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Folheto informativo
Suplemento alimentar 250 mg de citicolina e 0,75 mg de zinco por cápsula. Composição e apresentação: Citidina 5'-difosfocolina (citicolina) – 54,11%; Agentes de volume: Celulose microcristalina; Agente de revestimento: Gelatina; Antiaglomerantes: Talco, Estearato de magnésio; Água; Antiaglomerante: Sílica coloidal anidra; Óxido de Zinco – 0,20%. Embalagem de 60 cápsulas brancas. Propriedades: EyeCare NPO é um produto à base de citicolina e zinco que contribui para a manutenção de uma visão normal. A citicolina é uma substância que, no organismo humano, é metabolizada em colina. Esta intervém em diversos processos fisiológicos, nomeadamente em neuropatias ópticas como glaucoma, ambliopia e neuropatia óptica isquémica. A colina existe de forma natural no organismo humano e é um interveniente essencial na formação de células nervosas e na síntese de neurotransmissores. O zinco é o segundo mineral mais abundante no organismo humano e está presente em cerca de 200 enzimas. É um interveniente essencial em diversos processos fisiológicos nomeadamente no desenvolvimento do sistema neurológico, imunitário e reprodutor, entre outros. A citicolina e a função visual: A citicolina é um elemento fundamental na função visual uma vez que, como referido anteriormente, participa nos processos metabólicos das células nervosas, nomeadamente das que estão envolvidas na visão. A citicolina desempenha várias funções no ciclo deste tipo de células, uma vez que: 1) intervém na síntese de fosfatidilcolina, um componente primário das membranas neuronais; 2) é usada na síntese de acetilcolina, um neurotransmissor responsável pela propagação de sinais nervosos; 3) promove a síntese de diversos fosfolípidos, responsáveis pela reparação e regeneração das sinapses. Um aporte adicional de citicolina, em caso de défice, é útil na integridade das células nervosas e na comunicação entre as mesmas. O zinco e a função visual: O zinco é um mineral que contribui para a manutenção de uma visão normal e está presente em grandes concentrações na retina, particularmente no epitélio pigmentar. No olho, o zinco desempenha várias funções: 1) é co-factor das enzimas anti-oxidantes da retina: desidrogenase e catalase; 2) está envolvido no metabolismo retiniano; 3) evita a peroxidação dos lípidos e, consequentemente, danos nas membranas lipídicas, 4) regula o aporte de vitamina A. Toma diária recomendada: Tomar 2 cápsulas de EyeCare NPO com um copo de água, salvo indicação em contrário dada pelo médico. Condições de conservação: EyeCare NPO deve ser conservado em local fresco e seco, abaixo dos 25ºC. Data de durabilidade mínima: Não consumir EyeCare NPO após a data indicada na embalagem. Advertências: Os suplementos alimentares devem ser utilizados para um estilo de vida saudável e não como substitutos de um regime alimentar variado e equilibrado. Não exceder a toma diária recomendada. Adequado a diabéticos, intolerantes ao gluten ou à lactose. Manter fora do alcance das crianças. Não recomendado em caso de hipersensibilidade ou alergia a algum dos constituintes de EyeCare NPO. Em caso de gravidez ou amamentação, a toma deve ser feita sob indicação médica. Distribuido por: DAVI II – FARMACÊUTICA S.A. Estrada Consiglieri Pedroso, 71, Edifício D – 6º - Queluz de Baixo - 2730-055 Barcarena – Portugal.

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Artigo de Revisão

Intravitreal injection of pharmacological agents: From clinical trial to clinical practice

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INTRODUCTION

Intravitreal delivery bypasses the blood-retinal barrier, leading to a higher intraocular drug concentration for a longer period of time, while lessening the systemic toxicity. A wide variety of intravitreal pharmacological agents has been used: anti-infective (antibiotic, antifungal, and antiviral), anti-inflammatory (nonsteroidal anti-inflammatory agents, steroids and immunomodulators), anticancer agents, gas, anti-vascular endothelium growth factor (VEGF), among others[1]. Over the last decade, intravitreal corticosteroids and/or anti-VEGF have become the therapeutic backbone of several retinal disorders, including age-related macular degeneration (AMD), diabetic retinopathy (DR), retinal vein occlusions (RVO) and myopic neovascularization. Industry supported clinical research has helped propelling several drugs with encouraging visual and anatomic outcomes. With numerous novel therapies currently being investigated in clinical trials, the number of available drugs will likely continue to rise. High-quality imaging and the application of pharmacogenomic principles are probably guiding future therapies that through a comprehensive approach will hopefully meet the patients' needs and expectations.

We should keep in mind that everyday clinical practice differs greatly from a clinical trial setting and this inevitably affects the treatment results. The dependence on the center's resources (public or private) and agenda may delay the beginning of treatment, the interval between injections, between evaluations and injections (when performed separately), and even follow-up appointments. This usually leads to poorer than expected visual outcomes, patient dissatisfaction and physician frustration. Lack of patient motivation directly disturbs compliance and a vicious circle ensues. In order to provide the best possible treatment to our patients in a clinical setting, a balance between cost, effectiveness, compliance and agenda needs to be found.

The purpose of this paper is (1) to review the available drugs for intravitreal use, (2) to explore their approved indications and off-label use in the management of retinal diseases and (3) to present the treatment protocols currently being used at the Retinal Department of the Centro Hospitalar e Universitário de Coimbra (CHUC), Coimbra, Portugal.

1. AVAILABLE DRUGS FOR INTRAVITREOUS USE

1.1. ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR

Bevacizumab

Bevacizumab (Avastin®, Genentech, South San Francisco, CA) is a full-length antibody against VEGF isoforms that prevents binding of VEGF to its receptors[2,3]. The intravenous administration of Bevacizumab is approved by the United States (U.S.) Food and drug Administration (FDA) for the treatment of metastatic colorectal cancer[2]. Despite its inclusion in several clinical trials for the treatment of exudative AMD, diabetic macular edema (DME) and RVO, the drug has not received approval for intravitreous use. Its first use in exudative AMD dates back to 2005[4]. Because of similar

clinical effects at a remarkably lower cost[5,6], bevacizumab is still a commonly used off-label drug throughout the world.

Ranibizumab

Ranibizumab (Lucentis®, Genentech, Inc., South San Francisco, CA, USA) is a much smaller anti-VEGF antigen-binding antibody fragment that was found to achieve better retinal penetration than the full-length antibody[1]. Ranibizumab binds all VEGF isoforms with an affinity that is 5- to 10-fold higher than that of bevacizumab[7]. The drug was specifically developed for intraocular use and has been approved by the FDA, EMA and Infarmed for the management of exudative AMD, DME (European Medicines Agency) and macular edema secondary to RVO. Ranibizumab has been extensively studied and compared with other anti-VEGF agents since it was the first to receive approval for intravitreous injection (IVI).

Aflibercept

Previously known as VEGF trap-eye[8], aflibercept (Eylea®, Regeneron Pharmaceuticals, Tarrytown, NY, USA) is a soluble decoy receptor fusion protein specifically purified and formulated for intraocular injection[9]. Aflibercept is a chimeric molecule composed of an Fc fragment linked to the extracellular portions of the VEGFR1 and VEGFR2 receptors. It binds to all isoforms of VEGF and prevents activation of VEGF receptors[1]. The drug binds to VEGF with substantially greater affinity than bevacizumab or ranibizumab. The idea that this would translate into less frequent dosing through a substantially longer duration of action was later confirmed by several clinical trials[9-11] and led to its approval by the FDA, EMA and Infarmed for the management of exudative AMD, DME and macular edema secondary to CRVO in 2014.

1.2. CORTICOSTEROIDS

Corticosteroids have a wide range of functions and different action mechanisms. Besides reducing local inflammatory mediators, they act by diminishing VEGF levels, intraocular cell proliferation and stabilizing the blood-retinal barrier function while simultaneously increasing the activity and density of the gap junctions in the retinal capillary endothelium and improving oxygenation of ischemic areas[12]. Delivery of steroids to the vitreous cavity has been accomplished via direct injection through the pars plana, introduction of sustained-release or biodegradable implants, and injection of conjugate compounds[13].

Triamcinolone Acetonide

Intravitreal triamcinolone acetonide (IVTA) is a synthetic glucocorticoid corticosteroid that has been used in several intraocular diseases. One of its most common applications is macular edema (ME), a condition most frequently seen following intraocular surgery, RVO, DR and posterior segment inflammatory disease[14]. ME treatment varies depending on the underlying etiology, with uneven degrees of success. Due to its low cost and relative effectiveness, IVTA has been used in an off-label basis in refractory ME. However, this is frequently limited by its well-established side effects such as elevated intraocular pressure and cataract formation[12,13,15,16].

Dexamethasone

The dexamethasone drug delivery system (Ozurdex®, Allergan, Irvine, CA, USA) is a biodegradable, sustained-release device approved by the U.S. FDA and EMA for DME, macular edema secondary to RVO and non-infectious posterior uveitis. Ozurdex® is preloaded into a single-use applicator to facilitate injection of the rod-shaped implant directly into the vitreous. It provides 0.7 mg of dexamethasone in sustained release, administered via pars plana using the 22-gauge injecting applicator. Given the increased risk of cataract formation/progression, the U.S. FDA approved the drug only for pseudophakic patients or those that are phakic but with a scheduled cataract surgery. In Europe, Ozurdex® is indicated for pseudophakic patients or those who are considered insufficiently responsive to, or unsuitable for a corticosteroid sparing therapy.

When this delivery system is used, peak dexamethasone concentration is reached in the retina and vitreous at 2 months and is detectable for 6 months with minimal systemic absorption[17]. The pharmacokinetic profile of Ozurdex is thought to be similar between vitrectomized and nonvitrectomized eyes[18,19].

Fluocinolone Acetonide

The fluocinolone acetonide sustained delivery device (Iluvien®, Alimera Sciences, Alpharetta, GA, USA) is a small (3.5 x 0.37 mm), non-biodegradable cylindrical tube with a central drug–polymer matrix that releases 0.19 mg of fluocinolone acetonide in submicrogram doses into the vitreous cavity over a 3-year period with no systemic absorption[20]. The device is inserted into the vitreous cavity through a 25-gauge needle. Iluvien® received approval from the U.S. FDA to treat refractory macular edema in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure. Even though the drug is not approved by the EMA, several european countries have approved it, including Portugal. Cataract formation/progression is one of the most significant side effects[21].

2. INJECTION TECHNIQUE

After topical anesthesia and 5% povidone-iodine solution are applied in the conjunctival fornix, the 30-gauge injection needle is inserted via pars plana, 3.5-4.0 mm posterior to the limbus into the vitreous cavity, aiming towards the centre of the globe. Preferably, a different scleral site is used for subsequent injections. Although not an ubiquitous practice pattern since it has been postulated to paradoxically increase the risk of endophthalmitis[22,23], our treatment protocol involves, until a consensus document is approved, antibiotic prophylaxis with a topical quinolone 4id 4 days before and 4 days after the IVI.

3. INTRAVITREAL INJECTIONS IN THE MANAGEMENT OF RETINAL DISEASES

3.1. AGE-RELATED MACULAR DEGENERATION

3.1.1. BACKGROUND

AMD is a progressive, degenerative disease of the retina that occurs with increasing frequency with age[24]. Its neovascular form is the leading cause of irreversible vision loss in subjects >65 years of age living in economically developed countries[25,26], thus constituting a significant public health problem in regions where life expectancy is highest[24]. In the Coimbra Eye Study[27], the first AMD epidemiological study in a Portuguese population, the prevalence of early- (11.22%) and late-AMD (0.98%) were comparable to what has been described in other Western and Asian countries. As birthrates drop and life expectancy rises, the social burden of age-related conditions increases and a higher prevalence of AMD is expected in the future.

3.1.2. AVAILABLE TREATMENTS AND TREATMENT REGIMENS

Until the advent of anti-VEGF agents, the most frequently used treatments for neovascular AMD were thermal laser photocoagulation[28] and verteporfin photodynamic therapy (PDT)[29]. Despite initially promising results, neither of these treatment modalities proved to offer any significant chance for visual improvement[24]. Treatments targeting VEGF have revolutionized the management of neovascular AMD and are now considered the mainstay of therapy[24,30]. Three commonly used intravitreous VEGF inhibitors — bevacizumab, ranibizumab and aflibercept — have proved safe and effective for the treatment of exudative AMD, but only ranibizumab and aflibercept are approved by the U.S. FDA, EMA and Infarmed for this indication (Table 1).

Several non-inferiority trials have been conducted to compare the efficacy of bevacizumab vs. ranibizumab. The results of these trials (CATT[31,32], IVAN[33], MANTA[34], GEFAL[35] and LUCAS[5] studies) have shown that bevacizumab is comparable to ranibizumab and hence an effective treatment option for neovascular AMD. Stein et al[16] found

Table 1 | Currently available intravitreous anti-VEGF agents used in the clinical practice for the management of neovascular age-related macular degeneration.

	FDA approval	EMA approval	Infarmed approval	Relevant studies and level of evidence
Bevacizumab	No	No	No	• CATT Study[31,32] [1b] • IVAN Study[33] [1b] • MANTA Study[34] [1b] • GEFAL Study[35] [1b] • LUCAS Study[5] [1b]
Ranibizumab	Yes, at a dose of 0.5 mg	Yes, at a dose of 0.5 mg	Yes, at a dose of 0.5 mg	• ANCHOR Study[36,37] [1b] • MARINA Study[38,39] [1b] • PIER Study[49,50] [1b] • PrONTO Study[40] [1b] • EXCITE Study[51] [1b] • HORIZON Study[52] [1b] • SUSTAIN Study[42] [1b] • SAILOR Study[43] [1b]
Aflibercept	Yes, at a dose of 2.0 mg	Yes, at a dose of 2.0 mg	Yes, at a dose of 2.0 mg	• VIEW Studies[9] [1b]

Notes: The provided levels of evidence are based on the Centre for Evidence Based Medicine, Oxford (March 2009). Last assessed on 27th June 2015 at http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/
Abbreviations: FDA, US Food and Drug Administration; EMA, European Medicines Agency; Infarmed, Autoridade Nacional do Medicamento e Produtos de Saúde, I.P

Table 2 | Treatment regimens for the management of exudative AMD with anti-VEGF compounds.

	Monthly or bimonthly dosing	Treat and Extend Regimens	Pro re nata (PRN)
Treatment Schedule	- Continuous monthly or bimonthly dosing	- Initial monthly dosing until the macula is dry; than treatment is continued with gradual extension of the intervals between doses	- Initial 3 months loading dose, followed by as-needed dosing based on retreatment criteria
Advantages	- Maximum visual improvement and reduction of CRT	- Visual improvement and reduction of CRT - Decreased burden of frequent assessments and dosing - Decreased risks of frequent dosing	- Visual improvement and reduction of CRT - Decreased burden and risks of frequent dosing
Disadvantages	- High costs of frequent assessment and frequent dosing - Risks of frequent dosing (e.g. GA, stroke, etc)	- Few clinical trials have provided evidence for use of this regimen	- Despite less frequent injections, the number of clinical visits remains high
Mean number of visits in the 1st year	12	8	12
Mean number of injections in the 1st year	12	8	6
Clinical Trials Providing Evidence	• MARINA[38] • ANCHOR[36,37] • VIEW 1 and 2[9]	• LUCAS[5] • SALUTE[54]	• PrONTO[40] • HORIZON[52] • SAILOR[43] • SUSTAIN[42] • CATT[31] • GEFAL[35] • MANTA[34]

Notes: This table was adapted from Agarwal et al[30]
Abbreviations: CRT, central retinal thickness

that bevacizumab confers considerably greater value than ranibizumab for the treatment of neovascular AMD when the costs of a 20-year treatment of a hypothetical patient were compared between the two drugs. In spite of the strong body of evidence favoring the use of bevacizumab, the drug has not received approval for intravitreal use from FDA, EMA or Infarmed and has been used as an off label therapy for wet AMD since 2005.

The treatment protocols using IVI of anti-VEGF drugs for neovascular AMD have evolved from a monthly dosing (ANCHOR[36,37] and MARINA[38,39]) to a less rigorous, as-needed approach (PrONTO[40], HORIZON[41], SUSTAIN[42] and SAILOR[43]), in order to decrease treatment burden (Table 2). Despite minimizing the hazards associated with frequent dosing (potential increase in geographic atrophy[44,45] and an alleged higher risk of stroke, endophthalmitis, retinal tears and retinal detachment[24]), a trend toward worsening outcomes with less frequent dosing has been noted[30].

While most of the AMD clinical trials have evaluated monthly, quarterly, bimonthly, treat and extend (TAE) or *pro re nata* (PRN) treatment strategies, most retina specialists use different dosing regimens in their daily clinical practice[30]. According to the 2014 American Society of Retina Specialists (ASRS) Preferences and Trends (PAT) Survey, 78% of US retinal specialists (and 56% of international retinal specialists) treat neovascular AMD using the TAE regimen) employed in the LUCAS trial[5]. Freund et al[46] recently published a consensus article to consider the best-practice approach to the use of TAE with anti-VEGF agents, based on available scientific and clinical experience. A level 1 evidence for TAE is still lacking.

3.1.3. FROM TRIAL TO PRACTICE

The ophthalmologic community faces a huge dilemma in the management of neovascular AMD, with substantial controversies over the efficacy of substances, choice of

therapeutic regimens, exponentially growing costs from highly priced drugs, increasing patient numbers and disease chronicity with inherent monitoring needs[47].

A recent retrospective, interventional case series of 212 eyes treated in a clinical practice setting has shown that visual and anatomic improvements are maintained after 3 years using the treat-and-extend regimen with ranibizumab and bevacizumab[48].

The Seven Year Update of Macular Degeneration Patients (SEVEN-UP) study[53] was a multicenter, non-interventional cohort study to examine the 7-year results after entering the original ANCHOR[36,37]/MARINA[38] trials. This group had received 2 years of monthly ranibizumab, followed by an additional 2 years of as-needed ranibizumab treatment in the HORIZON protocol[52]. Compared with baseline, almost half of the eyes were stable, whereas one third declined by 15 letters or more[53]. Despite the small sample size (n=65), this study helped elucidate the challenges associated with the long-term management of wet AMD by showing that these patients remain at risk of vision loss many years after treatment. The best treatment regimen is yet to be determined. The best results were shown in clinical trials with a monthly regimen. However, due to extremely high costs and burden this is clinically unfeasible. During the last years our treatment protocol for newly diagnosed patients with typical neovascular AMD or retinal angiomatous proliferation involved a 3-month loading dose of IVI ranibizumab 0.5 mg/0.05 ml. Clinical and tomographic examination were performed after the 3rd injection and a PRN regimen was followed thereafter.

Retreatment criteria included visual acuity loss (≥5 ETDRS letters) and/or the presence of hemorrhage, fluid (intraretinal and/or subretinal) and/or pigment epithelial detachment (PED) in spectral domain optical coherence tomography (SD-OCT). When using Aflibercept 2.0 mg/0.05 ml, a bimonthly regimen was implemented in the first year after the 3-month loading dose, followed by PRN in the second year. Molecule switch was implemented whenever clinical response to the first drug subsided and always after a minimum of 3 injections.

More recently, a change to a treat and extend (TAE) regimen was implemented in our clinic, in agreement with the recent trends around the world[46]. Either ranibizumab or aflibercept are injected monthly until the retina is dry and a TAE regimen with a maximum interval of 3 months is then applied. In polypoid choroidal vasculopathy (PCV), PDT in association with intravitreal ranibizumab or aflibercept is used as a first line approach, provided that polyps are identified in indocyanine green angiography (ICGA).

The efficacy of any treatment regimen depends on its correct application. Economical and logistic restrictions and constrictions are responsible, all over the world, for an inadequate application of the chosen treatment regimen, with a great impact on the final efficacy.

Aflibercept 2q8 has shown to be as effective as monthly Ranibizumab. The implementation of this regimen can be applied with reduced burden (less number of injections and visits) and great efficacy, only in the first year. Aflibercept, with the 2q8 regimen in the first year and a 'treat and observe' strategy with a 3-month cap (that required injection)[9]; ranibizumab and bevacizumab with monthly regimens[36-39] or a PRN regimen with zero tolerance[32], are all able, like the TAE regimen[46], to improve vision in the first year and to preserve the VA gain in the second year.

When it is not possible to apply one of these treatment regimens in the first or following years, due to logistical or economical restrictions, then, a different strategy should be implemented in order to avoid unnecessary loss of vision. This adjustment in the treatment regimen, when necessary, should reflect the recent evidences coming from clinical trials and clinical practice, which include:

a. a better baseline VA is associated with a better final VA
b. a higher number of injections is associated with a better final VA (better results associated with 7 to 8 injections in the first year, 4 or more in the second year)
c. a retreatment before a VA drop occurs is associated with a better final VA
d. a long-term evaluation and treatment of AMD patients is associated with a better final VA (rarely a patient is discharged)

The chosen strategy should assure an early treatment, a minimum of seven to eight injections in the first year and four or more in the following years (in addition of allowing a reduction in the number of visits), and must include:

a) a green line for patients with exudative AMD assuring an earlier diagnosis and treatment
b) First year treatment scheduling:
   a. With Aflibercept: a loading dose of 3 injections followed by 2q8 in the first year.
   b. With Ranibizumab or Bevacizumab: a loading dose of 3 injections, followed by:
      i. two injections with a 6-weeks interval, and 3 bimonthly injections (total of 8 injections) or
      ii. a bimonthly regimen (total of 7 injections)

c) Treatment scheduling for the second and following years:
   a. quarterly treatment regimen that can be adjusted according to the evaluation visits.
d) Evaluation visits: a variable number of evaluation visits, after the loading dose, for adjusting the interval between injections, in the first and following years.

Whenever this strategy is implemented, at least 7 to 8 injections are assured in the first year (and four in the following years) and the number of visits can be decreased. The evaluation visits may allow for any correction in the prescheduled treatments. The results of this proposed regimen, although potentially inferior, for some patients, to those described for the treatment regimens with the best known results, are able to prevent vision loss in the majority of patients, while the burden is reduced.

3.2. DIABETIC RETINOPATHY

3.2.1 BACKGROUND

According to the PREVADIAB study[55], the prevalence of type 2 diabetes in the Portuguese population aged between 20 and 79 years old is 11.7% (95% confidence interval 10.8–12.6%). When pre-diabetic patients are taken together, this number rises to 34.9%, about 1/3 of the Portuguese population. Recently, the RETINODIAB study[56] found a prevalence of DR of 16.3% in a cohort of 52,739 Portuguese patients from a DR screening program in Lisbon and Tagus Valley region. Of these, 5484 patients (10.4%) had mild non-proliferative (NP) DR, 1457 patients (2.8%) had moderate NPDR, 672 (1.3%) had severe NPDR and 971 patients (1.8%) had proliferative DR requiring urgent referral to an ophthalmologist.

There is growing evidence that DR is the leading cause of visual impairment in working-age patients of industrialized countries[57]. Vision loss may arise from diabetic macular edema (DME), macular ischemia or vitreous hemorrhage[58].

A meta-analysis from the META-EYE Study group[59] involving individual participant data from population-based studies around the world found that 28 million of people suffer from vision-threatening DR. DME is the most frequent cause of visual impairment in patients with DR, occurring most often in patients with high levels of hemoglobin A1C and longer diabetes duration[59].

The increasing prevalence of diabetes worldwide emphasizes the importance of DME as a global public health issue.

3.2.2. AVAILABLE TREATMENTS AND TREATMENT REGIMENS

With the introduction of intravitreal anti-VEGF agents and corticosteroids, the therapeutic perspective for DME has undergone a seismic change[58]. These drugs are associated with favorable anatomical and functional outcomes in a large proportion of treated patients, with results replicated in multiple randomized controlled trials.

The IVI of anti-VEGF agents has been shown to be superior to focal and grid LASER photocoagulation[60-62], the gold standard treatment for DME since the Early Treatment Diabetic Retinopathy Study (ETDRS) in 1985[63]. Three commonly used intravitreous VEGF inhibitors - bevacizumab, ranibizumab and aflibercept, - have proved safe and effective for the treatment of DME[10,64,65], but only aflibercept and ranibizumab are approved by the FDA and EMA for this indication.

A recently published comparative-effectiveness randomized clinical trial from the Diabetic Retinopathy Clinical Research Network (DRCR.net), was conducted to compare intravitreous aflibercept (2.0 mg), bevacizumab (1.25 mg) and ranibizumab (0.3 mg) for the treatment of visually impairing DME[66]. The authors concluded that intravitreous aflibercept, bevacizumab and ranibizumab improve vision in eyes with center-involved DME, even though the relative effect depends on baseline visual acuity (VA). For mild baseline visual loss there were no apparent differences, on average, among study groups. However, for worse levels of baseline VA, aflibercept proved more effective than bevacizumab or ranibizumab[66].

In addition to anti-inflammatory properties, corticosteroids reduce the activity of VEGF by inhibiting the expression of VEGF and the VEGF gene[58]. The dexamethasone drug delivery system (Ozurdex®, Allergan, Irvine, CA, USA) is a biodegradable, sustained-release device approved by the U.S. FDA and EMA for DME. After promising results from the BOZURDEX study (a phase II randomized clinical trial that compared bevacizumab with the dexamethasone implant), the MEAD study[67] ultimately led to the FDA approval of the Ozurdex®. In this phase III, three-year, randomized, sham-controlled clinical trial in patients with DME, the dexamethasone implant proved safe and met the primary efficacy endpoint for improvement in BCVA. Significant cataracts requiring cataract surgery were found in 59% of the phakic eyes. Two patients (0.3%) developed uncontrolled elevated intraocular pressure that required trabeculectomy. In the FAME studies[21,68], Campochiaro et al found that the fluocinolone implant could provide substantial visual benefit for up to 3 years in the treatment of DME. In the 15 European countries (including Portugal)

Table 3 | Currently available intravitreous anti-VEGF agents and steroid implants used in the clinical practice for the management of diabetic macular edema.

	FDA approval	EMA approval	Infarmed approval	Relevant studies and level of evidence
Bevacizumab	No	No	No	• BOLT study[65,69] [1b] • Protocol T from DRCR.net[66] [1b]
Ranibizumab	Yes, at a monthly dose of 0.3 mg	Yes, at a monthly dose of 0.5 mg	Yes, at a monthly dose of 0.5 mg	• RESOLVE study70 • RISE and RIDE studies[60,64] [1b] • READ-2 Study[62] [1b] • Protocol I from DRCR.net[71,72] [1b] • Protocol T from DRCR.net[66] [1b]
Aflibercept	Yes, at a dose of 2.0 mg (every 8w after 5 initial monthly injections)	Yes, at a dose of 2.0 mg (every 8w after 5 initial monthly injections)	Yes, at a dose of 2.0 mg (every 8w after 5 initial monthly injections)	• VIVID and VISTA studies[10] [1b] • Protocol T from DRCR.net[66] [1b]
Dexamethasone implant	Yes, at a dose of 0.7 mg	Yes, at a dose of 0.7 mg	Yes, at a dose of 0.7 mg	• CHAMPLAIN study[73] [1b] • BEVORDEX study[74] [1b] • MEAD study[67] [1b]
Fluocinolone Acetonide Delivery Device	Yes, at a dose of 0.19 mg	No	Yes, at a dose of 0.19 mg	• FAMOUS study[20] [1b] • FAME A and B studies[21,68] [1b]

Notes: The provided levels of evidence are based on the Centre for Evidence Based Medicine, Oxford (March 2009). Last assessed on 17th July 2015 at http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/
Abbreviations: FDA, US Food and Drug Administration; EMA, European Medicines Agency; Infarmed, Autoridade Nacional do Medicamento e Produtos de Saúde, I.P

where it is currently approved, its use is limited for the treatment of vision impairment associated with chronic DME considered insufficiently responsive to available therapies. In the U.S., the FDA approved Iluvien® for the treatment of DME in patients previously treated with a course of corticosteroids that did not develop a significant rise in intraocular pressure.

3.2.3. FROM TRIAL TO PRACTICE

Most likely, distinctive pathophysiological features exist between recent-onset and chronic DME. The decision on the adequate therapeutic approach should take in consideration the chronicity of DME as well as the number of and response to previous treatment modalities.

As DME initially develops, VEGF-associated hyperpermeability, acute inflammation, and vascular dysfunction likely dominate[58]. In this setting, using an anti-VEGF drug seems to be the best possible strategy. On the other hand, chronic DME is likely associated with a higher non-VEGF cytokine milieu, chronic inflammation, and neuronal damage. This is probably a situation where corticosteroids may be more effective[58].

Regardless of the local ocular treatment chosen, evidence indicates that optimal systemic control of blood glucose, blood pressure, lipid parameters and physical exercise reduce complications related to diabetic retinopathy in the long term[75].

Our current treatment protocol (Fig 1) for newly diagnosed patients with focal DME is focal LASER photocoagulation of leaking microaneurysms. In cases of no clinical response or whenever diffuse DME is present, a 3-month loading dose with ranibizumab 0.5 mg/0.05 ml or aflibercept 2.0 mg/0.05 ml is started. Patients are observed after the loading dose. If a clinical response is achieved, regular clinical and OCT observation followed by an as needed treatment regimen is usually employed. More than one intravitreal injection may be prescribed between evaluation visits. In patients with persistent DME despite the use of anti-VEGF and a switch to a different anti-VEGF agent, the use of a steroid implant is the preferred treatment modality.

The implant of Dexametasone is our first option for non-responders to anti-VEGF, i.e. DME persistence with a tomographic reduction <20% in the central subfield thickness and/or VA improvement < 5 ETDRS letters. Patients need to be evaluated every 2 months after the implant and 2 to 3 implants may be needed in the first year. Some patients may respond to anti-VEGF again after a treatment period with costicosteroids.

The implant of Fluocinolone is indicated in chronic

DME with no response to anti-VEGF. According to our protocol, it is proposed in:

1 - Chronic DME diagnosed at least one year before and with:
   a. Non-response to anti-VEGF and
   b. At least 6 months of treatment and 3 or more anti-VEGF injections and
   c. Pseudophakic patients or with a programmed cataract surgery
2 - Chronic DME diagnosed at least one year before and with:
   a. Recent (less than six months) myocardial infarction or stroke and/or
   b. Absolute incapacity for monthly or less frequent visits to the Clinical centre and
   c. Pseudophakic patients or with a programmed cataract surgery

Patients are evaluated 1 month after the treatment and every 3 months after that.

3.3. RETINAL VEIN OCCLUSIONS

3.3.1. BACKGROUND

RVO is the second leading cause of retinal vascular disease after DR, with an estimated prevalence of 16.4 million adults worldwide[76]. When left untreated, visual impairment frequently develops, as well as other significant ocular complications[77]. Macular edema can be found in the vast majority of cases with central retinal vein occlusion (CRVO) and develops in 5-15% of eyes with branch retinal vein occlusion (BRVO)[78,79]. Both BRVO and CRVO are associated with a significant impairment in vision-related quality of life (as measured by the National Eye Institute visual function questionnaire, NEI- VFQ)[80].

3.3.2. AVAILABLE TREATMENTS AND TREATMENT REGIMENS

Following the recommendations of the CRVO and BRVO study groups[81,82], for many years the treatment of macular edema due to CRVO was based on clinical observation, while in BRVO grid laser photocoagulation was

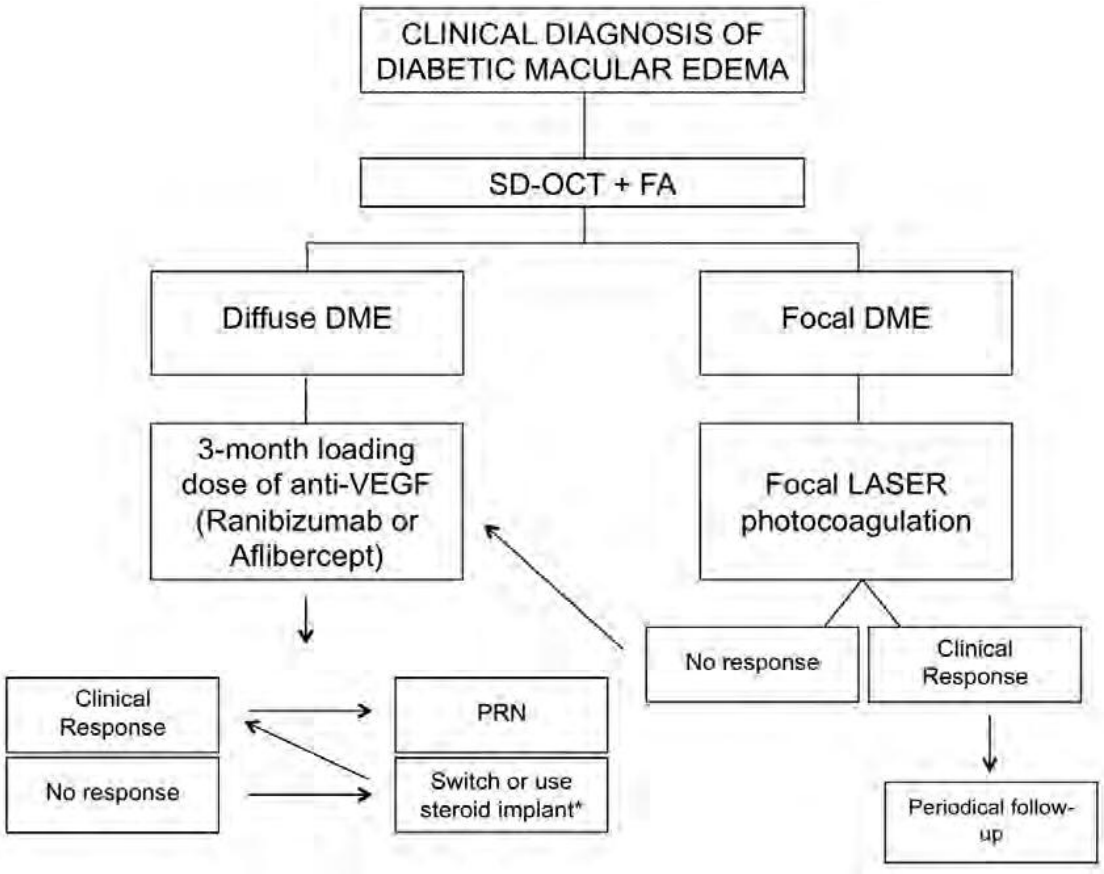

Fig. 1 | Diabetic macular edema treatment flowchart.

Table 4 | Currently available intravitreous agents used in the clinical practice for the management of macular edema secondary to retinal vein occlusion.

	FDA approval	EMA approval	Infarmed approval	Relevant studies and level of evidence
Bevacizumab	No	No	No	• Epstein et al[90] [2b] (CRVO) • Russo et al[91] [2b] (BRVO)
Ranibizumab	Yes, at a monthly dose of 0.5 mg	Yes, at a monthly dose of 0.5 mg	Yes, at a monthly dose of 0.5 mg	• CRUISE study[84,92] [1b] (CRVO) • BRAVO study[93] [1b] (BRVO) • HORIZON study[83] [1b] (CRVO and BRVO) • RABAMES study[94] [1b] (BRVO)
Aflibercept	Yes, at a monthly dose of 2.0 mg	Yes, at a monthly dose of 2.0 mg	Yes, at a monthly dose of 2.0 mg	• COPERNICUS study[85,95] [1b] (CRVO) • VIBRANT study[86] [1b] (BRVO)
Dexamethasone implant	Yes, at a dose of 0.7 mg	Yes, at a dose of 0.7 mg	Yes, at a dose of 0.7 mg	• GENEVA study[87] [1b] (CRVO and BRVO)

Notes: The provided levels of evidence are based on the Centre for Evidence Based Medicine, Oxford (March 2009). Last assessed on 17th July 2015 at http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/
Abbreviations: FDA, US Food and Drug Administration; EMA, European Medicines Agency; Infarmed, Autoridade Nacional do Medicamento e Produtos de Saúde, I.P; CRVO, central retinal vein occlusion; BRVO, branch retinal vein occlusion

applied. Over the last decade, significant innovations have reshaped the management of macular edema due to RVO. These include the FDA, EMA and Infarmed approval of anti-VEGF agents (ranibizumab and aflibercept) and dexamethasone implant for the treatment of visual impairing macular edema caused by either CRVO or BRVO (Table 4). Both compounds provided valuable anatomical and functional outcomes that have been reported in multiple randomized controlled trials[83-87]. However, head-to-head comparison studies sponsored by Novartis (COMRADE-B and COMRADE-C studies for BRVO and CRVO, respectively) have shown that ranibizumab is superior to the dexamethasone implant[80].

The use of steroids had already been investigated with intravitreal triamcinolone. In the SCORE study[88,89], intravitreal triamcinolone showed to be superior to observation for treating vision loss associated with macular edema secondary to CRVO[88] and BRVO[89]. Despite the promising results, the important adverse effects commonly associated with triamcinolone prevented its approval for the management of macular edema due to RVO.

Although not developed or licensed for intravitreal use, bevacizumab has long been used as an off-label therapy for macular edema due to RVO. Several studies have proven that the drug is safe and effective both for CRVO[90] and BRVO[91].

Like in exudative AMD and DME, the first clinical trials tested monthly regimens. However, a shift towards PRN or treat-and-extend approaches is being noted, accompanying the needs of a clinical practice approach.

3.2.3. FROM TRIAL TO PRACTICE

Our current treatment protocol for newly diagnosed patients with visually impairing macular edema due to CRVO or BRVO involves a 3-month loading dose with bevacizumab 1.5 mg/0.05 mL, ranibizumab 0.5 mg/0.05 mL or aflibercept 2.0 mg/0.05 mL, followed by a PRN regimen. More than one intravitreal injection may be prescribed between evaluation visits. In patients with persistent macular edema despite the use of anti-VEGF, switch to a different anti-VEGF agent or the use of the dexamethasone implant is our preferred approach.

3.4. MYOPIC NEOVASCULARIZATION

3.4.1. BACKGROUND

Even though myopia is already the most common eye condition worldwide, recent epidemiologic studies have shown that its prevalence is significantly increasing[96]. This increase is especially observed in Southeast Asia but European countries and the U.S. are also being affected by this global epidemic. Although education levels are associated with myopia, higher education seems to be an additive rather than explanatory factor[97]. Increasing levels of myopia carry a significant clinical and economic burden, by conveying an increased risk of the sight-threatening complications of high myopia[98]. The most fearsome consequence of pathologic myopia is choroidal neovascularization, which occurs in approximately 5%-10% of patients with pathological myopia[99].

3.4.2. AVAILABLE TREATMENTS AND TREATMENT REGIMENS

For a long time, LASER photocoagulation was the only treatment for extrafoveal myopic neovascularization. LASER scar expansion and recurrence of CNV were

frequently observed complications and led to the discontinuation of this treatment modality[99].

In cases of subfoveal CNV, photodynamic therapy (PDT) with verteporfin has proven safe and effective with stabilization of VA in 72% of the eyes with at 12 months[100]. Unfortunately, no significant benefit in visual outcome was found at 24 months[101]. Nowadays, the use of PDT remains a viable option, especially for patients with juxtafoveal CNV and whenever anti-VEGF therapy is unsuitable[102].

Anti-VEGF drugs are currently the gold standard for the management of myopic CNV[98,103] but only ranibizumab has received FDA, EMA and Infarmed approval for this indication. After the MYRROR study[104], aflibercept received approval for myopic CNV but only in Japan.

3.4.3. FROM TRIAL TO PRACTICE

Long-term results with ranibizumab and bevacizumab (used off label) for myopic CNV in clinical practice are similar. A recent study from Ruiz-Moreno et al[105] reported statistically significant improvements in visual acuity at 3 years but loss of statistical significance at 4, 5 and 6 years of follow-up.

In our department, myopic CNV is treated with a loading dose of 2 IVI of ranibizumab or Bevcizumab followed by an as needed approach. Retreatment is based on loss of visual acuity (≥5 ETDRS letters) and/or the presence of fluid on OCT and/or significant metamorphopsia.

3.5. MISCELLANEOUS CAUSES OF CNV

Miscellaneous causes of CNV include central serous chorioretinopathy, angioid streaks, choroidal rupture after blunt trauma, birdshot retinopathy, presumed ocular hitoplasmosis syndrome, white-dot syndromes or idiopathic forms. Due to its rare nature, clinical guidelines are not available for the management of these conditions. We usually employ an individualized approach based on the clinical findings and complemented by multimodal retinal imaging. We usually start with an IVI of ranibizumab or Aflibercept 0.5 mg/0.05 mL followed by an as needed treatment regimen.

4. CONCLUSION

Because of their chronic nature and poor visual outcomes when left untreated, neovascular AMD, DME, macular edema due to RVO and myopic neovascularization are important examples of retinal diseases that require IVI of therapeutic agents. The advent of intravitreal anti-VEGF drugs and corticosteroids has restyled the management of these conditions, allowing for better anatomical and functional results without significant side effects. However, monthly injections and monthly clinic visits may reduce long-term compliance and increase costs[46]. To optimize the benefit/risk ratio and cost- effectiveness of intravitreal treatment, flexible dosing strategies are increasingly being used in clinical practice (PRN and treat-and-extend regimens). These approaches are a lot easier to implement in a daily basis with acceptable results and patient compliance.

New agents are currently being developed, aimed at improving the patient's quality of life by minimizing visual impairment and treatment burden in these highly consequential and burdensome diseases.

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