Latin American Consensus on Age-Related Macular Degeneration

Francisco J Rodríguez MD1, Lihteh Wu MD2, Arturo Alezzandrini MD3, J Fernando Arevalo MD4, Joaquín Bafaluy MD5, Maria Hortensia Berrocal MD6, Cristian Carpentier MD7, Eduardo Cunha de Souza MD8, Michel Farah MD9, Jans Fromow Guerra MD10, Gregorio Gabela MD11, Federico Graue Wiechers MD12, Ricardo Infante de Germán Ribón MD13, Mauricio Maia MD14, Fernando Marcondes Henha MD15, Virgilio Morales Canton MD16, Hugo Ocampo MD17, Hugo Quiroz-Mercado MD18, Jose Antonio Roca Fernandez MD19, Juan Gonzalo Sánchez MD20, Patricio G. Schlottmann MD21, Marín A Serrano MD22, Walter Takahashi MD23

Affiliations: 1Fundación Oftalmológica Nacional, Bogota, Colombia, 2Instituto de Cirugía Ocular, San José, Costa Rica 3Oftalmos, Buenos Aires, Argentina, 4Wilder Eye Institute at Johns Hopkins University, Baltimore, MA, USA, 5Universidad Nacional de Rosario, Rosario, Argentina, 6Centro Oftalmológico Berrocal y Asociados, Santurce, Puerto Rico, 7Fundación Oftalmológica Los Andes, Santiago, Chile, 8Universidad de São Paulo (FMUSP), São Paulo, Brazil, 9Universidade Federal de São Paulo, São Paulo, Brazil, 10Colegio Nacional de Investigación en Ciencias Visuales México-ARVO, Mexico City, Mexico, 11Hospital Metropolitano, Quito, Ecuador, 12Instituto de Oftalmología Conde de Valenciana, Mexico City, Mexico, 13Fundación Oftalmológica Nacional, Bogota, Colombia, 14Instituto Brasileiro de Luta contra a Cegueira, São Paulo, Brazil, 15Escola Paulista de Medicine, Universidade Federal de São Paulo, São Paulo, Brazil, 16Asociación para Evitar la Ceguera en México I.A.P., Mexico City, Mexico, 17Clínica de Oftalmología de Cali, S.A., Cali, Colombia, 18Médico Consultante del Servicio de Retina, APEC, Mexico City, Mexico and Denver Health Medical Center, CO, USA, 19Universidad Peruana Cayetano Heredia, Lima, Peru, 20Instituto Nacional de Investigación en Oftalmología-INO, Medellin, Colombia, 21Organización Médica de Investigación, Buenos Aires, Argentina, 22Clínica Oftalmológica Centro Caracas, Caracas, Venezuela, 23Servicio de Retina e Vítreo, Departamento de Oftalmología, Universidad de São Paulo, São Paulo, Brazil.

Abstract
Age-related macular degeneration (AMD) is a chronic disease affecting the retina and is the most common cause of blindness in the ageing population in the developed world. Correct and timely diagnosis and classification allows physicians to estimate which patients are at high risk of progressing to more advanced stages of the disease.

In February 2012, 23 Latin American experts met in Cartagena, Colombia, to develop a Consensus on AMD. This paper summarizes the main points of the discussions including definitions, diagnosis, antiangiogenic treatments, and hopes for the future. Dry AMD remains untreatable but results from promising Phase II trials are awaited eagerly. Antiangiogenics, such as the licensed vascular endothelial growth factor (VEGF) inhibitors, aflibercept and ranibizumab, have revolutionized the treatment of wet AMD in recent years. These drugs work by inhibiting the choroidal neovascularization that causes the rapid vision loss in wet AMD. Another antiangiogenic, bevacizumab, is also commonly used off-label, but is not approved currently for intraocular use. However, barriers to treatment compliance, due to the frequency of monthly injections, can also affect the efficacy of these antiangiogenic therapies. Aflibercept has a longer duration of action compared with other treatments and thereby offers reduced injection frequency. By relieving patients of the need for monthly visits, it can help reduce the growing burden of AMD patients on healthcare resources.

Introduction
Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the elderly population of the developed world and is a chronic condition affecting the macula, resulting in reduction or loss of central vision. AMD is usually classified as early, intermediate, and advanced. There are two main types of advanced AMD – dry and wet – with the most common AMD pathology being the dry form (where degenerative changes in the retinal pigment epithelial cells [RPE] are seen), and which comprises 80% of all AMD cases. However, there is no effective treatment available currently for dry AMD. Wet AMD – the growth of abnormal new blood vessels under the retina – accounts for only 10% of all AMD cases, but 90% of blindness from this condition. Several therapies are available for wet AMD, but only antiangiogenic treatments and sometimes phototherapy can help prevent further vascularization.
In the United States, AMD is estimated to affect approximately 1.75 million people. Less is known on the prevalence in Latin America due to the limited number of epidemiology studies; however, one Colombian study by Rodríguez et al. reported an overall prevalence of 4.86% in a cohort of 535 volunteers.

In Cartagena, Colombia, in February 2012, 23 international experts from Colombia, Costa Rica, Brazil, Argentina, Mexico, Chile, Peru, Venezuela and Ecuador met to develop a Latin American consensus on AMD. These experts are also members of the Pan-American Retina and Vitreous Society, and most are members of PACORES (Pan-American Collaborative Retina Study Group), a Latin American group of eye specialists dedicated to the investigation of the most relevant diseases of the retina, vitreous, and macula.

The Latin American AMD Consensus group discussed the most relevant aspects of AMD and the full report is available at http://www.sprv.org/paginas/archforo/LATAM%20CONSENSUS_LAST_SPA.pdf. This paper represents a summary of this report and focuses on definitions, diagnosis, antiangiogenic treatments, and hopes for the future. Thanks to the advent of antiangiogenic therapy for wet AMD, a revolution in treatments has been achieved. However, challenges and controversy exist regarding subsequent clinical results and the regulatory barriers still do exist, which need to be addressed.

**Definitions**

Dry AMD is caused by degenerative changes in the RPE, which is clinically recognized by macular pigmentation, changes and deposition of drusen (small yellow or white accumulations of extracellular material), patchy areas of atrophy, and geographic atrophy (GA). The latter has been implicated in 20% of legal blindness cases in the USA. The progression of dry AMD is gradual and, by itself, rarely causes severe visual loss or blindness.

Wet AMD, also known as neovascular or exudative AMD, is caused by the development of abnormal, new blood vessels beneath and within the retina (choroidal neovascularization), which bleed or leak blood constituents, resulting in retinal scarring. The progression of wet AMD is usually more rapid than dry.

AMD is classified according to a scale of severity. Early AMD is characterized by any or all of the following: multiple small drusen, a few medium-sized drusen, or RPE abnormalities. Intermediate AMD is characterized by extensive medium-sized drusen and ≥1 drusen, or non-foveal GA. Advanced AMD is defined as GA involving the fovea or neovascular AMD.

**Diagnosis**

The early and intermediate stages of AMD are usually asymptomatic. Typical symptoms of late stage AMD include vision loss, vision blurring, metamorphosis, and scotoma; atypical symptoms include change of color perception, dissymmetry, light sensitivity, and sense of darkness.

A scoring system for AMD is used to characterize the disease stage, estimate the patient’s risk of progressing to more advanced disease, and choose the most appropriate treatment. In this way, asymptomatic patients can be identified who may otherwise go on to develop advanced disease without frequent monitoring.

The Age-Related Eye Disease Study (AREDS) Research Group has developed a severity score for AMD using highly complex stereoscopic photography – measuring drusen and pigmentary changes. The AREDS score has four classifications:

- AREDS 1 – no disease: no macular changes or few drusen <63 microns
- AREDS 2 – early stage: intermediate drusen between 63–124 microns or pigmentary changes
- AREDS 3 – intermediate: abundant, intermediate drusen, ≥1 large drusen >125 microns or non-foveal GA
- AREDS 4 – advanced: ≥1 GA with fovea center compromise, choroidal neovascularization, serous detachment, RPE hemorrhage, or disc form scar

AREDS has also developed a simplified severity score for AMD, taking into account drusen size, depigmentation, and degree of GA – both the left and the right eye are assigned a risk factor for the presence of ≥1 large drusen and pigment changes. By summing the risk factors across both eyes, a five-step scale (0 to 4) provides an approximate 5-year risk for developing AMD.

Optical coherence tomography (OCT)
is a non-invasive technique that takes high-resolution images of the retina using light interferometry, and allows easy diagnosis of retinal and subretinal conditions such as AMD. Current management of exudative AMD requires the use of anti-VEGF drugs, and OCT is advised before starting the treatment. In fact, most treatment programs are based on OCT findings to decide whether or not to continue with anti-VEGF drugs. Diagnosis of non-responder AMD patients is based on the absence of change or increase of subretinal or intraretinal fluid after a loading dose of anti-VEGF drug compared with the baseline OCT and/or vision loss greater than 15 letters.

**Antiangiogenic treatments**

Current treatment for wet AMD is focused on blocking ocular vascular endothelial growth factor (VEGF) in the eye using monoclonal antibodies or fragments, and fusion proteins. Two VEGF-inhibiting drugs are approved: ranibizumab (Lucentis®, Genentech/Novartis; FDA approved in 2006), and aflibercept (Eylea®, Regeneron/Bayer, FDA approved in 2011). An alternative drug, bevacizumab (Avastin®, Genentech/Roche), has been used off-label since 2005 but it has not formally been approved for intraocular use.

**Ranibizumab**

Ranibizumab is the Fab fragment of a recombinant, humanized murine monoclonal antibody, which was developed specifically for intraocular use. It binds all forms of VEGF-A, inhibiting angiogenesis and reducing vascular permeability.

The FDA approval was supported by data from two pivotal level 1 studies: ANCHOR (anti-VEGF antibody for the treatment of predominantly classic choroidal neovascularization in AMD) and MARINA (Minimally Classic/Occult Trial of the Anti-VEGF antibody Ranibizumab in the treatment of neovascular AMD).

- In the ANCHOR study, patients with classic membranes were randomized to receive either 24 monthly injections of ranibizumab (0.5 mg) or photodynamic therapy (PDT). After 24 months, 90–96% of patients in the ranibizumab group lost <15 letters in vision compared with 64–66% receiving PDT; 34–41% of the ranibizumab group gained ≥1 letters compared with 6% receiving PDT.

- In the MARINA study, patients with minimally classic and occult membranes were randomized to receive 24 monthly injections of ranibizumab (0.5 mg or 0.3 mg) or placebo. In the eyes treated with ranibizumab, 90–95% lost <15 letters compared with 53–64% receiving placebo; 25–34% of the ranibizumab group gained ≥15 letters compared with 4–5% receiving placebo.

The frequency of intraocular injections has generated a number of issues including patient compliance, cost, and logistic feasibility. Since the completion of ANCHOR and MARINA, a number of new studies have examined alternative injection frequencies – including PIER, SAILOR, EXCITE, SUSTAIN, and PrONTO.
In the PIER study (level 1), patients were treated with a monthly injection for 3 months and then one injection every 3 months thereafter. After 24 months, the improvement in vision gained in the first 3 months was lost, showing the importance of maintaining the injection schedule. Efforts to extend the dosing intervals forfeited previous benefits in clinical outcome.

The EXCITE study (level 1) was similar to the PIER study but used monthly injections of ranibizumab (0.3 mg) as the control group. After 12 months, the gain in vision was higher in the monthly group (0.3 mg) compared with the 3-month group (0.3 mg and 0.5 mg).18

The SAILOR study (level 1) applied three loading doses of ranibizumab followed by monthly injections (0.3–0.5 mg) according to visual acuity and optical coherence tomography (OCT). Visual acuity improved after the loading dose, but then decreased, showing superior results than the PIER study, but not superior to MARINA or ANCHOR.11

The SUSTAIN study (level 1) applied three loading doses of ranibizumab (0.3 mg) followed by injections according to visual acuity and OCT. After 12 months, most of the visual acuity gained during the loading phase was maintained until the end of the study.19,20

The PrONT0 study (level 3) applied three loading doses of ranibizumab (0.5 mg) followed by a monthly control injection according to visual acuity and OCT. After 24 months, patients gained 11.1 letters over the levels of baseline visual acuity.21

**Afiblercept**

Afiblercept, also known as VEGF Trap-Eye, is a chimeric protein formed by the fusion of VEGF-1 and -2 receptor domains and the Fc segment of a human IgG, resulting in a higher VEGF-binding affinity than either ranibizumab or bevacizumab. It was designed specifically to block all members of the VEGF family, including isoforms of VEGF-A and -B, and Placental Growth Factor (PIGF).22

The FDA approved afiblercept in November 2011 for treating neovascular AMD, and this was based primarily on the results of two identical pivotal multicenter studies – VIEW 1 and VIEW 2 – aimed at defining the non-inferiority of afiblercept compared with ranibizumab.13

**Bevacizumab**

Bevacizumab is a humanized monoclonal antibody (93% human, 7% murine) that inhibits all forms of VEGF-A – received FDA approval in 2004 for the treatment of metastatic choroidal cancer.23

Systemic bevacizumab has been applied in ophthalmology with a 5 mg/kg dose successfully demonstrating a reduction in the neovascular membrane and in the OCT thickness, and an improvement in visual acuity.26 Intravenous bevacizumab has never been widely adopted despite the fact that intravitreal application uses 500 times less of the drug, is therefore more economic, and has a better safety profile due to the reduced systemic dose.27

In 2005, Rosenfeld et al. first described the treatment of AMD using intravitreal bevacizumab (1.25 mg).12 Since then, several small retrospective efficacy and safety studies have been published and bevacizumab is now in widespread off-label use.27 A retrospective study of intravitreal bevacizumab injection in human eyes...
evaluating two doses of bevacizumab (1.25 mg and 2.5 mg) by the PACORES group did not detect any differences between the two groups.\(^{29}\) Bevacizumab appears to be well tolerated by most patients. A retrospective study of 4,303 injections in 1,319 eyes only reported a 1.5% incidence of systemic AEs (elevated blood pressure and other cardiovascular events). The rate of ocular complications was low: endophthalmitis (0.16%), uveitis (0.09%), and retinal detachment (0.02%).\(^{29}\)

Despite the fact that the safety and efficacy of bevacizumab had not been reported in randomized, multicenter studies prior to the Comparison of AMD Treatments Trials (CATT) study,\(^{21}\) its use became widespread due to its low cost. In fact, 2-year results from CATT also showed that ranibizumab and bevacizumab had less gain on visual acuity, whether instituted at enrollment or after 1 year of monthly treatment, and that there appeared to be a persistence of higher rates of serious adverse events with bevacizumab, although this interpretation is uncertain because of the lack of specificity to conditions associated with inhibition of VEGF.\(^{30}\)

A systemic review recently evaluated whether off-label bevacizumab is as well tolerated as licensed ranibizumab, and whether it can be justifiably offered to patients as a treatment for AMD. Evidence from head-to-head trials has raised concerns about an increased risk of ocular and multiple systemic AEs with bevacizumab. Therefore, clinicians and patients should continue to carefully weigh up the benefits when choosing the best treatment.\(^{21}\)

### Conclusion and hopes for the future

AMD is a chronic disease and it is vital for patients that important developments for its treatment are on the horizon. We have learned and developed our treatment of wet AMD with ranibizumab and off-label bevacizumab. It is also encouraging to see the emergence of other antiangiogenics such as the VEGF Trap-Eye ( aflibercept for intraocular injection), which differs from the two above in that it has a longer-lasting effect. External or intravitreal administered radiotherapy will also most likely play an important role, either in a combined form with antiangiogenics or as monotherapy in some cases of AMD.\(^{31}\)

### REFERENCES

18. Böls M, Schmidt-Erethul U. Ranibizumab EXCITE study: Exploring the value of optical coherence tomography for the management of ranibizumab therapy in age-related macular degeneration. 8th EURITRA Congress. Vienna, Austria.