

Anti-VEGF Therapy for Retinal Diseases Treatment: Recommendations for its Practice in Colombia

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Abstract

Objective: To display local experience on treatment for retinal diseases with anti-vascular endothelial growth factor (anti-VEGF) therapies and to raise awareness regarding patient-centered care, recognizing the role of medical specialists in determining the most appropriate treatment mainly based on scientific evidence, but also considering the successful experience and practice handling each patient, based on their unique and individual characteristics.

Method: Review and comparison of scientific literature according to the authors experience to diagnose and treat diseases involving intraocular injections, focusing on Neovascular Age-related Macular Degeneration (NV-ARMD), Diabetic Macular Edema (DME), Diabetic Retinopathy (DR), Macular Edema due to Branch Retinal Vein Occlusion (BRVO), Central Retinal Vein Occlusion (CRVO) and Subretinal Neovascularization associated with Pathological Myopia (PM).

Results: The review confirms that, when speaking of drug classes, treatment algorithms or patient profiles, different agents of the same therapeutic class can result in variable efficacies or safety profiles. The clinical relevance represented by the adequate assessment of post-treatment results must be considered, but specially, the careful screening to determine the most appropriate agent and regimen in the intention to treat a patient. Though recommendations and treatment guidelines for pathologies exist, protocols in individualized management and exposure of these real-life experiences are necessary, since not all patients or all retinal diseases respond in the same way to each therapeutic agent.

Conclusion: Efficacy and safety using anti-VEGF therapies are extremely important when it comes to providing truly patient-centered care. There is no therapeutic solution, intervention or alternative that fits all complex ocular diseases, so it is important to weigh the available evidence, the experience and the expectations of both patients and prescribers. This will allow to get access to the appropriate therapeutic alternatives, in a timely manner, always considering the efficacy and safety profiles, active pharmacovigilance and the costs associated with the therapeutic alternatives used locally.

Keywords: Intraocular Injections; Anti-VEGF; Neovascular Age-related Macular Degeneration; Diabetic Macular Edema, Diabetic Retinopathy (DR); Macular Edema; Vein Occlusion; Subretinal Neovascularization; Pathological Myopia (PM)

Abbreviations

Anti-VEGF: Anti Vascular Endothelial Growth Factor; ARMD: Age Related Macular Degeneration; BP: Blood Pressure; BRVO: Branch Retinal Vein Occlusion; CNV: Choroidal Neovascularization; CRT: Central Retinal Thickness; CRVO: Central Retinal Vein Occlusion; DM: Diabetes Mellitus; DME: Diabetic Macular Edema; DR: Diabetic Retinopathy; ECLAC: Economic Commission for Latin America and the Caribbean; HbA1c: Glycated Hemoglobin; ICO: International Council of Ophthalmology; IETS: Instituto de Estudios Tecnológicos en Salud (Institute of Technology Health Studies); INVIMA: Instituto Nacional de Vigilancia de Medicamentos y Alimentos;

ME: Macular Edema; MNVM: Macular Neovascular Membrane; NPDR: Non-proliferative Diabetic Retinopathy; NV-ARMD: Neovascular Age Related Macular Degeneration; OCT: Optical Coherence Tomography; PRN: Pro Re Nata or as Needed; PRP: Pan Retinal Photocoagulation; RVO: Retinal Vein Occlusion; RVOS: Retinal Vein Occlusion Study; vPDT: Verteporfin Photodynamic Therapy

Introduction

Eye health is a safeguard for individual, family, and social development; therefore, visual impairment becomes a global public health problem due to its implications both at the human level and socioeconomically. Currently, there are 285 million visually impaired people globally, of whom 39 million are blind and 246 million have low vision. Approximately, 90% of the global burden of visual impairment is confined to developing and low-income countries; it should be emphasized that this impairment may be prevented or cured in up to 80% of the total worldwide [1].

Eyecare remains an area of little attention when it comes to health policies in our region; hence, it is necessary to promote awareness to conduct regular reviews, establish and report experiences on proactive and ongoing treatments, increase therapeutic efficacy and especially identify and evaluate new therapeutic alternatives for currently untreated eye diseases [2].

As retina specialists from different academic centers and public and private care in Colombia, we acknowledge the need to present our recommendations based on pathophysiology, pharmacodynamics and experience in the use of available therapies for the management of retinal diseases, clearly established as a major public health problem affecting an increasing number of Colombians.

Available therapeutic approaches: Introduction to the use of Anti-VEGF

As the population ages, retinal alterations have become more frequent. Many of these diseases are associated with the imbalance in the interaction of growth promoters and inhibitors, which generate an impaired angiogenesis process [3].

Elevated levels of intraocular VEGF are associated with intraocular neovascularization, a common vascular abnormality in many retinal conditions, such as NV-ARMD, DME, DR, occlusive diseases of the retina such as BRVO and CRVO, and macular neovascular membranes (MNVM) in high myopia. It has been shown that blocking the action of VEGF, through direct intravitreal injection, restores and improves visual function in these clinical conditions. The rise of anti-VEGF therapies has dramatically changed the treatment paradigm for several common and serious diseases of the retina, leading to a significantly better prognosis and better visual outcomes.

Several molecules have been developed to act directly on the VEGF or to intervene in its genetic expression; some of them are used as therapy in cancer treatment [4,5]. Molecules that are approved for use as ophthalmic treatments are: ranibizumab (Lucentis; Novartis AG, Basel, Switzerland) and aflibercept (Eylea; VEGF-Trap Eye, Bayer AG, Germany); others are under investigation or are used off-label as in the case of bevacizumab (Avastin; F. Hoffman - La Roche LTD, Basel, Switzerland). Table 1 summarizes the molecular characteristics of anti-VEGF molecules [6].

Of the three anti-VEGF therapies available in Colombia (aflibercept, ranibizumab, and bevacizumab), only two (aflibercept and ranibizumab) have been approved for use in retinal diseases by Instituto Nacional de vigilancia de Medicamentos y Alimentos (INVIMA), an institution under the direction of the Ministry of Health and Social Protection [7]. Table 2 describes the anti-VEGF compounds used in Colombia to treat retinal conditions.

Evidence, experience and recommendations for the use of anti-VEGF therapies in the treatment of retinal diseases in Colombia Age-related macular degeneration (ARMD)

ARMD is the leading cause of irreversible blindness in people over 55 years of age in the developed world. It is a chronic condition that affects the macula, resulting in a reduction or loss of central vision. Wet/neovascular ARMD is characterized by the growth of new

Parameter	Aflibercept	Bevacizumab	Ranibizumab
Size Molecular weight (kDa)	115	149	48
Binding affinity target of action	VEGF-A VEGF-B PlGF	VEGF-A	VEGF-A
Binding affinity Kd for VEGF ₁₆₅ (pM)	0.5	58-1100	46-192
PD VEGF suppression time (days)	71	NA	36
Ocular PK Intravitreal half-life (days)	4.5-4.7 (rabbits) 11 (humans)	4.32-6.61 (rabbits) 3.1 (monkeys) 6.7-10 (humans)	2.6-2.88 (rabbits) 3-3.2 (monkeys) 7.1 (humans)
Systemic PK Serum half-life in human (days)	5-7	21	0.25
Composition	Recombinant fusion protein comprising portions of human VEGFR-1 and VEGFR-2 extracellular domains, fused to the Fc portion of human IgG1	Monoclonal Antibody	Antibody fragment
Immunogenic component:	Portion Fc of human IgG	Humanized IgG	NO

Table 1: Molecular characterization of anti-VEGF molecules.

Da: Kilodalton, Fc: Fraction of the Complement, VEGF: Vascular Endothelial Growth Factor, PlGF: Placental Growth Factor, Ig: Immunoglobulin, pM: Picomolar, PD: Pharmacodynamics, PK: Pharmacokinetics, Kd: Dissociation Constant.

Source: [5,6].

Product (Manufacturer/Holder of Marketing Authorization)	Compound (Generic Name)	Indication Approved by INVIMA (*)	Date of Approval
Eylea (BAYER PHARMA A.G.)	Aflibercept	*Treatment of Age-Related Macular Degeneration (wet ARMD) *Treatment of Macular Edema (ME) Secondary to Central Retinal Vein Occlusion (CRVO)*Treatment of ME secondary to Branch Retinal Vein Occlusion (BRVO) *Treatment of Diabetic Macular Edema (DME) *Treatment of Myopic Choroidal Neovascularization (Myopic CNV) *Treatment of Age-Related Macular Degeneration (ARMD) of the neovascular (wet) type *Treatment of visual impairment due to Diabetic Macular Edema (DME)	06/19/2012
Lucentis (NOVARTIS PHARMA AG)	Ranibizumab	*Treatment of visual impairment due to ME secondary to Retinal Vein Occlusion (RVO) (Branch Retinal Venous Occlusion [BRVO] or Central Retinal Vein Occlusion [CRVO]) *Treatment of visual impairment due to Choroidal Neovascularization (CNV) secondary to Pathological Myopia (PM)	07/6/2007
Avastin (Hoffmann-La Roche)	Bevacizumab	NA	09/20/2005

Table 2: Anti-VEGF therapies used for the treatment of retinal diseases in Colombia.

* Information Source: Summary of product characteristics (SPC) for medications - Health Marketing Authorization INVIMA [7].

abnormal blood vessels under the retina, representing only 10 - 20% of all cases of ARMD, but 90% of the blindness associated with this condition [8].

Prevalence and risk factors in the Colombian population

In 2009, a study of ARMD prevalence and risk factors was carried out in four cities in Colombia (Bogotá, Cali, Bucaramanga and Barranquilla). Most of the participants were women (70.8%) and the average age was 67.1 years (range: 55 - 95; SD 8.7). The prevalence of ARMD in the general group was 4.86% (CI 95: 2.94 - 6.78). The prevalence of advanced ARMD by age group was 0.7% for the 55 - 59 age group, 1.0% for 60 - 69 years, 8.0% for 70 - 79 years, and 22.7% for those over 80 years. The prevalence of early ARMD was 11.8% (CI 95: 8.9 - 14.6). The prevalence in smokers was 6.4% (CI 95: 2.5 - 10.4) and in non-smokers was 2.4% (CI 95: 0.3 - 8.2). The prevalence was higher in people with low level of education (9.3%) than in people with higher level of education (2.9%) [9]. These results show statistics resembling those reported in other epidemiological studies worldwide [10].

In March 2012, the Pan-American Retina and Vitreous Society and The Angiogenesis Foundation held a panel of ARMD experts in Bogotá, and published the report entitled *Advocating for Improved Treatment and Outcomes for Wet Age-Related Macular Degeneration* [11]. This report discussed the challenge of diagnosing and treating patients with the wet form of the disease in a timely and effective manner. Strategies were presented to address the social impact of the disease, as to reduce secondary visual loss: education of physicians (at all levels of care) and to the general population (including the State); research and epidemiological analysis associated with the disease; timely and reliable diagnosis (based on reference technology); opportunity in initial care and follow-up by specialized physicians; treatment protocols as per the drug used; and ensuring supply of the drug if required.

Freun., *et al.* published a review article in 2015 on different treat-and-extend regimens in retinal diseases [12]. For the treatment of wet macular degeneration there are currently two medical treatment regimens. One is the PRN approach (pro re nata or as needed), in which three loading doses are applied until no fluid, followed by optical coherence tomography (OCT) and visual acuity determination, thereby establishing the need to administer intravitreal antiangiogenic agents in case of recurrence of the disease, with the limitation of failing to diagnose and treat in time fluid recurrence, resulting in irreversible loss of vision. Because of this, in recent years, the treat-and-extend scheme has been defined as the therapy of choice in the different treatment guidelines at the Western level, with which greater control has been found with respect to patient follow-up and visual acuity stability, thanks to earlier diagnoses of recurrence and greater exposure to antiangiogenic agents.

The treat-and-extend scheme (Figure 1) consists of fixed treatment doses until remission of the disease. This criterion is met when there is no fluid on OCT, no new hemorrhages in the clinical examination, or two optical tomography scans showing no changes in retinal volume, associated with no variation in visual acuity. These findings are considered the maximum response to medical treatment [12].

Treat-and-Extend Regimen

Maximum response indicators in initial monthly injections

1. Complete resolution of SRF and IRF with no new retinal hemorrhage.
2. No further reduction of SRF or IRF on OCT for at least two consecutive visits in the absence of new retinal hemorrhage.
3. No further flattening of serous or vascularized pigment epithelial detachment.
4. No further improvement in BCVA, in its definition of maximal response.

Figure 1: SRF: subretinal fluid, IRF: intraretinal fluid, OCT: optical coherence tomography, BCVA: Best-Correct Visual Acuity. Taken and modified from reference: [12].

Subsequently, the therapy interval is extended by 2 weeks, up to a maximum of 10 to 12 weeks between each dose, without neovascular activity (Figure 2). It should be noted that retinal pigment epithelium detachment was not considered a sign of neovascular activity.

Extension Phase
Based on OCT and BCVA FA or IGA: RAP or PV Maximum extension 12 weeks.

Treat-and-Extend Regimen
Keys to extend the extension phase
1. Continuous absence IRF or SRF 2 consecutive injections.
2. IRF or SRF stabilization 2 consecutive injections.
3. No hemorrhage.

Figure 2: SRF: Subretinal Fluid, IRF: Intraretinal Fluid, OCT: Optical Coherence Tomography, BCVA: Best-Correct Visual Acuity, RAP: Retinal Angiomatous Proliferation, PV: Polypoidal Vasculopathy, FA: Fluorescein Angiography, IGA: Indocyanine Green Angiography. Taken and modified from reference: [12].

In the scheme described, the interval is reduced or shortened by one to two weeks in the case of recurrence of evident neovascular disease, such as slight accumulation of intra- or subretinal fluid, loss of visual acuity of less than six letters, or the presence of extrafoveal hemorrhages, even with stable visual acuity. If the recurrence is severe, evidenced as a large accumulation of fluid at the retinal level or visual loss of more than 6 letters, or subfoveal hemorrhages, the case should be individualized, the cause sought, and the monthly treatment regimen advised to be resumed (Figure 3).

The study of choice to determine if there is neovascular activity, and used in each of the ophthalmological controls, is the optical coherent tomography of the macula. The second option is fluorescein angiography, especially in case of recurrence of the disease. There are also concerns on leakage despite having OCT in normal parameters, or investigation of unexplained vision loss.

Currently, in Colombia there are no data from governmental entities referring to the treatment situation of patients with wet ARMD, and it is unknown whether the treatment schemes are undertaken as suggested in the literature. Based on the current limitation of access to anti-VEGF therapies in our country, one may assume that the possible statistics are very similar to those reported in recent real-life studies for the treatment of this disease, in which it is demonstrated that patients are undertreated with less than the ideal doses to preserve vision and prevent blindness [13].

Diabetic macular edema

Diabetes Mellitus (DM) is now considered a global epidemic. Diabetic retinopathy (DR) is a microvascular complication affecting one in three people with MD [14]. It is the third cause of irreversible blindness globally, but the first in people of productive age in developing countries [15]. Specifically, in Colombia, prevalence of diabetes is 7.2%, statistics determined by ECLAC (Economic Commission for Latin America and the Caribbean - WHO) and corroborated by the 2017 National Health Interview Survey [16]. Considering that at least 12% of diabetic patients will have DME, an estimated population of 425,879 people with the disease may be identified.

These statistics reassert the importance of epidemiological studies to guide the most appropriate management in patients with DM and compromise of the retina.

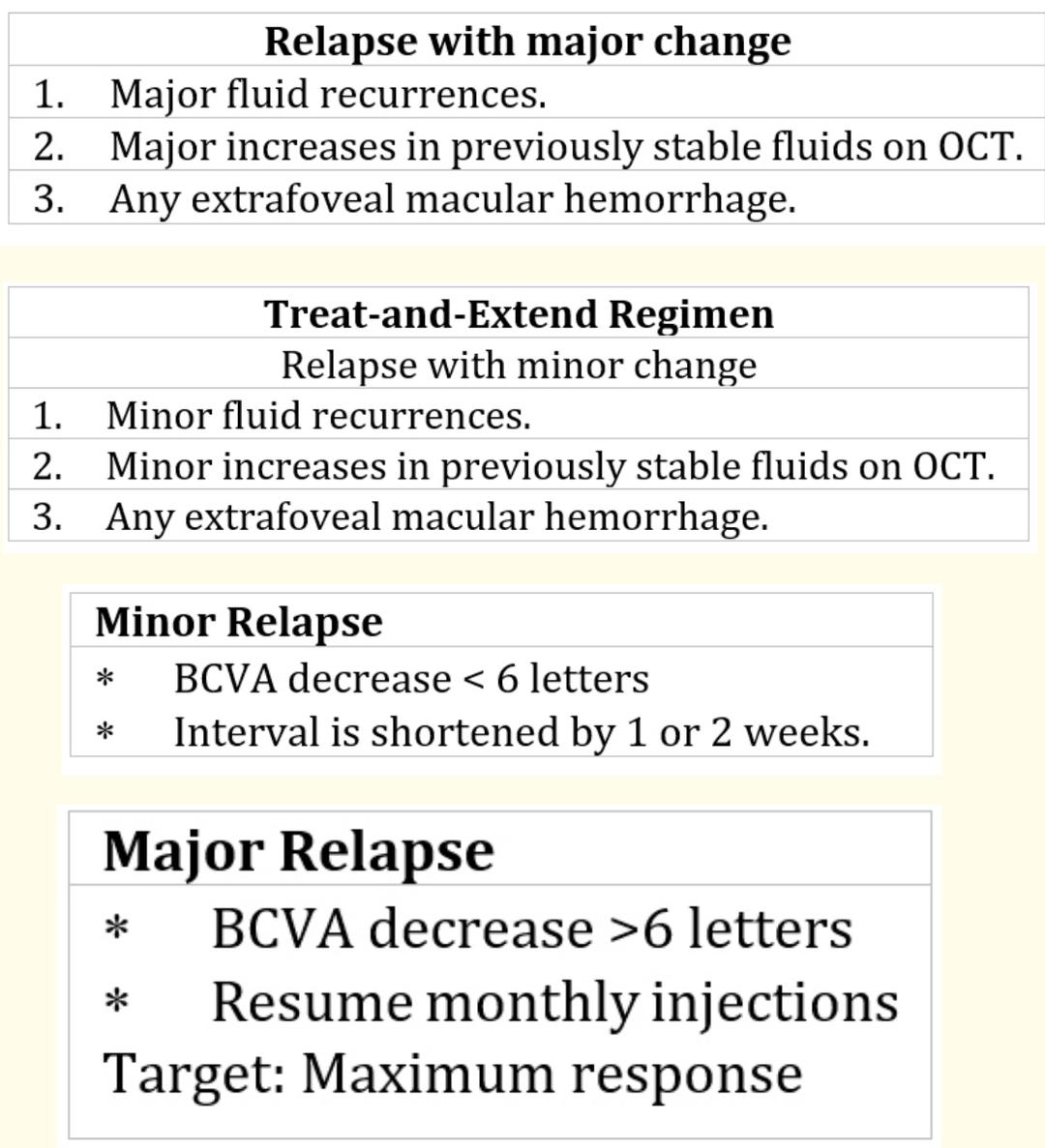


Figure 3: OCT: Optical Coherence Tomography, BCVA: Best-Correct Visual Acuity.
 Taken and modified from reference: [12].

Several studies have demonstrated that besides the management of macular edema (ME) with local measures, optimal control of blood glucose, blood pressure (BP) and lipids is equally important to avoid retinal complications arising from this systemic decompensation. In regions such as the United States, Australia, Europe, and Asia, 34.6% of the population with DM has some degree of DR and 10.2% the risk of visual loss due to this complication [14,17]. It is important to note that there are no epidemiological studies in Colombia illustrating the reality of the problem in our patient population; this constitutes a great limitation for the development of cost-effective programs in the management of diabetic patients.

However, in 2016 the Colombian Ministry of Health informed in the Eye Health Situation Analysis (Agreement 519/2015) the increase in diabetic retinopathy from one year to the next, reporting a prevalence of 12.86 per 100,000 inhabitants in 2009 and 19.76 in 2014. When disaggregated by sex, the estimated prevalence for women was 10.41/100,000 in 2009 and 19.51 in 2014, indicating an increase

of 9.1/100,000 in the six years analyzed. Furthermore, men reported a prevalence of 9.20/100,000 in 2009 and 16.06 in 2014, with an increase of 6.86 per 100,000 inhabitants in the six years [18].

The latest barometer report estimates 415 million people with DM worldwide by 2015, a figure that may rise to 642 million by 2040 [19]. For South and Central America, this accounts for 29.6 million by 2015, with a projection of 48.8 million by 2040. In Colombia, 134 patients with diabetes were interviewed, of whom 28% had DR and 12% DME. Twenty-five percent of patients (1 in 4) do not believe that their disease is well controlled.

Interestingly, they claimed to be five times more concerned about vision loss than about other diabetes-related complications. Nonetheless, 10% of patients never consulted their physician about the visual implications of diabetes. Three major barriers to the proper management of DR and DME were identified: 1) Time: 53% of patients reported long waiting times for an appointment; 2) Geographical location: 35% of patients expressed that care sites were far from home; and 3) Costs: 13% of patients stated that ophthalmologic examinations were very expensive [20].

The data referred to above are of paramount importance in the context of this document. The approach and consensus must extend beyond designing a pharmacological management protocol based on anatomical findings (OCT and fundus photography) and visual outcomes.

Today, the management of the diabetic patient in Colombia can be defined as “fragmented” management, i.e. patients are generally referred to internists, endocrinologists, general ophthalmologists, or optometrists. The patient is only referred to the retinologist for significant vision loss because it warrants specialized evaluation. Consequently, the signs and symptoms are usually very advanced, and a greater percentage of resources could be allocated instead to education and prevention, seeking greater knowledge of the disease among patients. This would allow them to make earlier consultations before there is irreversible damage to the retina, a common practice with renal, cardiac and other target organ damage [21-24].

Evidence of current management of diabetic macular edema

When reviewing the DME articles and management guidelines, one may observe that the regimens are similar to those already mentioned, thereby confirming the importance of the classification of diabetic retinopathy.

In this sense, the guidelines of the International Council of Ophthalmology (ICO) are taken as an example (Table 3). Based on this classification, the decision to refer the patient to the ophthalmologist can be taken in situations of high availability of resources or in the case of intermediate or limited courses [14].

Diabetic Retinopathy	Findings Observable on Dilated Ophthalmoscopy
No apparent DR	No abnormalities
Mild nonproliferative DR	Microaneurysms only
Moderate nonproliferative DR	Microaneurysms and other signs (e.g., dot and blot hemorrhages, hard exudates, cotton wool spots), but less than severe nonproliferative DR
Severe nonproliferative DR	Moderate nonproliferative DR with any of the following: *Intraretinal hemorrhages (≥20 in each quadrant); *Definite venous beading (in 2 quadrants); *Intraretinal microvascular abnormalities (in 1 quadrant); *No signs of proliferative retinopathy
Proliferative DR	Severe nonproliferative DR and 1 or more of the following: Neovascularization Vitreous/preretinal hemorrhage
Diabetic Macular Edema	Findings Observable on Dilated Ophthalmoscopy
No DME	No retinal thickening or hard exudates in the macula
Noncentral-involved DME	Retinal thickening in the macula that does not involve the central subfield zone that is 1 mm in diameter
Central-involved DME	Retinal thickening in the macula that does involve the central subfield zone that is 1 mm in diameter

Table 3: International classification of diabetic retinopathy (DR) and diabetic macular edema (DME).

Taken and modified from ICO International Council of Ophthalmology | Guidelines for Diabetic Eye Care. Copy- right © ICO January 2017.

Several therapeutic regimens have been developed according to the state of diabetic retinopathy, but all have in common the optimization of systemic management. The control of glycated hemoglobin (HbA1c) is strongly emphasized as a parameter of good blood glucose management. In fact, the barometer highlights the importance of the decrease in HbA1c: a 1% decrease implies 37% fewer microvascular complications, 43% fewer amputations or less severe vessel damage, 21% fewer DM-related deaths, 14% fewer myocardial infarctions and 12% fewer strokes [25]. In other words, systemic control constitutes the mainstay of the management of patients with retinal damage due to DM. In diabetes, the triggering factor for VEGF is ischemia, generated in turn by microvascular damage secondary to sustained hyperglycemia and associated factors (HBP, dyslipidemia, etc).

Management of DR/DME in Colombia

In the ideal scenario, the first objective is to improve systemic conditions: to aim for an HbA1c with values around 7%, adequate control of blood pressure and lipids. If there is no DR, or if it is mild to moderate, clinical follow-up is recommended at defined intervals according to guidelines of the International Council of Ophthalmology (ICO). Any diabetic patient with or without adequate control of the disease could live with DME, whose management will be defined later. If there is severe non-proliferative DR (NPDR), close monitoring is recommended to follow the development of proliferation. Pan retinal photocoagulation (PRP) should be considered in patients with high risk or poor compliance.

If there is proliferative DR (PDR), pan retinal photocoagulation associated with the use of anti-VEGF is recommended [26,27]. The use of PRP has been known since the 1980s, and since 2006 anti-VEGF has become part of the therapeutic arsenal [28].

In patients with DME, the therapy of choice is the use of anti-VEGF [29-33]. As a second alternative, experts have defined the use of intravitreal steroids, among which are sustained-release dexamethasone intravitreal implants as well as triamcinolone injections [34]. It should be noted that the laser has retained its therapeutic value, and in our setting it continues to be a very useful cost-effective strategy. In this sense, it is used as a laser adjuvant in grid and focal lasers [35].

In case of advanced proliferative diabetic retinopathy, vitreous hemorrhage, and tractional retinal detachment, the patient will require vitreo-retinal surgery.

In the management of the diabetic patient, success is based on multidisciplinary management. Although anti-VEGF, depot steroids, micropulse laser, and surgery are often effective control strategies, so long as the systemic process is not controlled, alterations will continue to occur and local measures will lose their effect, making treatment ineffective if approached from the retinal strategy as the primary management.

Retinal vein occlusion (RVO)

As discussed in several sections of this document, VEGF plays a very important role in the pathogenesis of various retinal disorders with potential risk of visual loss, such as RVO, supported by the results of major clinical studies [37-42].

Rogers, *et al.* report highly global results in their study of RVO prevalence, which involves approximately 16.4 million people, being the standardized prevalence by age and sex 5.2 per 1000 (95% CI: 4.40 - 5.99) for any type of RVO, most frequently among Hispanics [43]. Thus, RVO is considered a chronic disease requiring individualized management, centered on the particular needs of the patient, and which must be rigorously monitored for proper assessment and evolution of the disease.

In ME secondary to vein occlusions, VEGF, like other cytokines, also plays a very important role in their development with potential risk of visual loss, supported by the results of major clinical studies [37-42]. Nevertheless, the two types of retinal vein occlusions (central retinal vein occlusion [CRVO] and branch retinal vein occlusion [BRVO]) are different entities in terms of pathogenesis, natural course and visual and morphological prognosis. Edema is greater in CRVO compared to BRVO [44].

There are both local and systemic risk factors that must be taken into consideration by internal medicine to improve treatment. In the absence of known risk factors, if the patient is young, or in the case of bilateral presentation, patients should be referred for hematology and rheumatology evaluation. At the time of diagnosis, a fluorescein angiography should be performed, provided that intraretinal hemorrhages make it possible, as to establish the degree of ischemia, both macular and peripheral, in the two entities. It is recommended to

continue monitoring with OCT to evaluate both the retinal thickness and the presence of the external limiting membrane and the ellipsoid zone. On the basis of these last two assessments, the visual prognosis of the patients may be established.

Different algorithms have been proposed in the literature for the adequate management of RVO, with the purpose of standardizing its management by means of anti-VEGF agents. There is strong evidence supporting that the use of anti-VEGF agents substantially improves outcomes in patients with this disease [45-47], provided that treatment is initiated as early as possible. Delay in receiving treatment for six months led to irreversible vision loss [45]. Both ranibizumab and aflibercept have been analyzed in clinical experiments with BRVO or CRVO patients, who were randomized to one of two doses of each drug [37,38,48]. After six months, those in the sham treatment arms were crossed to a treatment arm with each molecule. Although treatment with each anti-VEGF for six months resulted in a rapid decrease of edema, the group treated later failed to achieve the same visual gains as the two groups initially treated with the aforementioned drugs.

Another option for the management of RVO-associated ME is the use of intravitreal steroids, either with a sustained-release dexamethasone intravitreal implant (every 4 to 6 months) or with a triamcinolone intravitreal injection [49,50], which modulate the production of cytokines and growth factors. The reason why these are regarded as second choice treatment in some clinical studies is due to their local side effects, such as glaucoma and cataract formation [51,52].

In our experience and based on the availability and access of anti-VEGF therapies, we consider performing treatments alone or combined with anti-VEGF in conjunction with laser photocoagulation, taking into account the fluorescein angiography and OCT results. The laser is indicated only when the patient presents neovascularization of the retina or neovascular glaucoma. In view of the current economic difficulties and the results of the Branch Vein Occlusion Study (BVOS), where laser was available for the treatment of ME from CRVO in patients with visual acuity less than 20/40, resulting in favorable results compared to no treatment [53], laser could be adopted as salvage treatment, in case of unavailability of the aforementioned therapies (anti-VEGF and steroids).

We usually use the PRN strategy and the treat-and-extend regimen based on the response. Campochiaro, *et al.* conclude that after edema resolution with monthly intravitreal ranibizumab therapy, in subjects with BRVO, visual results were maintained at 15 months of treatment, with no statistically significant differences between subjects treated with PRN and those given monthly injections [54].

Pathological myopia

Pathological myopia is defined as a refractive error of more than -6 diopters or an axial length of more than 26.5 mm, with typical changes in the fundus [55]. Pathological myopia is the most frequent cause of choroidal neovascularization (CNV) in young people and the second most frequent cause of age-related macular degeneration in the general population [56]. CNV is a complication that may lead to loss of central vision and occurs in approximately 5.2% to 10.2% of high myopia [57,58]. The development of CNV produces visual loss, which has a profound impact on productivity, quality of life and professional performance expectations in young people [59]. There is general agreement that intravitreal antiangiogenic agents are the first-line treatment for myopic CNV, with good long-term functional and anatomical results [60]. Initial evidence was based primarily on retrospective studies and clinical experience, and a growing number of randomized clinical trials have been published, not to mention that there are several in progress. One such experiment was RADIANCE [61], in which intravitreal ranibizumab was compared with verteporfin photodynamic therapy (vPDT), demonstrating improvement in visual acuity at 12 months in the ranibizumab treatment arm. Another important study was MYRROR [62], in which aflibercept was compared to placebo. It also showed improvement in visual acuity at the end of follow-up. It has been proven that age, best corrected basal visual acuity, myopic CNV location, pre-existing chorioretinal degenerative changes (lacquer cracks and chorioretinal atrophy), and previous photodynamic therapy are correlated with visual outcome after anti-VEGF treatment for myopic CNV [63].

Discussion

As previously mentioned, of the three anti-VEGF drugs available in Colombia (aflibercept, ranibizumab, and bevacizumab), only two (aflibercept and ranibizumab) are approved for use in retinal diseases by the Instituto Nacional de Vigilancia de Medicamentos y Alimentos (INVIMA), an institution under the direction of the Ministry of Health and Social Protection (Table 1).

Similarly, we have outlined our recommendations and experiences based on published treatment guidelines and real-life evidence on the use of these agents to treat the conditions described. Figures 1-3 illustrate the regimen reported by Freund, *et al.* for wet age-related macular degeneration, which in our opinion should be used as the basis for the treat-and-extend regimen for macular edema due to diabetic retinopathy and macular edema due to vein occlusions.

It is important to note that with any class of drugs or treatment algorithms for any patient, different agents of the same class may exhibit varying efficacy or side effect profiles. This prompts us to consider the clinical importance of properly assessing post-treatment outcomes, but, above all, of carefully selecting the most appropriate agent and regimen to treat the patient. Although there are recommendations and treatment guidelines, individualized management protocols and exposure to these real-life experiences are necessary, since not all patients nor all retinal diseases respond equally to each agent.

In the previous sections, we have presented the reported evidence and, in some cases, the evidence of local use in the management of patients and patient subgroups with particular clinical aspects and characteristics; any recommendation to treat patient subgroups in the same manner is not based on the evidence reported and published [33,64].

In head-to-head studies comparing the three anti-VEGF agents for the management of DME, it has been found that after one and two years of treatment there are varying responses to the different drugs. Differential factors among the 3 anti-VEGFs are observed in the therapeutic response (VA and CRT) in addition to the concomitant use of laser. Although at two years of follow-up the CRT outcome is similar for all three drugs, it is evident that in the first year, and especially in the first six months, bevacizumab has a lower effect than the other two drugs and requires an increased use of laser. In the group of patients having the worst basal visual acuity, who did not receive laser, the decreasing CRT response was more evident with aflibercept (-209 microns) than with bevacizumab (-144 microns) and ranibizumab (-153 microns) [65]. For DME, specialists seek to achieve maximum response in the shortest possible time. In order to improve visual prognosis by exposing photoreceptors to oxidative factors generated in macular edema for a shorter time, anti-VEGFs generating an adequate therapeutic response during the first year that is maintained in the second year should be considered due to their long-term cost-effectiveness.

There is no single treatment for all retinal diseases. The different treatment paradigms for various diseases are complex and may vary in how long satisfactory results are obtained.

Consequently, the purpose of this document is to share the evaluation of the literature on treatment for each particular clinical condition and to provide guidance on patient eligibility criteria, guidelines for initiating and conducting treatment, including anti-VEGF intervals and doses, as well as follow-up and pharmacological surveillance required to guide therapy and establish criteria for continuation and cessation of therapy; it is important to modify or discontinue treatment if the expected response is not being obtained.

Some studies and reported clinical experience have identified significant problems with the composition and storage of bevacizumab, raising serious concerns about its safety when used extensively. The risk of an adverse event or devastating complication, such as acute eye inflammation or endophthalmitis, increases when a drug is reused in a manner not indicated by the manufacturer [66,67].

There are several reports evidencing and comparing the rate of serious ocular adverse events, such as severe intraocular inflammation, in patients receiving off-label treatment with bevacizumab [67] or other vascular complications, both ocular and systemic, that should be considered when selecting this treatment modality. In this way, experts would seek to reduce the rare possibility of devastating events that could lead to blindness and even death, situations that can potentially occur with any of the three anti-VEGFs, but which would have a more complex implication should it result from the use of an off-label drug.

The community of ophthalmologists should be aware of the potential systemic vascular complications involving the cardiovascular system, central nervous system, gastrointestinal tract, kidneys, and lungs [66,67]. Likewise, different international ophthalmologic societies and regulatory institutions have alerted on outbreaks of serious ocular adverse events in patients treated with bevacizumab [65,70-74] and have warned that the notification and reporting rate of spontaneous adverse events understate the risk of using an agent not formulated for this purpose.

The episodes of severe inflammation and adverse events described may occur due to impurities that can be tolerated intravenously, but not through the eye [73,74]. It is very important to note that the administration of bevacizumab in major clinical studies was performed using a single vial for each injection and under strict conditions of preparation and trial protocol. Each batch of re-packaged bevacizumab was subjected to sterility, purity and potency tests [66], thereby limiting the ability to generalize safety conclusions from these experiments to the real-life practices of preparing dilutions and aliquots of each vial.

The Colombian legislation is not clear in this regard. After the IETS (Instituto de Estudios Tecnológicos en Salud [Institute of Technology Health Studies]) conducted studies on bevacizumab, the Ministry of Health considered authorizing the use of bevacizumab for wet ARMD only. However, the document from file No. 201624002244491, dated 01-12-2016, has a paragraph that needs special attention: "It is important to emphasize that any prescription outside the use approved by the marketing authorization is the responsibility of the treating physician, as stipulated in articles 12 and 13 of Act 23/1981, which read as follows...." That is, if physicians decide to treat pathologies other than MNVM with bevacizumab, they must have exclusive informed consents clarifying to the patient that the use remains off-label in all entities, including wet MNVM, as well as DME and CRVO/RVO. The fact that the Ministry has included this drug in the UNIRS list (uses not included in the marketing authorization) does not confer on it the status of a drug approved for wet ARMD; it remains off-label, but "recognized" by the Ministry for this indication. INVIMA has yet to clarify how the fractionation of the drug will be managed, and if upon filling out the MIPRES (Health Ministry application on My Prescription), when choosing the "ampoule" option, an entire ampoule of the drug will be dispatched without fractionation, or if "ampoule" refers to a fractionated dose in an authorized site and endorsed by INVIMA. As can be inferred, there are still very large legal loopholes for retinologists when they choose to use bevacizumab as therapy, loopholes that must be clarified in conjunction with INVIMA and the Ministry of Health to ensure safety for both retinologists in their practice and patients when they are guaranteed a fractionation system compliant with Good Manufacturing Practices.

This situation warrants further study of the current reality concerning the so far poorly called medical autonomy, which we hope to work on and publish about promptly from ACOREV (Asociación Colombiana de Retina y Vítreo [Colombian Retina and Vitreous Association]).

It is therefore necessary to present and support the need for a program to ensure the proper handling, storage, and distribution of bevacizumab to reduce the risk of contamination. Clinical specialists and patients require transparency and responsibility in terms of proper management and off-label use, which should be supervised and monitored in accordance with the considerations of the Colombian health system and policies. Quality assurance and pharmacological surveillance procedures should include bioavailability, potency, sterility, and purity testing. This program should also include the ability to measure and monitor patient outcomes and adverse events.

It is worth mentioning that the strict limitations required in clinical experiments are not always applicable in real-world clinical practice, as adherence to the rigorous timing and regimens of treatment guidelines and algorithms is not always possible. Many factors affect patients' ability to schedule and attend visits, as well as access to indicated anti-VEGF therapy and treatments for comorbidities. Ophthalmologists require flexibility to offer treatment regimens that address individual patient characteristics and circumstances and that reflect a constantly evolving evidence foundation. This is therefore an invitation to expose and share local experience on the protocols used in our clinical practice as real-life evidence in the treatment of retinal diseases.

Conclusion

The authors of this document recognize that for the different anti-VEGF therapeutic options currently available in Colombia there is sufficiently robust evidence regarding their use in the treatment of retinal diseases.

The characteristics of our population, as well as the characteristics of medical care and interdisciplinary management of patients, together with the particular aspects of our health system and access to anti-VEGF therapies, make it necessary to establish a continuous dialogue for the development of a scientifically and clinically solid framework for the use of these therapies in our country.

It is critical to recognize that efficacy and safety in the use of anti-VEGF therapies are of paramount importance when it comes to providing a true patient-centered care.

The joint work proposed from a platform that exploits the collaborative work and exposes and shares real-life experiences, as discussed in this document, will address unsatisfied needs and fill gaps to ensure access to appropriate treatment at the right time, with the need for pharmacovigilance of available therapies and in line with actual cost considerations for the patient and institutions.

It is worth noting that at present, and based on the objectives of established and ongoing health programs in our country, the recommendations contained in this document, which gather available solid evidence and the best collective experience of specialists, contribute as an argument for the appraisal and evolution of treatment guidelines and algorithms, specifically in retinal diseases where anti-VEGF therapies are indicated and recommended.

Conflicts of Interest

The author declares no conflict of interest.

Bibliography

1. Bourne RRA, et al. "Magnitude, temporal trends, and projections of the global prevalence of blindness and distance and near vision impairment: a systematic review and meta-analysis". *The Lancet Global Health* 5.9 (2017): e888-897.
2. Bayer Innovación. "Pérdida de la visión, principal causa de discapacidad en edad avanzada". 4 (2015): 15.
3. Amadio M, et al. "Targeting VEGF in eye neovascularization: What's new? A comprehensive review on current therapies and oligonucleotide-based interventions under development". *Pharmacological Research* 103 (2016): 253-269.
4. Campochiaro PA, et al. "Anti-Vascular Endothelial Growth Factor Agents in the Treatment of Retinal Disease". *Ophthalmology* 123.10 (2016): S78-S88.
5. Tah V, et al. "Anti-VEGF Therapy and the Retina: An Update". *Journal of Ophthalmology*. 2015 (2015): 1-13.
6. Zhang Y, et al. "Anti-VEGF treatment for myopic choroid neovascularization: from molecular characterization to update on clinical application". *Drug Design Development and Therapy*. 3413 (2015).
7. Consultas registros sanitarios INVIMA. 4 (2016): 14.
8. Han F, et al. "Profile of ranibizumab: efficacy and safety for the treatment of wet age-related macular degeneration". *Therapeutics and Clinical Risk Management* 343 (2012).
9. Rodríguez JR, et al. "Prevalencia y Factores de riesgo en degeneración macular relacionada con la edad en Colombia". *Revista Sociedad Colombiana de Oftalmología* 42 (2009): 117-127.
10. Wong WL, et al. "Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis". *The Lancet Global Health* 2.2 (2014): e106-16.
11. The Angiogenesis Foundation. "Advocating for Improved Treatment and Outcomes for Wet Age-Related Macular Degeneration". (2012).
12. Freund KB, et al. "Treat-And-Extend Regimens with Anti-vegf Agents in Retinal Diseases: A Literature Review and Consensus Recommendations". *Retina* 35.8 (2015): 1489-1506.
13. Holz FG, et al. "Multi-country real-life experience of anti-vascular endothelial growth factor therapy for wet age-related macular degeneration". *British Journal of Ophthalmology* 99.2 (2015): 220-226.
14. ICO International Council of Ophthalmology | Guidelines for Diabetic Eye Care (2017).
15. Solomon SD, et al. "Diabetic Retinopathy: A Position Statement by the American Diabetes Association". *Diabetes Care* 40.3 (2017): 412-418.
16. Colombia, editor. Encuesta nacional de salud 2007: resultados nacionales. 1st edition. Bogotá: Ministerio de la Protección Social, República de Colombia (2009): 342.
17. Sivaprasad S, et al. "Prevalence of Diabetic Retinopathy in Various Ethnic Groups: A Worldwide Perspective". *Survey of Ophthalmology* 57.4 (2012): 347-370.
18. Gaviria A, et al. Arciniegas L Análisis de la Situación visual en salud convenio 519 (2015).
19. DR Barometer. "The Diabetic Retinopathy Barometer Report: Global Findings". International Federation on Ageing. Toronto, ON. Canada (2017).

20. DR Barometer. "The Diabetic Retinopathy Barometer Report: Colombia". *International Federation on Ageing* 129 (2017): 16-24.
21. Riccardi G., et al. "Association between retinopathy and impaired peripheral arterial circulation in insulin-dependent diabetic patients". *Arteriosclerosis* 8.5 (1988): 509-514.
22. El-Asrar AM., et al. "Retinopathy as a predictor of other diabetic complications". *International Ophthalmology*. 24.1 (2001): 1-11.
23. Kramer CK., et al. "Diabetic Retinopathy Predicts All-Cause Mortality and Cardiovascular Events in Both Type 1 and 2 Diabetes: Meta-analysis of observational studies". *Diabetes Care* 34.5 (2011): 1238-1244.
24. Nguyen-Khoa B-A., et al. "Hospitalized cardiovascular events in patients with diabetic macular edema". *BMC Ophthalmology* 11 (2012).
25. Stratton IM., et al. "Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study". *BMJ* 321.7258 (2000): 405-412.
26. Photocoagulation treatment of proliferative diabetic retinopathy. Clinical application of Diabetic Retinopathy Study (DRS) findings, DRS Report Number 8. The Diabetic Retinopathy Study Research Group. *Ophthalmology* 88.7 (1981): 583-600.
27. "Photocoagulation treatment of proliferative diabetic retinopathy: relationship of adverse treatment effects to retinopathy severity. Diabetic retinopathy study report no. 5". *Developments in Ophthalmology* 2 (1981): 248-261.
28. Stewart MW. "Anti-VEGF Therapy for Diabetic Macular Edema". *Current Diabetes Reports* 14.8 (2014).
29. Massin P., et al. "Safety and Efficacy of Ranibizumab in Diabetic Macular Edema (RESOLVE Study): A 12-month, randomized, controlled, double-masked, multicenter phase II study". *Diabetes Care* 33.11 (2010): 2399- 2405.
30. Mitchell P., et al. "The RESTORE Study". *Ophthalmology* 118.4 (2011): 615-625.
31. Nguyen QD., et al. "Ranibizumab for Diabetic Macular Edema". *Ophthalmology* 119.4 (2012): 789-801.
32. Korobelnik J-F., et al. "Intravitreal Aflibercept for Diabetic Macular Edema". *Ophthalmology* 121.11 (2014): 2247- 2254.
33. Wells JA., et al. "Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema". *Ophthalmology* 123.6 (2016): 1351-1359.
34. Elman MJ., et al. "Randomized Trial Evaluating Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema". *Ophthalmology* 117.6 (2010): 1064-1077.e35.
35. Photocoagulation for diabetic macular edema. "Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group". *Archives of Ophthalmology* 103.12 (1985): 1796-1806.
36. Amoaku WM., et al. "Defining response to anti-VEGF therapies in neovascular AMD". *Eye* 29.6 (2015): 721
37. Campochiaro PA., et al. "Ranibizumab for Macular Edema following Branch Retinal Vein Occlusion". *Ophthalmology* 117.6 (2010): 1102-1112.e1.
38. Brown DMN., et al. "Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study". *Ophthalmology* 117.6 (2010): 1124- 1133.e1.
39. Clark WL., et al. "Intravitreal Aflibercept for Macular Edema Following Branch Retinal Vein Occlusion". *Ophthalmology* 123.2 (2016): 330-336.
40. Ogura Y., et al. "Intravitreal Aflibercept for Macular Edema Secondary to Central Retinal Vein Occlusion: 18-Month Results of the Phase 3 GALILEO Study". *American Journal of Ophthalmology* 158.5 (2014): 1032- 1038.e2.
41. Heier JS., et al. "Intravitreal Aflibercept Injection for Macular Edema Due to Central Retinal Vein Occlusion". *Ophthalmology* 121.7 (2014): 1414-1420.e1.

42. Bhisitkul RB., *et al.* "Predictive Value in Retinal Vein Occlusions of Early Versus Late or Incomplete Ranibizumab Response Defined by Optical Coherence Tomography". *Ophthalmology* 120.5 (2013): 1057-63.
43. Rogers S., *et al.* "The Prevalence of Retinal Vein Occlusion: Pooled Data from Population Studies from the United States, Europe, Asia, and Australia". *Ophthalmology* 117.2 (2010): 313-319.e1.
44. Campochiaro PA., *et al.* "Ranibizumab for Macular Edema Due to Retinal Vein Occlusions: Implication of VEGF as a Critical Stimulator". *Molecular Therapy* 16.4 (2008): 791-799.
45. Berger AR., *et al.* "Optimal Treatment of Retinal Vein Occlusion: Canadian Expert Consensus". *Ophthalmologica* 12, 234.1 (2015): 6-25.
46. Campochiaro PA., *et al.* "Sustained Benefits from Ranibizumab for Macular Edema following Central Retinal Vein Occlusion: Twelve-Month Outcomes of a Phase III Study". *Ophthalmology* 118.10 (2011): 2041-9.
47. Brown DM., *et al.* "Sustained Benefits from Ranibizumab for Macular Edema Following Branch Retinal Vein Occlusion: 12-Month Outcomes of a Phase III Study". *Ophthalmology* 118.8 (2011): 1594-1602.
48. Boyer D., *et al.* "Vascular Endothelial Growth Factor Trap-Eye for Macular Edema Secondary to Central Retinal Vein Occlusion". *Ophthalmology* 119.5 (2012): 1024-1032.
49. Narayanan R., *et al.* "A randomised, double-masked, controlled study of the efficacy and safety of intravitreal bevacizumab versus ranibizumab in the treatment of macular oedema due to branch retinal vein occlusion: MARVEL Report No. 1. *British Journal of Ophthalmology* 99.7 (2015): 954.
50. Scott IU., *et al.* "Baseline Predictors of Visual Acuity and Retinal Thickness Outcomes in Patients with Retinal Vein Occlusion: Standard Care versus Corticosteroid for Retinal Vein Occlusion Study Report 10". *Ophthalmology* 118.2 (2011): 345-352.
51. Haller JA., *et al.* "Dexamethasone Intravitreal Implant in Patients with Macular Edema Related to Branch or Central Retinal Vein Occlusion". *Ophthalmology* 118.12 (2011): 2453-2460.
52. Haller JA., *et al.* "Randomized, Sham-Controlled Trial of Dexamethasone Intravitreal Implant in Patients with Macular Edema Due to Retinal Vein Occlusion". *Ophthalmology* 117.6 (2010): 1134-1146.e3.
53. Iacat-Bernard AG., *et al.* "Steroids and Macular Edema from Retinal Vein Occlusion". *European Journal of Ophthalmology* 21(6_suppl) (2011): 37-44.
54. Argon laser photocoagulation for macular edema in branch vein occlusion. The Branch Vein Occlusion Study Group. *American Journal of Ophthalmology* 98.3 (1984): 271-282.
55. Campochiaro PA., *et al.* "Monthly Versus As-Needed Ranibizumab Injections in Patients with Retinal Vein Occlusion". *Ophthalmology* 121.12 (2014): 2432-2442.
56. Neelam K., *et al.* "Choroidal neovascularization in pathological myopia". *Progress in Retinal and Eye Research* 31.5 (2012): 495-525.
57. Yetik H., *et al.* "Structural features of attached retina in rhegmatogenous retinal detachments". *Retina* 24.1 (2004): 63-68.
58. Grossniklaus HE and Green WR. "Pathologic findings in pathologic myopia". *Retina (Philadelphia, Pa)* 12.2 (1992): 127-133.
59. Wong TY., *et al.* "Epidemiology and Disease Burden of Pathologic Myopia and Myopic Choroidal Neovascularization: An Evidence-Based Systematic Review". *American Journal of Ophthalmology* 157.1 (2014): 9-25.e12.
60. Yoon JU., *et al.* "Prognostic factors for visual outcome after intravitreal anti-VEGF injection for naive myopic choroidal neovascularization". *Retina* 32.5 (2012): 949-955.
61. Lai TYY., *et al.* "Long-term outcome of intravitreal anti-vascular endothelial growth factor therapy with bevacizumab or ranibizumab as primary treatment for subfoveal myopic choroidal neovascularization". *Eye* 26.7 (2012): 1004-1011.

62. Wolf S., *et al.* "RADIANCE: a randomized controlled study of ranibizumab in patients with choroidal neovascularization secondary to pathologic myopia". *Ophthalmology* 121.3 (2014): 682-692.
63. Ikuno Y., *et al.* "Intravitreal Aflibercept Injection in Patients with Myopic Choroidal Neovascularization: The MYRROR Study". *Ophthalmology* 122.6 (2015): 1220-1227.
64. Qureshi F., *et al.* "Primary intravitreal ranibizumab for myopic choroidal neovascularization". *Seminars in Ophthalmology* 26.2 (2011): 52-54.
65. Jampol LM., *et al.* "Diabetic Retinopathy Clinical Research Network. Anti-Vascular Endothelial Growth Factor Comparative Effectiveness Trial for Diabetic Macular Edema: Additional Efficacy Post Hoc Analyses of a Randomized Clinical Trial". *JAMA Ophthalmology* 134.12 (2016).
66. Diabetic Retinopathy Clinical Research Network, Wells JA., *et al.* "Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema". *The New England Journal of Medicine* 372.13 (2015): 1193-1203.
67. Berger A and Sharma S. "Severe intraocular inflammation/endophthalmitis Following off-label treatment with intravitreal bevacizumab". *Ophthalmology Scientific Update*. Toronto (2009).
68. Sharma S., *et al.* "Rate of serious adverse effects in a series of bevacizumab and ranibizumab injections". *Canadian Journal of Ophthalmology* 47.3 (2012): 275-279.
69. Falavarjani KG and Nguyen QD. "Adverse events and complications associated with intravitreal injection of anti-VEGF agents: a review of literature". *Eye* 27.7 (2013): 787-794.
70. Azmeh AM. "Ocular and Systemic Vascular Adverse Events Following Intravitreal Bevacizumab Injection". *Ophthalmology & Visual Science* 1.1 (2016): 1004.69.
71. Fielden M., *et al.* "Acute intraocular inflammation following intravitreal injection of bevacizumab- -a large cluster of cases". *Acta Ophthalmologica* 89.8 (2011): e664-e665.
72. Hall R., *et al.* "Incidence of ocular complications following intravitreal Bevacizumab (Avastin®) injections". Paper presented at: 72nd Annual Meeting of the Canadian Ophthalmological Society 22, Toronto, Ontario. Abstract 1434 (2009).
73. Holland S., *et al.* "Outbreak of acute intraocular inflammation after Bevacizumab intravitreal injection: An epidemiological investigation. Paper Presented at: 72nd Annual Meeting of the Canadian Ophthalmological Society 22, Toronto, Ontario. Abstract 1444 (2009).
74. Orozco-Hernández A., *et al.* "Acute sterile endophthalmitis following intravitreal bevacizumab: case series". *Clinical-Ophthalmology* 8 (2014): 1793-1799.

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