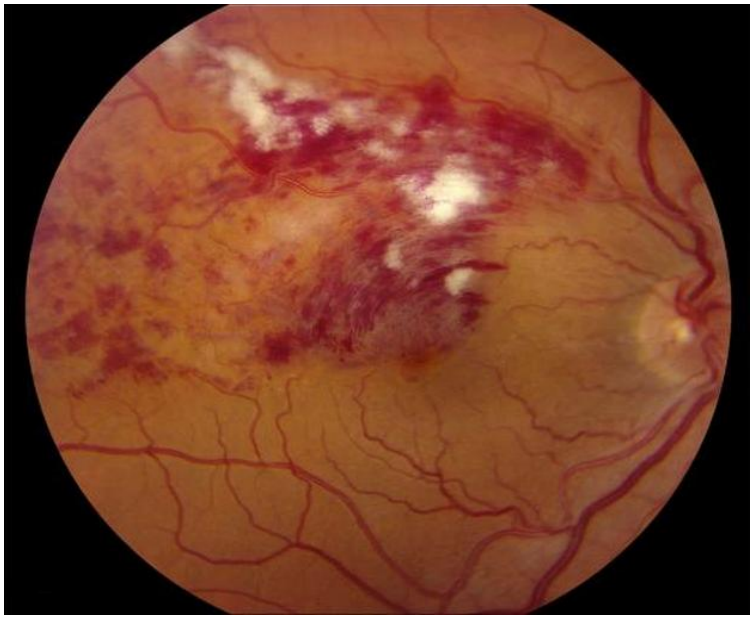

Fig. 1 – A typical image of BRVO (Used by permission from www.willseye.org)

ME is generally present in the sector of the macula drained by the obstructed vein and there is scarce data on its incidence. It is described as developing in 5-15% of eyes over a 1-year period by Rogers et el[36] and in 15% at 7.5 months following the onset of BRVO by Shroff D

and colleagues[37]. ME is defined as an accumulation of subretinal fluid, as well as a swelling of the Muller cells in the macular area.

ME is the most important cause of visual loss in BRVO.

With time the biomicroscopic findings become more subtle. ME may resolve or even increase with possible hard exudates deposition. Collateral vessels and microvascular abnormalities develop to help drain the affected area. Epiretinal membrane and macular pigment epithelial changes as a result of chronic cystoid ME are sometimes seen in the late phase of BRVO.

Macular BRVO

In macular BRVO the obstruction is limited to a small venous vessel draining a specific sector of the macula located between superior and inferior temporal arcades[38]. It has a variable clinical presentation and course which may elude more conventional examination techniques and require fluorescein angiography to confirm or establish its presence by showing a delayed filling of the affected vein in the early phases and pointing out the arteriovenous crossing which is the cause of the obstruction. Generally it seems to have a more benign course than its major counterpart.

In both cases it is important to differentiate simple edematous forms of BRVO from the ischemic ME using fluorescein techniques as it may help to design the type of treatment and define the possible visual function outcomes.

Main examination techniques

1. Fluorescein Angiography (FA) shows delayed filling of the involved venous branch, whereas venous vessels of the other quadrants have a normal filling. The foveal avascular zone may be enlarged secondarily to the break of the perifoveal capillary arcade which, in cases with distinct areas of capillary non perfusion within one disc

diameter of the foveal center, are considered to have macular ischemia (Fig.2). The late angiographic vessels may show ME which may also present cystoid aspects. FA is especially useful in detecting the presence of a nonperfused retina, and the possible neovascularization with significant implications on its treatment. In occlusions with a longer duration one may observe intraretinal microvascular anomalies with leakage and formation of collateral vessels.

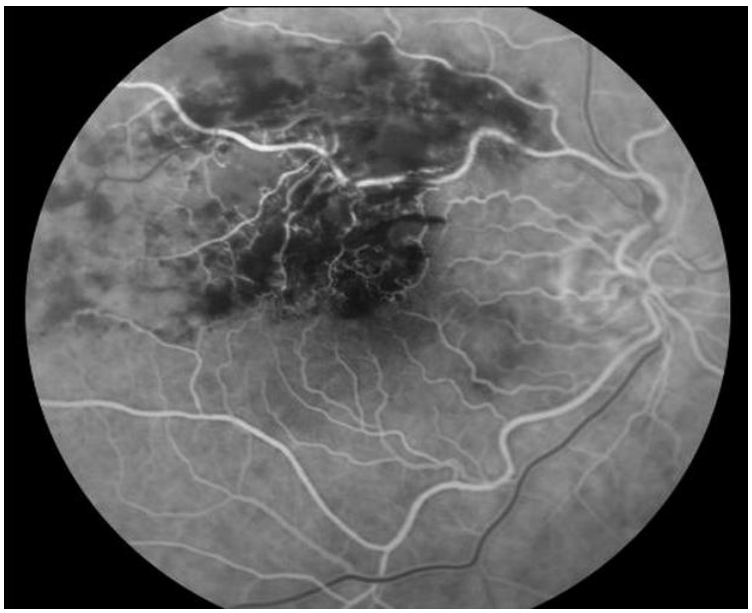

Fig. 2 – Angiographic aspect of previous figure (Used by permission from www.willseye.org)

FA is an invasive technique for examining the circulation of the retina and choroid using a fluorescent dye and a specialized camera. It involves injection of sodium fluorescein into the systemic circulation, and then an angiogram is obtained by photographing the fluorescence emitted after illumination of the retina with blue light at a wavelength of 490 nanometers. The test uses the dye tracing method.

Sometimes FA evaluation of ME may be difficult because it is not always associated with wide blood-retinal barrier[39] and optical coherence tomography becomes necessary to assess the severity of ME as well as accompanying its evolution.

2. Therefore, Optical Coherence Tomography (OCT) evaluations are always necessary in evaluating the degree and severity of ME and it is nowadays the most important tool in accompanying and guiding the treatment of ME (Fig. 3).

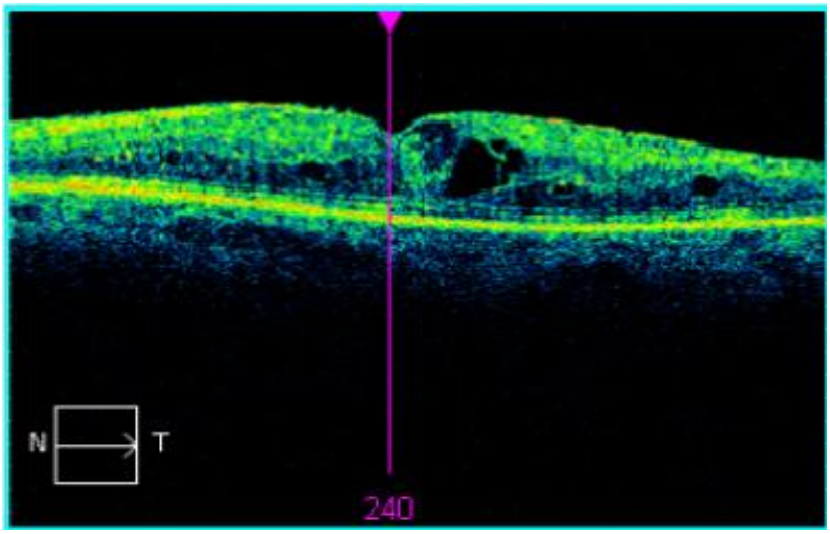

Fig 3- Image of cystoid macular edema in a case of major BRVO

OCT must be carried out at diagnostic time before treatment and during every follow up visits as frequency and type of treatment depends largely on OCT results when measuring retinal thickness and in special quantifying foveal thickness (Fig.4).

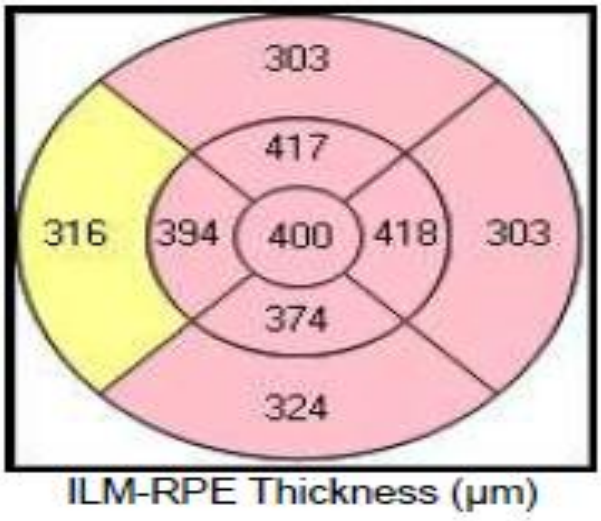

Fig 4. Macular thickness measurements of previous OCT.

OCT is a non-invasive technique based on an optical signal acquisition and processing method. It captures micrometer-resolution, three-dimensional images from within optical scattering media (e.g., biological tissue). Optical coherence tomography is an interferometric technique, typically employing near-infrared light. The use of relatively long wavelength light allows it to penetrate into the scattering medium and is commercially used in various forms including obtaining detailed images from within the retina.

MATERIAL AND METHODS

An extensive revision of literature has been made looking for articles generally from 1984 up to now, using Pubmed as the main basis of resource.

Levels of evidence were decided in order to organize articles according to clinical and epidemiological impact. In our work they were based on US Agency for Health Research and Quality:

Clinical Evidence Level 1. 1a: The evidence arises from metaanalysis of controlled, randomized and well designed essays. 1b: The evidence arises from at least one randomized controlled essay.

Clinical Evidence Level 2. 2a: The evidence arises from at least one controlled, non randomized and well designed study. 2b: The evidence arises from at least one not completely experimental well designed study such as a cohort study. It refers to a situation in which the application of an intervention is beyond the control of researchers even though its effect can be assessed.

Clinical Evidence level 3. The evidence arises from descriptive, non-experimental, well designed studies such as comparative studies, correlation studies or case and control studies.

Clinical Evidence level 4. The evidence arises from documents or view points of expert committees or clinical experience of renowned authorities or a study of series of cases.

Published guidelines from the Royal College of Ophthalmologists of Britain in 2010[40], Sociedad Espanola de Oftalmologia, Spain also in 2010[41] and GER Grupo de Estudos de Retina, Portugal in 2012[42] were taken into account for validation of data available and orientation throughout this work.

TREATMENTS

Macular edema following BRVO should be addressed as soon as possible to improve functional outcomes and well designed research done in recent years has in some ways changed the way one should treat this pathology. In a somehow chronological fashion we will try to present all main treatments studied along the time.

1. LASER TREATMENT

Laser treatment continues to be mentioned as one of the preferred methods mainly because of the randomized studies done in the late seventies and early eighties and published by the Branch Retinal Vein Occlusion Study (BVOS) in September 1984[1].

LASER (Light Amplification by Stimulated Emission of Radiation) was first mentioned in ophthalmology by Meyer-Schiwickerath who used a xenon arc photocoagulator to produce therapeutic burns in the retina but it was quickly superseded by the gas argon laser as the active medium emitting energy at blue and green wavelengths with absorption at the level of the pigment epithelium.

The standard argon laser treatment, as advocated by the Branch Vein Occlusion Study Group in their paper published in 1984, for macular edema following BRVO, consisted in performing photocoagulation, under topical anesthesia, to achieve a “grid” pattern over the area of leakage indentified by the FA in the macular region, extending no closer to the fovea than the edge of the foveal avascular zone and not extending peripheral to the major vascular arcade.

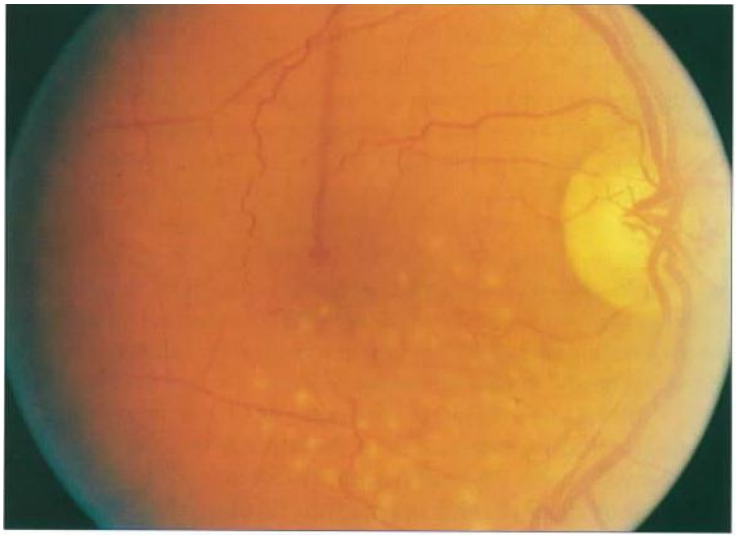

Fig. 5 – Image taken immediately after treating ME in BRVO with grid laser.

The eyes were rechecked in 4 months time with a new FA and additional laser treatment was applied in case there were still untreated leaking areas and persisting foveal edema.

In this study one of the inclusion criteria for treatment of macular edema was the existence of sufficient clearing of intraretinal hemorrhage for safe laser.

In other studies, when the presence of gross swelling of the retina and/or intraretinal hemorrhage close to the fovea could make it difficult to precisely identify the fovea, treatment was postponed until hemorrhages and/or edema cleared enough for secure treatment.

The Branch Vein Occlusion Study (clinical evidence level 1)

The BVOS Group produced an extremely well designed work which involved 5 participating centers in the United States of America with information being received from July 1977 to February 1984. A BVOS Coordinating Center in Baltimore was created and rigid rules decided upon the study to make it as reliable as possible. It was sponsored by the National Eye Institute and it was created to answer 3 questions of which one was "Can photocoagulation improve visual acuity in eyes with macular edema reducing vision to 20/40 or worse?".

To answer all the questions four separate groups were created, of which group III (eyes at risk for vision loss from macular edema) had 139 patients with recent (3 to 18 months since onset) BRVO with macular edema reducing visual acuity (VA) to 20/40 or worse. It has to be mentioned that some patients in group III could also be assigned to the group described as eyes at risk for the development of neovascularization and even vitreous hemorrhage. For group III only, 24 eyes were assigned to no treatment group (control) and 30 eyes to argon laser treatment in a randomized fashion, while the other patients with ME also shared other groups.

The reason why no patient was eligible before three months elapsed after occlusion was because there was a clinical impression that spontaneous improvement often occurred during that period.

VA was measured by an annually certified masked examiner and special front-lighted Diabetic Retinopathy Study charts with Snellen letters were used for better visions and Sloan letters for low visual acuity (20/160 to 20/200). Eyes assigned to the treatment group had a FA and laser done within one month after this exam. Photocoagulation was performed by experienced senior staff ophthalmologists following a standard protocol which aimed at obtaining a "grid" pattern over the area of capillary leakage and laser extending no closer to

the fovea than the edge of the foveal avascular zone. The eye was re-evaluated at four months with FA and additional treatment was performed if untreated leaking areas and foveal edema persisted with continued loss of visual acuity. After this, patients continued to be reviewed every four months and a repeat FA performed at annual intervals. The average duration of follow-up was 3.1 years. Analysis of visual results based on the 78 eyes that were examined at three years of follow-up indicated average visual acuity of 20/70 in the control group and 20/40 to 20/50 in the treated group and of the treated eyes 65% gained two or more lines from baseline and maintained it for at least two consecutive visits versus 37% of control eyes.

Of control eyes 17% lost two or more lines from baseline maintained for two consecutive visits versus 12% of treated eyes.

In the study there is also a weak suggestion that laser treatment is more beneficial for hypertensive than non hypertensive patients. It is important to mention that there was only one complication and it was related with apparent perforation of Bruch's membrane that did not affect visual function.

The BVOS recommends treatment for patients with branch vein occlusion and VA reduced by macular edema to 20/40 or worse after 3 months.

However we have to stress that:

1. The study did not address patients with an early diagnosis;
2. nor cases were VA was better than 20/40.
3. It was also mentioned the extreme care taken during treatments as performed by very experienced surgeons and avoiding lasering over intraretinal hemorrhages or collateral vessels and away from the foveal center zone.
4. And the improved functional outcomes were quite limited.

Subthreshold grid laser treatment (clinical evidence level 2)

The subthreshold grid laser treatment defended by several authors including Battaglia et al in 2006[3] to minimize the impact of laser scarring was a randomized, prospective trial to compare the effectiveness of this type of treatment using infrared micropulse diode laser (SGLT) with that of threshold grid laser treatment (TGLT) performed with krypton, in the treatment of ME secondary to BRVO. The reason why krypton was used was an attempt to minimize the damage to RPE cells, sparing the inner retina layers. The results were tested by OCT measurements of the macular central area and foveal thickness (FT) defined as the distance from the inner retinal surface to the inner border of the retinal pigment epithelium. Total macular volume (TMV) was determined by the sum of the volumes of the 9 quadrants obtained by a central macular thickness map measuring 3.45mm in diameter. Inclusion criteria were similar to the main BVOS study and 36 patients assigned randomly into 2 groups. In this study the laser power for SGLT was determined by means of a single test burn, delivered in a macular area involved by edema which brought about a medium white burn in a continuous wave. After the first treatment, supplemental laser applications were planned in those eyes showing unchanged or increased FT after 12 months. Patients were evaluated every 6 months by an independent examiner who refracted the patients and performed OCT scans. At 6 months the mean FT and TMV was reduced by half of its original value in TGLT whereas in SGLT similar results only happened at 12 months. After 1 year, there was no difference in the mean FT and the mean TMV values between the 2 groups.

Unfortunately this clinical evidence 2 study demonstrated some problems which did not seem to have been answered later on as suggested by the authors:

1. It was difficult to establish the appropriate laser dosage for SGLT.

2. It was not possible to assess if SGLT uptake was obtained during treatment because the laser application was not visible ophthalmoscopically and the greater number of spots used may infer that some areas could have been re-treated inadvertently.
3. The mechanisms of action of SGLT, taking into account the selective damage of RPE cells, may be related to the release of cytokines and growth factors or even we may speculate that the clinical improvement may be related to spreading and migration of RPE cells at the margin of the lasered sites pointed out 6 years ago by Roider et al in a pilot study entitled subthreshold (retinal pigment epithelium) photocoagulation in macular diseases and published in the british journal of ophthalmology.

Current guidelines on laser treatment of ME

Grid laser in the capillary diffusion of ME is mentioned in the English and Spanish guidelines published in 2010 and Portuguese one in 2012 who recommend it in accordance with BVOS study when vision loss persists for more than 3 months and visual acuity (VA) is within the range of 20/40 to 20/200 with complete absorption of macular hemorrhages. However, if ME is due to a lack of macular perfusion, said laser treatment is not recommended.

Personal comments

It is unwise to leave chronic cystoid macular edema for a few months as permanent loss of central vision may result. A good guide to severity is degree of visual loss. If visual acuity is affected, the macula will be at risk of irreversible cystic change and laser treatment in this situation is probably indicated although in some cases of ME and no areas of capillary non-perfusion some patients may actually improve without any treatment.

Although we know that ME may resolve without any treatment, one should pay special attention to the type and extension of FA and OCT as well as VA changes in order to decide if an early treatment should be instituted.

Also functional improvement is slow and modest, and although secondary scotomas may be avoided with careful treatment applied by experienced surgeons, one should actively consider other options, even including rescue laser as some type of combined therapies, that should provide rapid and complete restoration of vision. In patients in active professional life, a relative loss of vision could be extremely distressing especially if taking a long time for a clear improvement.

2. TRIAMCINOLONE

Triamcinolone acetonide has been mentioned since 2002 for the treatment of BRVO in several case reports. However it was only in 2009 that a proper randomized trial, clinical evidence level 1, has produced a reliable study on a 12 month early basis on the effect of triamcinolone and compared it with the then gold standard laser treatment.

Degenring RF and colleagues from the Ruprecht-Karls-University Heidelberg presented a case report[4] in 2003 where intravitreal 25mg triamcinolone was injected in 1 patient with macular BRVO lasting for 2 years and another with CRVO. They mentioned an improvement in VA, OCT and FA 5 weeks later in both cases but there has been no follow up and the presentation was just a simple, non viable reminder that triamcinolone could be an agent to be used in a few cases resistant to laser treatment.

Chen SDM and colleagues from Oxford Eye Hospital in UK published a case report in 2004[5] in which a 38 year old man with a 2-month history of poor vision (counting fingers) caused by ischemic ME secondary to BRVO and no systemic changes was offered a 4mg intravitreal

injection of triamcinolone. 2 weeks post-op the ME disappeared and visual acuity improved to 6/36 and later on to 6/24. There was no more relevant information on this report except for it drawing attention to this treatment as a possibility in the ophthalmic armamentarium of ME due to BRVO.

In 2005 Jonas JB and the same group from the Ruprecht-Karls-University Heidelberg University published an article in Eye[6] with the purpose of evaluating the effect of intravitreal triamcinolone acetonide in BRVO. They designed a comparative nonrandomized clinical interventional study which included 28 eyes (clinical evidence level 3) and used a 20-25mg intravitreal injection of triamcinolone which showed a significant improvement in VA in the non ischemic cases with ME in a short period of time and a high percentage of cases with increased intraocular pressure (IOP). However this was not a randomized study, the numbers were too small for a proper statistical analysis and the follow up time too short.

Again in 2005 Çekiç O et al from the Department of Ophthalmology of the Columbia University in USA presented a clinical evidence level 3 paper[7] where they performed a retrospective chart review of 13 eyes that underwent 4mg injections of triamcinolone for ME due to BRVO, some of them in a repeated way. The paper does not come to any significant result and is not well structured with many variables which neutralize all attempts to reach any significant conclusion. An idea of a high number of cataract formation especially in cases where injections were repeated and 62% of patients with increased IOP is all what one can extract from this paper.

Eye in 2008 presented a paper signed by Patel PJ, Zaheer I and Karia N from Southend Hospital in UK[8] in which they attempted to assess the long-term safety and efficacy of intravitreal triamcinolone acetonide in the management of retinal vein occlusions. Of the 13 eyes followed up prospectively, 8 were cases of ME due to BRVO. They were able to follow up patients for at least one year and in almost all cases the initial VA and macular thickness

improvement has faded away by the 12th month. It once more showed an increase in IOP but no other significant complications.

The Standard Care vs. Corticosteroid for Retinal Vein Occlusion (SCORE) Study Report 6 (clinical evidence level 1)

All studies since 2002 did not bring out any light on this issue until the SCORE Study Report[9,10], clinical evidence 1 trials, have finally produced a multicenter, randomized robust study to investigate the relationship between baseline center retinal thickness measured by OCT and best corrected visual acuity (BCVA) in eyes with macular edema associated with retinal vein occlusion and to investigate other factors associated with baseline VA letter score. The SCORE Study sponsored by the National Eye Institute was a clinical investigation designed to compare 1-mg and 4-mg doses of intravitreal triamcinolone with standard laser care for vision loss associated with macular edema secondary to perfused CRVO and BRVO. The 2 primary objectives of the SCORE-BRVO trial were:

1. To determine whether intravitreal triamcinolone at 1-mg and 4-mg doses produced greater visual benefit, with an acceptable safety profile, than grid photocoagulation, when appropriate, for the treatment of vision loss associated with macular edema secondary to BRVO;
2. To compare the efficacy and safety of the 1-mg and 4-mg triamcinolone doses.

Participants and physicians were masked to the intravitreal triamcinolone dose (1-mg vs. 4-mg) but not to the treatment assignment of standard laser care vs. triamcinolone. The prespecified primary efficacy evaluation was performed at month 12. The primary outcome measure was the proportion of participants who experienced a gain in VA letter score of 15 or more from baseline to month 12. Standard laser care consisted of either grid photocoagulation if there was no dense macular hemorrhage or, in such a case, observation at 4-month intervals

until treatment could be applied. Study visits were planned for every 4 months throughout 36 months. The 4-mg dose used was decided as it was the most popular dose in most studies up to the moment and the 1-mg dose because it was a quantity just enough to exceed the concentration necessary to saturate the glucocorticoid receptors in the cell cytoplasm and at the same time supposedly to cause less steroid related side-effects. Retreatment criteria were identical for all 3 treatments and, if needed, participants had a repeat treatment at 4-month intervals and its criteria were according to the original treatment.

Four hundred and eleven patients took part on this trial and were enrolled from November 2004 until February 2008 at 75 clinical sites. The mean duration of macular edema was 4 months, the mean baseline BCVA was 20/80 and the mean center point thickness was of about 523 micron based on OCT.

The month 12 primary outcome visit was completed by 88%, 89% and 91% of patients in the standard laser care, 1-mg and 4-mg groups, respectively. For eyes without a dense hemorrhage and randomized to standard laser care, the mean number of treatments in 12 months was 1.8 and in those with a dense hemorrhage at baseline was 0.7. In the triamcinolone groups the mean number was 2.2 in the 1-mg and 2.1 in the 4-mg.

The percentage of participants with a gain in VA letter score of 15 or more at month 12 was similar in the 3 groups: 28.9%, 25.6% and 27.2% respectively in the standard laser care, 1-mg and 4-mg groups. All 3 groups had a similar gain of approximately 4 to 6 in mean VA letter score from baseline to month 12 and there was also a similar percentage loss of lines in all 3 groups in the order of 11 to 15%. However the 4-mg group performed better at month 4 when compared with the other groups (P=.002, based on analysis of variance). After month 12, mean change from baseline in VA letter score has always been better with standard laser care.

As far as OCT measurements they also showed a better performance by the 4-mg group at month 4 and a similarity of all 3 groups at month 12.

As far as side-effects, 41% of the 4-mg group initiated IOP lowering medication through the 12 months compared to 7% in the 1-mg and 2% in the standard laser care group. No surgical antiglaucoma procedure was performed in the first year but 1 participant in the 4-mg group received a trabeculectomy and another in the same group a shunt to control IOP unrelated to neovascular glaucoma in the following months. The new-onset of lens opacities in the first 12 months was 13% in standard laser care, 25% in the 1-mg and 35% in the 4-mg groups. Cataract surgery was more frequent between months 12 and 24 in the 4-mg group with 35 eyes receiving surgery compared to 8 in the 1-mg and 5 in the standard laser care group.

In summary,

- The results of the SCORE-BRVO trial demonstrate no significant differences among the treatment groups for a gain in VA letter score of 15 or more at 12 months;
- Though an early positive treatment response of a gain in VA of 15 letters or more was observed at month 4 in the 4-mg triamcinolone group;
- After month 12 and up to month 36, the mean improvement from baseline VA letter score was greatest in the standard laser care group;
- The OCT measured effect produced similar results for the first 12 months and onwards;
- The rates of adverse effects (AEs) were higher in the 4-mg group when it comes to increased IOP (41%);
- The rate of new lens opacities formation through the 12 months was greater in the 2 triamcinolone groups with the 4-mg having the highest frequency (35%);

We have to stress that the 128 participants in this trial which have been followed up to 36 months is higher than that of the cohort studied in the Branch Retinal Vein Occlusion Group for argon laser treatment in macular edema (group III) published in 1984 which followed 78 eyes for as long as 36 months.

Current guidelines of the use of triamcinolone in BRVO with ME

Triamcinolone, either at 1 mg or 4 mg dosage, has worse medium to long term results when compared to standard grid laser treatment. Besides, its side effects with the 4mg dosage are extremely high when considering intraocular pressure and cataract formation. Therefore, it is not anymore a valid option for treatment of ME following BRVO.

Personal comments

Since grid photocoagulation is a better treatment than triamcinolone, my feeling is that gains in VA from either treatment options continue to be rather modest and better alternatives should be looked for.

Interesting the fact that 4mg triamcinolone obtains significant VA and central macular thickness gains at month 4 and one would imagine that 1 single injection of triamcinolone followed by grid laser treatment, as reported by Parodi MB and colleagues in 2008[43] could have positive results in a medium term follow up. However, this seems to have been the only reliable but small study supporting this combination and triamcinolone has indeed been abandoned for the treatment of this pathology.

3. DEXAMETHASONE IMPLANTS

Dexamethasone is a potent, water-soluble corticosteroid that can be delivered into the vitreous cavity by an implant (DEX implant;ozurdex, Allergan, Inc.,Irvine,CA) which is composed of a biodegradable copolymer of lactic acid and glycolic acid containing micronized dexamethasone. This complex gradually releases the total dose of dexamethasone over a period of several months after insertion into the eye. Corticosteroids have potent anti-inflammatory effects and inhibit the synthesis of VEGF, prostaglandins and other cytokines.

Ozurdex Geneva Study Part 1(clinical evidence level 1)

The first paper was published in 2010 and was entitled "Randomized, Sham-Controlled Trial of Dexamethasone Intravitreal Implant in Patients with Macular Edema Due to Retinal Vein Occlusion" [12]. The objective of the study was the evaluation of safety and efficacy of DEX implant 0.35mg and 0.7mg compared with a sham procedure over a period of 6 months in eyes with vision loss due to ME secondary to both BRVO and CRVO.

In this study two separate randomized, prospective, multicenter, masked, sham-controlled, parallel-group clinical trials were conducted for regulatory purposes.

Patients were recruited in 24 countries between November 2004 and March 2008 and duration of ME was required to be between 6 weeks and 9 months in patients with CRVO and between 6 weeks and 12 months in patients with BRVO. Eligible patients had to have best corrected VA (BCVA) between 20/200 and 20/50 in the study eye and better than 20/200 in the nonstudy eye and retinal thickness in the central subfield, measured by OCT, had to be above 300 micron in the study eye.

One has to notice that rescue laser treatment was prohibited in this study unless required for patient care. The use of prohibited substances was recorded as an escape treatment but these patients, with rare exceptions when using medications considered major protocol violations, were not required to discontinue from the study, and their efficacy and safety outcomes were included in the intent-to-treat analyses.

The outcome measures were, in first place, the time to reach a 15-letter gain from baseline BCVA but The Food and Drug Agency in USA requested that the primary outcome in the first study to be the proportion of eyes achieving at least a 15-letter improvement from baseline at day 180 and accepting the earlier mentioned outcome measure to be considered in the second study. Secondary outcome measures included several points of which we mention the central retinal thickness using OCT.

A total of 1267 patients, of which 66% had BRVO, were engaged in the study and randomized using a 1:1:1 allocation ratio. A minority (17%) had duration of ME less than 90 days.

Eyes receiving DEX implant 0.7mg or 0.35mg achieved a 15-letter improvement in BCVA significantly faster than the eyes with sham treatment. At day 180 the cumulative response rate was 41% in the DEX implant 0.7mg, 40% in the DEX implant 0.35mg and 23% in the sham group. The best results for DEX implants occurred from day 30 to day 90 with a peak at day 60 (29% as compared with sham treatment). At day 180, the proportion of eyes achieving at least a 15-letter gain with DEX implant 0.7mg group was 22% which was not statistically different from the sham group (18%). But if one excludes those patients whose last visit was later than day 180, taking into account that the DEX implant was designed to deliver therapeutic levels of dexamethasone for only 6 months, then the difference between the DEX implant 0.7mg group (26.4%) and the sham group (17%) had a statistical significance ($p=0.017$). As far as the 2 doses of DEX implants there were no statistically differences throughout the study. Interesting to note that the first of the 2 studies did not meet its primary regulatory end point at day 180 although the difference between DEX implant 0.7mg and sham was statistically significant on days 30 to 90. The second study did meet its primary end point (time to 15-letter gain) for DEX implant 0.7mg vs. sham. At days 30, 60 and 90 the proportion of eyes achieving at least 10,11,12,13 or 14 letters of improvement from baseline BCVA was significantly greater in both DEX groups than in sham ($p<0.001$) but at day 180 only the DEX implant 0.7mg still presented a statistically difference against sham ($p<0.040$). During the study a decrease in vision of 15 letters or more was always most likely in the sham group. As far a central thickness the mean decrease was significantly greater with DEX implant 0.7mg and 0.35mg than with sham treatment at day 90 but not at day 180.

Interesting to note that:

1. The response to treatment in the BRVO and CRVO subgroups was qualitatively similar to the responses seen in the overall population;
2. the mean BCVA slowly improved over the study among BRVO eyes treated with sham and gradually declined to below baseline levels among CRVO eyes treated with sham;
3. A post hoc subgroup analysis base on the duration of ME at baseline found that the response to treatment was often greater among eyes with a shorter duration of ME.

On the safety analysis field the overall incidence of ocular AEs was significantly higher in the DEX implant groups as compared to sham (62.9% and 61.9% respectively against 42.8%) but most of them were related to the time of injection itself (conjunctival hemorrhage, eye pain, conjunctival hyperemia) with no consequences at all. Ocular hypertension occurred in 4% of eyes with 0.7mg DEX implant and 3.9% with 0.35mg and 0.7% in the sham group and they were transient in the treatment groups with a peak of slightly less than 16% by day 60. Cataract formation was mentioned to occur in 7.3% of cases with 0.7mg, 4.1% in the 0.35mg group and 4.5% in the sham group although the time of the study (180 days) was probably too short to proper analysis of cataract development.

Personnel comments

The study did not make a proper differentiation between BRVO and CRVO although they are different disease entities in terms of natural history and sites of occlusion. However a prospectively defined subgroup analysis based on baseline diagnoses (BRVO/CRVO) was included in the protocol and its results confirm that CRVO is a more visually disabling disorder and these eyes did not respond as well to treatment and also they were less likely to improve without therapy.

A positive finding (also verified in SCORE study) was that the shorter ME duration at baseline was associated with greater improvements in BCVA after DEX implant.

One of drawbacks of the results was that the response to DEX treatments seems to be of limited duration.

If the control group happened to have been the laser group instead of sham one could have learnt more about the comparative benefits of each treatment but presumably sham was chosen because there is evidence that laser photocoagulation can improve vision in eyes with ME associated with BRVO and not with CRVO; also in between 30 to 50% of BRVO cases they may improve vision within 6 months to better than 20/40 with no treatment.

Ozurdex Geneva Study Part 2 (clinical evidence level 1)

In 2011[26] the same group evaluated the safety and efficacy of 1 or 2 treatments with DEX over an extended period of 12 months and published it in a paper entitled "Dexamethasone Intravitreal Implant in Patients with Macular Edema Related to Branch or Central Retinal Vein Occlusion – twelve-month results"[12]. This was an open label extension of the previously mentioned work designed to further evaluate the safety of DEX implants with 0.7mg injected in all patients as needed at 6 months according to pre-defined criteria. All patients who completed the 180 day study and presented with BCVA of less than 20/20 or retinal thickness of more 250 micron were eligible for a 0.7mg DEX implant. Of the 1196 patients who completed the 180 day study, 997 received a 0.7mg injection. With exception to cataracts, there were no statistically significant differences in the incidence of ocular AEs between patients who received 2 injections of DEX implant and patients who had been treated initially with sham and received DEX implant at day 180. During the study, cataract formation was reported in 39.8% of eyes retreated DEX 0.7/0.7 group, 19.8% in the 0.35/0.7 group and 10.5% in the delayed treatment group. As far as the concerns on IOP, there was also a peak of

ocular hypertension at day 60 after the second injection and, overall, 32.8% of study eyes in the retreated DEX 0.7/0.7 group had at least a 10 mmHg increase in IOP from baseline at the some point during the 12 month study period. Almost all these cases had IOP resolved by day 180 either with observation alone or with medication.

Among patients who received 2 treatments with DEX implant 0.7mg the same profile of BCVA improvement was observed. To note that those patients on the sham group who received later a 0.7mg DEX implant were not able to reach the same level of improvement as the other patients.

As mentioned in the previous study, the increased cataract formation could have been due to the slow development of lens opacities after the first injection and/or due a cumulative effect.

In summary, the benefits and AEs were statistically the same for the 6 month period and the extended one, except for cataract formation which increased significatively by month 12.

Current guidelines of the use of DEX implants in BRVO with ME

The results of both studies suggest that 0.7mg DEX implant (ozurdex) should be considered in the treatment of ME following BRVO. This therapy has been approved by FDA and EMA for use in ME secondary to BRVO.

Personnel comments

Recent sub analysis of the Geneva Study suggests that the sooner one starts the treatment the better the visual outcome as the probability of not gaining at least 15 letters is 57% in eyes treated at 6 months, 34% at 3 months and 16% at 1 month. Again the issue of who should be treated and who will improve without any treatment should be addressed in future studies which could try to predict and decide on this important issue.

Another comment should be directed to the fact that neither study addressed the question of when should be the optimum time for a retreatment procedure.

Questions remain as how many DEX implant injections are needed for the complete treatment of macular edema due to BRVO (if there is a complete resolution at all) or if combined therapies should be instituted, taking advantage of the timings where BCVA and foveal thickness are its best level.

4. ANTI-VEGF DRUGS

Anti VEGF drugs have been increasingly tried as aqueous and vitreous elevated levels of VEGF have been demonstrated in ME secondary to BRVO[32,33] and it seems to be at the moment the mostly commonly used treatment for this condition at this stage.

4.1 RANIBIZUMAB

The BRAVO trial (clinical evidence level 1)

Ranibizumab (Lucentis, Genentech, Inc., South San Francisco, CA) is a humanized, affinity-matured VEGF antibody fragment that neutralizes all isoforms of VEGF-A and their biologically active degradation products.

The BRAVO 6-month, phase III, multicenter, randomized, injection controlled study with an additional 6-months of follow up was designed to evaluate the efficacy and safety of intravitreal injections of ranibizumab in patients with ME secondary to BRVO[13].

The study consisted of 3 randomized groups in which one had 6 monthly initial injections of 0.3mg ranibizumab, another of 0.5mg and the 3rd one, the same number of sham injections and for the same period. After the first 6 months there was a 180 day observation period in

which all patients could receive monthly ranibizumab if they met specific pre-defined criteria (VA less than 20/40 or mean central macular sub-field thickness above 250 micron as per OCT). In this study rescue grid laser treatment was allowed after the first 3 months, as per the BVO study, if hemorrhages have cleared sufficiently for safe laser and Snellen BCVA was less than 20/40 or FT above 250 micron and cumulatively if the patient in the previous 3 months did not gain at least 5 letters in BCVA or the decrease in FT was less than 50 micron.

In this trial 397 patients were included from July 2007 to November 2008 at 93 centers in the USA. The mean time for diagnosis of BRVO to screening was 3.5 months with duration of less or equal to 3 months in 65% of patients and mean BCVA was 20/80 with a mean FT of 520.5 micron.

The primary efficacy outcome was the mean change from baseline BCVA at month 6 and at this date patients who received a 0.3mg injection gained a mean 16.6 letters (95% confidence interval), those with a 0.5mg injection a mean of 18.3 letters and sham with a mean of 7.3 letters (all with the same confidence intervals). There was a significantly greater improvement of BCVA in treated patients over sham during all phases of the study with special impact on the first 7 days. Also mean improvement was better in all sub-groups of patients whose diagnosis was made before 3 months of screening time (sham 8.2 letters, 0.3mg 17 letters and 0.5mg 19.9 letters).

At month 6, 55.2% and 61.1% of participants in the 0.3mg and 0.5mg ranibizumab groups have gained 15 or more letters from baseline BCVA compared with 28.8% of the sham group.

The anatomical changes accompanied the visual function results as far as FT was concerned.

When safety outcomes were analyzed, the ocular side effects have been low and serious AEs point to 1 case of endophalmitis in the 0.5mg group and 1 retinal detachment in the 0.3mg group. The serious nonocular AEs, which can be potentially associated with systemic VEGF

inhibition, were subject to close scrutiny and described in the study where they were not considered to be of a statistically significant value.

This study proves that VEGF plays a very important part of the treatment of ME following BRVO. We should point once more the beneficial result in visual acuity where more than 65% of patients treated with ranibizumab were better than 20/40 at month 6 compared with only 42% in the sham group.

Another finding was the need of rescue grid laser which was 54.5% in the sham group, 18.7% in the 0.3mg and 19.8% in the 0.5mg group.

Personnel comments

Ranibizumab are well tolerated injections with a low incidence of ocular and nonocular side effects and excellent results at 6 months, especially if initiated early in time. The main question remains of those cases where a patient with BRVO may do well without any treatment. Presumably, and for the time being, treating physicians would have to weigh the potential benefits of this treatment against the odds of a possible cure with no treatment at all which may take quite some time. How many injections are really needed? Should a loading dose of 1 injection be followed by monthly follow ups with OCT+BCVA and repeat injections be given in a per needed basis? Can we predict the outcome of ranibizumab treatments in these cases? Although different pathologies, how can we justify the use of 6 initial loading doses of ranibizumab in BRVO while we are currently using only 3 initial ones in AMD?

The HORIZON trial (clinical evidence level 1)

The HORIZON trial (Clinical trials.gov identifier NCT00379795)[15] was designed to obtain additional information in 2 patient cohorts in which one of them were patients with ME after

retinal vein occlusion who had completed the BRAVO and CRUISE studies. This open-label, single arm, multicenter extension trial contained patients who had completed BRAVO and CRUISE and its purpose was to assess the long-term safety and efficacy of intraocular ranibizumab injections in patients with ME after retinal vein occlusion. Primary outcomes were incidence and severity of ocular and nonocular AEs and secondary outcomes included mean change from baseline BCVA at 6, 12, 18 and 24 months, mean change from baseline FT by OCT at 6 and 12 months and the percentage of patients with FT less than 250 micron at 12 months.

It enrolled 608 patients of which 304 had completed BRAVO study and patients were seen at least every 3 months and given an intraocular injection of 0.5mg if they met predefined criteria:

- If mean center subfield thickness was equal or greater than 250 micron or if there was evidence of persistence or recurrent ME deemed to be affecting the patient's visual acuity based on the investigator evaluation.

Patients with BRAVO were also eligible for rescue grid laser therapy if BCVA was less than 20/40 caused by ME. Follow-up during this trial was planned for up to 24 months or until 30 days after FDA approved ranibizumab treatment for retinal vein occlusions in accordance to protocol defined in FDA approval.

Among patients who completed month 12, the mean number of injections was 2.0, 2.4 and 2.1 in the sham/0.5mg, the 0.3/0.5mg and 0.5mg groups respectively. The majority of BRAVO patients who completed month 12 of HORIZON had 0 to 3 injections during the first 12 months (while the majority of CRVO patients had 1 to 6 injections). About 9% (18/205) of BRVO participants who completed month 12 received rescue grid laser therapy.

The most commonly reported ocular AEs were retinal hemorrhages (11.8%, 24.3% and 21.2% in the sham/0.5, 0.3/0.5 and 0.5mg groups respectively); conjunctival hemorrhages (15.1%,

20.4% and 14.4% in the same groups). The frequency of ocular serious AEs was low. The most common nonocular AEs were hypertension and nasopharyngitis. A total of 11 deaths were reported without any direct relationship established. Nonocular serious AEs were rare and related to other studies on the effects of intraocular ranibizumab.

At month 12 of HORIZON the mean change in BRAVO baseline in BCVA letter score was 15.6, 14.9 and 17.5 in the sham/0.5mg, 0.3/0.5mg and 0.5mg groups respectively and BCVA remained stable in BRVO patients over the first 12 months.

In the same period the percentage of improvement of 15 or more letters from BRAVO baseline was 51.5% in the sham/0.5mg group, 50% in the 0.3/0.5mg and 60.3% in the 0.5mg group. The percentage of patients with a snellen score of 20/40 or better was 69.7% (sham/0.5mg), 65.2% (0.3/0.5mg) and 61.6% (0.5mg) which is rather relevant if we understand that in USA 20/40 is the minimum level for driving in many states. At month 12 the mean reduction in FT was 291.4 in the 0.3/0.5mg, 330.6 in the 0.5mg groups and 304.5 in the sham/0.5mg group.

In conclusion, this study found out that 0.5mg injections of ranibizumab on as needed basis were well tolerated by the patients with ME, no new safety events were identified and benefits were maintained if one would re-inject only if BCVA was less than 20/40 or FT above 250 micron.

Current guidelines of the use of ranibizumab in BRVO with ME

FDA and EMA have given approval for 0.5mg ranibizumab injections in macular edema secondary to BRVO.

Personnel comments

Ranibizumab seems to stabilize a large number of patients with BRVO after treatment in BRAVO and HORIZON trials and is one of the most important tools in dealing with ME secondary to BRVO.

The fact that this study was an open label nonrandomized may have created some limitations into drawing specific conclusions for the amount of injections needed after a "loading" dose. We do not know for sure how many injections are needed to fully stabilize a case of ME due to BRVO. Supposedly one should see patients very regularly and decide when to inject upon visual acuity levels together with OCT images of FT.

Guidelines refer only to VA on the decision when to treat ME but I feel a conjunction of BCVA + OCT FT would give a better guidance on when and how to treat. And finally we do not know what is the final visual outcome in patients who had resolution of their ME. Further studies are warranted to answer some questions which have been left on the way.

4.2 BEVACIZUMAB

(best studies reached only a clinical evidence level 3)

Bevacizumab (Avastin, Genentech Inc., San Francisco, USA) is a full-length humanized monoclonal antibody which inhibits all the biological active forms of VEGF and continues to lack a well designed level 1 study. However, it is widely used *off label* in comparable schemes as for ranibizumab although clinical evidence level 3 studies published worldwide seem to suggest, in average, the use of 2-3 injections in a period of 6 months[41].

There were many anecdotal case reports like the one published in Acta Ophthalmologica Scandinava in 2006 entitled "intravitreal bevacizumab treatment of macular oedema due to central retinal vein occlusion"[16]. It describes a case of CRVO with sudden loss of vision to

20/200 and an elevation of macular thickness of 662 micron. An intravitreal injection of 1.5mg of bevacizumab in 0.3ml Ringer's solution was administered (as per case report presentation although one knows that no dilution should be done). At the final follow-up examination 8 weeks later, VA was 20/25 and macular has been reduced to normal levels.

In the same year Rabena MD and colleagues[17] published an article where they describe their experience in treating patients with ME secondary to BRVO. In this paper 27 consecutive patients were reviewed retrospectively with a mean follow up of 5.3 months and an average of 2 injections per case on a 1.25mg/0.05ml dose extracted from the commercially available 25mg/ml vial. In this study, treatment was offered to patients with ME who had poor outcomes after grid laser or triamcinolone therapy and this was one of the obstacles for a fair assessment besides the fact that they were offered this treatment on average after 20 months of diagnosis. At baseline the mean BCVA was 20/200 and it improved to 20/100 at the first month after the 1st injection, at 3 months and throughout the study but with a wide range at the last follow up (20/30 to 20/200, median 20/80 and $P < 0.001$ at each time point). There were no relevant AEs and this seems to be the most relevant issue in this paper.

Kreutzer and colleagues at the Department of Ophthalmology of the Ludwig-Maximillians-University in Munich presented a paper in 2008[18] with the purpose of evaluating the results on VA and FT of bevacizumab in BRVO patients. Their case series involved 34 patients which were followed during 6 months in a prospective, consecutive and non-comparative way after repeated injections of 1.25mg bevacizumab. Mean letters improvement was 19.9 ($p= 0.003$) and mean decrease in FT was 158 micron. The study suggested a beneficial effect of using bevacizumab in treating ME secondary to BRVO.

Chung EJ and collaborators[19] analyzed prognostic factors for visual outcome after bevacizumab for ME due to BRVO in the same year looking into results of the treatment of 50 consecutive cases to conclude that the preoperative presence of macular ischemia could be

useful in predicting the outcome of VA after intravitreal bevacizumab. It divided participants in 2 groups depending on early letters gain and between-group comparisons demonstrated that the eyes with 5 or more letters gain at 1 month after initial treatment (early gainers) resulted in significantly better visual outcome after an average follow up of 7.94+/- 4.17 months and a mean 2 injections. The early gainers were cases where there was no macular ischemia at the beginning of the treatment. Although the studies presented many limitations it has suggested one should be more careful when deciding prolonged treatments in cases presenting significant macular ischemia in baseline FA.

Prager et al in 2009[20] presented a 12-month prospective trial to evaluate functional and anatomical changes after bevacizumab injections in persistent ME following retinal vein occlusion. Patients with ME longer than 3 months were included in the study (21 with BRVO) and required to have a baseline FT of at least 250 micron in OCT. All patients received a loading dose of 3 monthly injections of 1mg (0.04ml) bevacizumab and were retreated if OCT showed evidence of intraretinal or subretinal fluid. There was a mean of 8 injections in the proposed 12 month study interval. Baseline mean VA was 20/100 ranging from 20/800 to 20/26 and final mean BCVA had increased from 50 to 66 letters (20/50) ($p < 0.001$) while retinal thickness had decreased to 309 micron (-249 micron, $p<0.01$). When sub-diving the groups into CRVO and BRVO it was noticeably that only in the latter group there was a statistically significant difference in efficacy outcomes. There were no serious ocular or systemic AEs although the sample was very small as in most studies using this anti-VEGF drug.

In developing countries bevacizumab is sometimes the only available anti-VEGF product to be used in these type of ocular diseases and an interesting prospective, interventional, nonrandomized case series study conducted in Nepal and published in 2012[44] presented its results which pointed to the average use of 3.1 injections with a range from 1 to 6 and a 12

month follow up. BCVA improved in 76% of the eyes and in 55.5% it improved more than 3 lines while it remained the same in 21% and deteriorated in 3%. We note that grid laser therapy was also used in some recurrent cases with many exudates. Although the present work seems to point out the benefits of bevacizumab therapy, it lacks a strict follow up, FA evaluations and control cases needed for a study to obtain a high level of evidence.

Current guidelines of the use of bevacizumab in BRVO with ME

Bevacizumab is used as an *off label* product in the treatment of BRVO as its efficacy and safety are not yet completely established.

Personnel comments

The main handicap of using bevacizumab at this stage has to do with the fact that there are no clinical evidence 1 studies mainly due to the obstruction of the pharmaceutical company which owns both bevacizumab for non ocular diseases and ranibizumab for ocular purposes. The fact that it has to be manipulated either in pharmacy or surgical theatres adds to the discussion of a possible contamination although rigid protocols on how to use bevacizumab should minimize this possibility.

This *off label* product is widely used throughout the world and it is mentioned in several guidelines applying generally 2-3 injections over a period of 6 months and then on a per needed basis in accordance to OCT+VA testing over time. Its efficacy and safety in AMD has been the subject of CATT and IVAN large studies respectively in USA and Britain and latest results are supposedly coming this year which may help in assuring physicians on its usage.

4.3 PEGAPTANIB SODIUM

(Clinical evidence level 2)

"Pegaptanib Sodium for Macular Edema Secondary to Branch Retinal Vein Occlusion"[21] is a well designed, prospective, randomized, dose finding study by Wroblewski et al in 2010 which was supposed to assess the efficacy and safety of intravitreous pegaptanib sodium (Macugen; EyeTech Pharmaceuticals/Pfizer Inc, New York, USA) for the treatment of ME secondary to BRVO.

Macugen as a 40-kDa ribonucleic acid aptamer that binds $VEGF_{165}$ selectively, the isoform that exerts especially pathogenic effects in animal models of ischemia-mediated ocular neovascularization and diabetes-induced breakdown of the blood-retinal barrier.

It enrolled 20 participants from 3 different eye practices in USA with BRVO of than 1 month and less than 6 month duration, BCVA in between 20/40 and 20/320 and central FT above 250 micron. They were randomized into a 3:1 proportion for 0.3mg or 0.1mg of pegaptanib sodium at baseline, followed by subsequent injections at weeks 6 and 12 and thereafter at the investigator discretion up to week 48 on a study which lasted until week 54.

The study consistently provided rapid and sustained improvement of VA in subjects with BRVO for a 54-week period. More than half the subjects gained at least 3 lines of vision by 30 weeks and maintained these benefits for the duration of the study. When compared with the other anti-VEGF most commonly used, it supposedly benefits from the fact that it has a selectivity for $VEGF_{165}$ avoiding the concerns of blocking all VEGF isoforms, some of them have protective effects on retinal neurons and in the maintenance of capillaries in a variety of studies.

As with other studies, this does not help on establishing an optimum treatment interval and duration as it seems that continued treatment after week 54 may be necessary and of benefit based on the natural history of the disease.

Personnel comments

The facts that it was an uncontrolled study with a small population create great limitations to this study. At the same time it seems that interest in this product for the treatment of BRVO has faded away as it is increasingly difficult to find other recent trials of pegaptanib sodium.

4.4 VEGF TRAP-EYE

VEGF Trap-Eye is a fully human fusion protein, consisting of soluble VEGF extracellular receptors 1 and 2, which binds all isoforms of VEGF-A, VEGF-B along with the related Placental Growth Factor (PIGF). VEGF Trap-Eye is a specific and highly potent blocker of these growth factors. It is specially purified and contains iso-osmotic buffer concentrations allowing for injection into the eye[23].

In a study which evaluated the binding kinetics of ranibizumab and bevacizumab and VEGF Trap (also known as aflibercept) it was demonstrated that VEGF Trap had a higher affinity for VEGF-A than the other two; it also showed it was more efficient in inhibiting the activation of VEGFR1 and VEGFR2 as well as VEGF-A induced calcium mobilization and migration in human endothelial cells[22]. Only VEGF Trap bound human PIGF and VEGF-B and inhibited VEGFR1 activation and human endothelial cells migration induced by PIGF. All these data differentiate VEGF Trap from ranibizumab and bevacizumab in terms of its markedly higher affinity for VEGF-A, as well as its ability to bind VEGF-B and PIGF.

Copernicus and Galileu studies for the treatment of macular edema due to CRVO (clinical evidence level 1) using 2mg monthly injections over a period of 6 months and then as per required up to 12 months demonstrated a beneficial visual result and a favorable security level. Patients received an average 3.9 injections in Copernicus over the next 28 weeks after the first 6 months and an average 2.5 injections during the same period in the Galileu trial.

Copernicus trial demonstrated that at month 12, 55.3% treated with VEGF-Trap Eye presented gains superior to 15 letters (mean 16.2) against 30.1% of patients treated with sham injections.

In Galileu at month 12, 60.2% of treated patients presented with letter gains superior to 15 (average 16.9) while the group with sham injections had a gain of 32.4% (average 3.8 letters).

There is no clinical evidence 1 concluded study at the moment on VEGF-Trap Eye for the treatment of BRVO but, on clinicaltrials.gov, there is a registered entry for a trial entitled "Study to assess the clinical efficacy and safety of VEGF Trap-Eye (Intravitreal Aflibercept injection), also commercially known as EYLEA in patients with Branch Retinal Vein Occlusion (BRVO)", (NCT01521559), sponsored by Regeneron Pharmaceuticals.

VIBRANT trial "VEGF Trap-Eye In Branch Retinal Vein Occlusion: an Anti-angiogenesis Trial" is a double masked, randomized, active controlled study of the Efficacy, Safety and Tolerability of Intra-vitreal Administration of VEGF Trap-Eye in Patients with Macular Edema secondary to Branch Retinal Vein Occlusion. Intravitreal Aflibercept is an investigational compound in phase III clinical development for ME following BRVO. The number of participants are around 180 randomized into 1:1 VEGF-Trap EYE 2mg q4weeks vs. laser gold standard, with the primary end point being the proportion of patients gaining at least 15 letters in BCVA and key secondary end point the change in central retinal thickness by OCT in week 24, followed by an open label period up to 52 weeks where VEGF Trap-Eye is used q8 weeks prn and rescue laser if its criteria is met by week 36.

Personnel comments

VEGF Trap-Eye seems to be an attractive proposition as it is demonstrated its higher affinity for VEGF-A than its counterparts ranibizumab, bevacizumab and pegaptanib sodium.

Its effect in the eye seems to last longer as per other studies and maybe we are facing a product which will deal with ME in a more rapid and stable way than the alternatives available at the moment.

One will have to wait for the final results of the VIBRANT study to be able to assess its real efficacy and safety in BRVO especially because in the new design whose study is being undertaken at the moment the evaluation on treatment is made every 4 weeks and then every 8 weeks after week 24.

5. COMBINED THERAPIES

Combined therapies are currently being studied in order to minimize the number of required treatments although, up to now, there has been no clinical evidence level 1 published trials.

Subthreshold grid laser combined with triamcinolone acetonide

The combination of intravitreal triamcinolone with grid laser photocoagulation has been the subject of some studies with suggestions of an improved functional outcome. The rationale was based on the hypothesis that a significant BCVA improvement might be obtained by combining triamcinolone, which leads to a rapid but transitory effect, with grid laser photocoagulation which has a slower but long-lasting effect.

Parodi MB and colleagues published in 2008[43] a small prospective randomized pilot trial including 24 eyes either treated with subthreshold grid diode laser (SGLT) alone or SLGT combined with a single injection of triamcinolone acetonide (SGLT-IVTJ). In this clinical

evidence level 2 study, 13 eyes were allocated to SGLT and 11 to SGLT-ITVJ. SGLT was done using an infrared diode laser with a 125 micron spot diameter, 0.3s exposure and 15% duty cycle. In this group patients experienced a sham injection for comparison. The SGLT-ITVJ group had a 4mg triamcinolone injection followed by laser treatment 4 weeks later.

Primary outcomes were the decrease in mean FT on OCT and the proportion of patients that gained at least 10 letters at month 12. 3 months after the treatment a significant improvement in BCVA has been shown in the SGLT-IVTJ as compared with the SGLT group, which was maintained until the end of the study. At twelve months 10 patients of the SGLT-IVTJ gained at least 10 letters (91%) and 1 maintained the same BCVA. In the SGLT group 2 patients lost 4 lines (20 letters, 15%), 3 (23%) maintained the baseline BCVA and 62% gained at least 10 letters. FT accompanied the BCVA changes. The mean number of lines gained was 3.4 and 1.3 in the SGLT-IVTJ and SGLT groups respectively and 54% of the injection group registered an increase in intraocular pressure which was treated in all cases with timoptol 0.50%. In this work these authors emphasize again the potential benefits of using SGLT laser as there seems to be no laser marks afterwards and demonstrate that an addition of a single injection of 4mg triamcinolone improves the visual function outcomes at 12 months.

Personnel comments

Again the percentage of increased intraocular pressure with triamcinolone is quite high (54%) and the study involved only a small number of patients and a relatively short follow up if the intention was to compare with standard laser treatment.

Combined treatments involving bevacizumab with other therapies

Bevacizumab and grid laser was the subject of many reports of which I point out the clinical evidence 3 study by Hayashi A in 2011[45] where 44 eyes were studied retrospectively with a

mean follow up of 77.2 weeks +/-12.4 weeks. Patients had bevacizumab as a primary treatment and after 2 or 3 monthly injections, depending on the degree of macular edema, 43.2% underwent laser therapy in a grid fashion to prevent the recurrence of edema. In the other 56.8%, laser was not needed. The mean BCVA and FT improved significantly after injections but laser did not seem to add to a better improvement in this study.

Donati S and colleagues published a prospective study in 2012[46] to evaluate long term effects of bevacizumab alone versus bevacizumab and laser treatment. This prospective interventional study included 18 consecutive eyes showing ME secondary to BRVO and BCVA loss. Inclusion criteria were BCVA equal or worse of 20/40, FT greater than 250 micron and the presence of BRVO for more than 3 months. One group had 3 monthly injections only, while the 2nd group had the same 3 injections combined with grid laser photocoagulation according to BVOS guidelines and 1 week after the first injection. Re-injections were performed in both groups after month 3 if ME recurred. In the group of injections only, the median baseline FT decreased from 420 micron to 323 micron at month 12 (p=0.06) and median baseline BCVA improved from 0.6logMAR to 0.2logMAR. At 12 months both treatments seem to be equal effective although the study suggests there will be fewer injections in the group where laser was performed. Again the small numbers involved does not make it a robust trial but it leaves suggestions of improvements in combined therapies.

Combined treatment involving *bevacizumab and triamcinolone* have also been the subject of several clinical evidence level 3 and 4 studies and I would just mention Ehrlich R et al[47] which reported in 2010 a 6 month retrospective consecutive case series on the outcomes of 16 patients with retinal vein occlusion injected with 1.25mg of bevacizumab combined with 2mg of intravitreal triamcinolone, 8 of which were cases of BRVO. This was an uncontrolled work

which reviewed the charts of patients who were injected with both solutions in the same visit. In this study this combination did not offer statistically better results than bevacizumab alone. Increased intraocular pressure was reported in 31% of patients.

Bevacizumab and DEX implants were the subject of a prospective, non-randomized, open-label investigation[48] (clinical evidence level 3) which aimed at demonstrating if there was a synergistic effect on this combination. The trial, published in Retina in 2012, consisted of 34 eyes with retinal vein occlusion (22 with BRVO) and inclusion criteria of baseline FT greater than 300 micron and BCVA of 20/40 or worse and lasted for 6 months. Each patient received bevacizumab injection at baseline followed by DEX implant 0.7mg 2 weeks later and seen every 4 weeks. Retreatment with bevacizumab was considered if FT increased by 50 micron from the lowest recorded level or if BCVA decreased by 6 snellen letters. 82% patients needed an additional injection of bevacizumab. 97% of patients gained vision during the study and mean BCVA letters gain was 12.9, 12.3, 16.7, 14.1, 11.0 and 16.8 for visits at 4 weeks to 6 weeks, 2 months, 3 months, 4 months, 5 months and 6 months respectively. 18% of patients had ocular hypertension which was controlled with no other relevant side effects. The study is an interesting proposition which seems to demonstrate a potential synergistic effect with a better functional outcome and the prolonged time between injections. Limitations of this study include a small sample size and short duration of follow-up.

Personnel comments

Grid laser has always been associated to combinations with other drugs as it is an accepted method of treating BRVO and it seems, in most cases, that it may bring a more sustained improvement when combined with anti-VEGF agents. The combination of bevacizumab with triamcinolone did not bring any advantages but a combined therapy of bevacizumab with

DEX implant could probably result in fewer intravitreal procedures to obtain a more sustained result. However all these studies have low clinical evidence levels and they only suggest ways into the future.

DISCUSSION

Medical management of retinal diseases has arguably come to dominate clinical practice and has resulted in better delivery of patient care and this is one of the key points when looking into the future to avoid the occurrence of BRVO.

Nevertheless, when it occurs and there is evidence of clinically significant macular edema, one has to assess the existence and severity of peripheral and macular retinal ischemia as it may change the way we should treat ME in BRVO.

The general consensus is that treatments should start as soon as possible and intravitreal injections, either of sustained release dexamethasone or anti-VEGFs, turned out to be in the first line of the treatment. It should be considered adding rescue grid laser whenever there is no macular ischemia and ME does recur after injections as evidence suggests a better long term outcome especially with new lasers which tend to avoid macular scarring and induced scotomas.

The main problems remain as when and how to treat ME and, in case of intravitreal injections, which should be the most adequate regime and for how long.

The options between anti-VEGFs and DEX implants will depend on the general condition of the patient as concerns with safety in the elderly and other patients with co-morbities should be taken into account as well as those with a tendency for ocular hypertension or glaucoma and younger patients and the fear of causing early cataract formation.

A combination of anti-VEGFs and DEX implants seem to be also a good option whenever safety issues are safeguarded in the particular patient.

Triamcinolone is not a first line consideration anymore as it has been superseded by DEX implants with better results, fewer complications and less injections on evidence level 1 studies.

The choice between bevacizumab and ranizibumab will point to the latter if one chooses to follow only existing clinical evidence 1 trials.

But we have to point out that CATT[49] and IVAN[50] publicly funded multicenter, randomized clinical trials respectively in the United States of America (National Eye Institute) and United Kingdom (National Institute for Health Research Health Technology Assessment Programme) designed to compare efficacy and safety of ranibizumab versus bevacizumab for the treatment of neovascular age-related macular degeneration (wet AMD) have demonstrated the same levels of safety when results were statistically worked out and, although these results cannot be directly transposed to BRVO because patients health profiles are not exactly the same, one should have a reasonable idea of its relative safety.

Ocular and non-ocular AEs in the diabetic and retinal vein occlusions ME trials were reported with a frequency and severity similar to those seen in the wet AMD trials when using ranibizumab[51].

Questions remain in terms of patients follow up: If using anti-VEGFs shall we follow them monthly with BCVA and FT measurements? And for how long? When re-treating patients with ME following BRVO shall we use both OCT and BCVA results? Most probably, an acceptable way of dealing with these issues is to define a personalized protocol for each patient within the published guidelines in different countries in which both OCT and BCVA will be used to guide retreatments as well as enlarging the interval between follow ups as

times go on and sustained results start to show up, especially if VEGF Trap Eye shows relevant results in the presently ongoing clinical evidence 1 trials on BRVO.

In times of economic hardship around the world and especially in countries like Portugal where a serious financial/economical problem exists and will persist for a long time, one has to take into serious account the economic impact[22] of all treatments looking for cheaper alternatives with possibly the same safety profiles and visual outcomes.

Smiddy WE[24] has produced a well worked on paper to relate costs and treatment benefits for ME due to diabetes and retinal vein occlusion. Its main outcome measures were VA saved, cost of therapy, cost per line saved, cost per line-year saved and costs per quality adjusted life years (QALYs). In his work he stresses the fact that new treatment modalities may present benefits as few letters rather than several lines of VA and expensive ongoing therapies to maintain these modest benefits. Smiddy mentions that the relatively low magnitude of the VA differences, the high prevalence of these diseases, the relatively high treatment costs and the high treatment burden for an individual patient raise cost-benefit and ethical issues on a personal and systemic level.

In UK if bevacizumab was used for treatment of wet AMD instead of its clinical approved equivalent, taking into account an estimated 17.295 eyes, the National Health Service (NHS) could save up to 84 million pounds per year as mentioned several times during 2012 in some articles and reports published in British Medical Journal and even BBC[52-54].

This figure comes from the IVAN trial[50] which measured the cost of AMD treatment per year either using ranibizumab or bevacizumab. It concluded that, if used monthly, treating with ranibizumab costs 9.656 sterling pounds against 1.654 pounds with bevacizumab and if used on an "as needed basis" the cost of ranibizumab comes down to 6.398 sterling pounds against 1.509 pounds when using bevacizumab.

An extensive work by Thunyarat A and colleagues[55] on the use of comparative effectiveness research to inform policy decisions on the inclusion of bevacizumab for the treatment of macular diseases in Thailand's pharmaceutical benefit package published in 2012 is worthwhile reading as it resumes the problems facing countries in economic difficulties and the well done reports by governments and ophthalmologists alike in order to find the best solutions for the patient´s care.

CONCLUSION

Macular edema secondary to BRVO has nowadays more efficient ways to deal with, especially when early treatment is instituted and intravitreal injections considered. An association between them or with grid laser treatment may be desired and one should individualize the need of repeat treatments as it varies from patient to patient. Economic considerations must be taken into account as well as all questions related to safety and efficacy when deciding a protocol treatment for each patient.

Nevertheless more studies are warranted on the best way to follow up these patients.

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