Universitat de Girona
Facultat de Medicina

COMPARISON OF TWO TREATMENT PATTERNS WITH AFLIBERCEPT FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION: A COHORT STUDY

FINAL DEGREE PROJECT

AUTHOR: ORIOL BORRULL ÁVILA
TUTORS: FLOR ESCALADA GUITIERREZ
XAVIER CASTELLS CERVELLÓ
FACULTY OF MEDICINE, UdG
GIRONA, JANUARY 2017

I would like to thank my outstanding and brilliant tutor, Dra Flor Escalada whose leadership and vision steered this project from day one. Also, to the whole team of Ophtalmology Department of Hospital Josep Trueta and C.A.P Güell for their continued support and encouragement. It was always a pleasure coming to work every day with such lovely and engaging people, without their generous support all this would not have been possible.

This project is dedicated to my dear family, my greatest support.

INDEX

1.LIST OF ABREVIATIONS

AMD Age-related macular degeneration

ARM Age-related maculopathy

CNV Choroidal neovascularisation

DME Diabetic macular edema

EMA European Medicines Agency

FDA Food and Drug Administration

MRSS Macular risk scoring system

NEI VFQ National Eye Institute Visual Function Questionnaire

OCT Optical coherence tomography

PlGF Placental growth factor

RPE Retinal pigment epithelium

RVO Retinal vein occlusion

VEGF Vascular endothelial growth factor

VA Visual acuity

VI Visual impairment

2.ABSTRACT

Background:

Age-releated macular degeneration (AMD) is a very prevalent disease worldwide and it is the most common cause of severe vision loss in developed countries. Choroidal Neovascularization (CNV), previously known as "wet AMD", is the most aggressive form of AMD. Nowadays, new pharmacological therapies are being developed, such as anti-vascular endothelial growth factors (anti-VEGFs) that have changed the progression of the illness, but AMD is still a chronic disease. Aflibercept (Eylea®) is one of the most used drugs for treating CNV due to the good results in the latest clinical trials. There is still a lack of published data about the results in the group of patients with bilateral affection of CNV AMD.

Objectives:

The goal of this study is to determine if the concurrent treatment with Aflibercept (Eylea®) of both eyes in the same intervention has better results (a reduction of more than 5% of the fovea thickness measured by optical coherence tomography (OCT)) than treating each eye with one week of separation.

Design:

A multi-centric cohort study in the Ophthalmology Department of Hospital Universitari de Girona Doctor Josep Trueta (Girona), Hospital Santa Caterina (Salt), Hospital de Figueres (Figueres), Hospital Comarcal de Blanes (Blanes), Hospital de Palamós (Palamós) and Hospital d'Olot I Comarcal de la Garrotxa (Olot).

Method:

85 patients with more than 50 years and bilateral NVC AMD from Girona province will be recruited in our study. The two cohorts are going to be done with the patients who receive the treatment with Aflibercept the same day and with those who refuse being treated the same day and are going to receive the injections with 7 days of separation. Each patient is going to be followed during one year since initiating the treatment. This prospective cohort study will be realized in 3 years at the area of Girona.

Key words

Age-related macular degeneration (AMD); Choroidal Neovascularization (CNV); Bilateral; Optical coherence tomography (OCT); Aflibercept; Eylea®

3.INTRODUCTION

3.1CONCEPT

Age-related macular degeneration(AMD) is the late stage of a variety of morphological changes in the retina that occur in the aging eye (from de age of 50 years), and are collectively called age-related maculopathy (ARM)(1), that involves the loss of the person's central field of vision.

It is the most common cause of blindness in developed countries and is labelled a “priority eye disease” by the World Health Organization. It causes loss of central vision, affects negatively the quality of life and has also been associated with depression and poor mental health (2,3). It is considered the main reason of legal blindness (visual acuity (VA) inferior than 1/10) from the age of 55 years in industrialized societies (4).

The classical AMD was classified into either of two categories: dry or atrophic and wet, neovascular or exudative. Nowadays, AMD is classified in three stages according to the severity: early AMD, intermediate AMD and severe AMD, including in this category the geographic atrophy and the neovascularization (5).

3.2EPIDEMIOLOGY

Despite of being a very prevalent illness, the prevalence data are variable according to the definition of AMD and the classification systems that have been used. Most of authors use the AMD concept to refer to the neovascular or the geographic atrophy while others consider AMD the simply presence of drusen in people older than 50 without other ocular diseases. This absence of an international definition and classification makes difficult to know the real prevalence of the illness during the last decades as we know it, but recent studies have shown no big differences with the previous ones.

WORLDWIDE PREVALENCE

In 2010, an estimated 32’4 million people were blind (defined as presenting visual acuity of less than 3/60), and roughly 191 million people had moderate-to-severe vision impairment (defined as presenting visual acuity of less than 6/18 but equal to or better than 3/60) (6).

Macular degeneration, mainly age-related, was estimated to be the cause of 7% of blindness and 3% visual impairment worldwide; cataracts and undercorrection or refractive error represented more than 50% of all cases (7).

From 1990 to 2010, the prevalence of blindness and visual impairment due to macular degeneration increased because of population growth and the relative increase of older adults(7).

USA

Previous population-based surveys on AMD which have used standardized classification protocols based on fundus photography have reported varying prevalence. The Beaver Dam Eye Study from USA found late AMD in 7'7% in their cohort aged 75-86 years old. Age-related macular degeneration remained the leading cause of severe visual impairment, defined as best-corrected visual acuity of poorer than 20/40 in the better eye (8), in this population over the 20 years of the study (9).

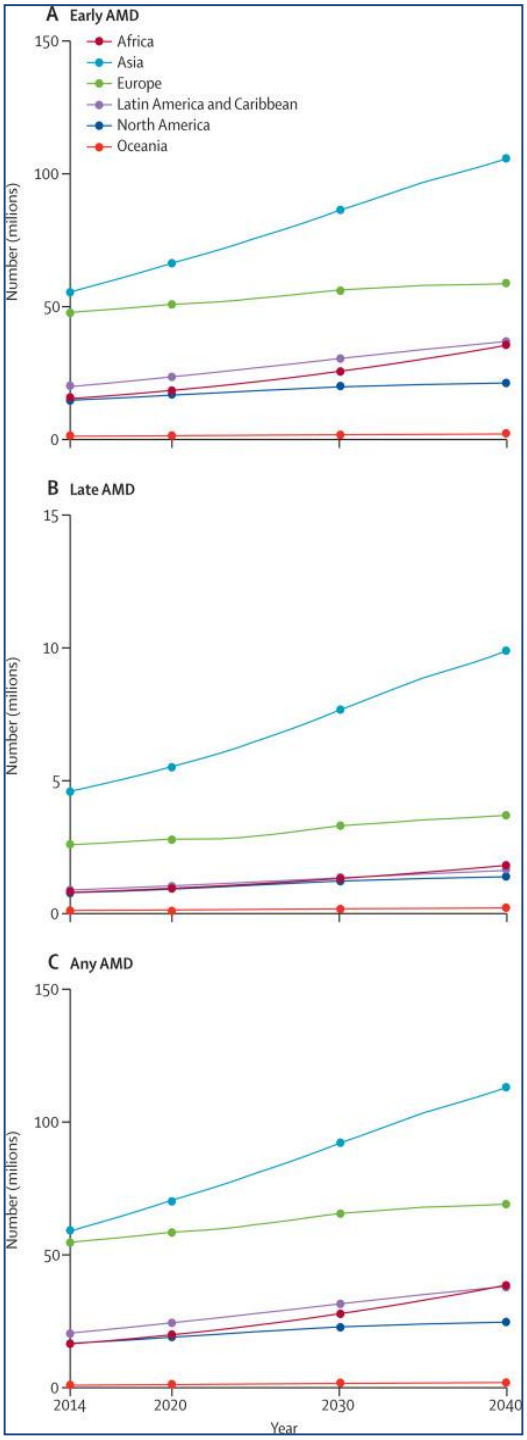
EUROPE

The prevalence of geographic atrophic AMD is 1'2% and 2'3% of neovascular AMD. The prevalence of bilateral AMD is 1.4% (10).

In the Spanish population aged ≥65 years the overall prevalence of ARM and AMD is 10'3% and 3'4%, respectively. AMD increased from 1'3% in individuals aged 65–74 years to 8'5% in those aged ≥80 years. Neovascular and atrophic AMD accounted for 1'9% and 1'5% of individuals, respectively (11).

PROJECTION OF THE ILLNESS

In the year 2020, global projected cases of any age-related macular degeneration are 196 million, rising to 288 million in 2040, with the largest number of cases in Asia. Europe is expected to be second to Asia in the number of projected cases 69 million (12).



Graphic 1-Projected cases of any AMD. Extracted from (12).

3.3 RISK FACTORS

All the factors that determine why AMD appears are still unknown but few of them like the age, genetics or smoking have been clearly related with this illness.

AGE

The incidence of AMD is strongly related with the age. Focal reservoir of acellular debris between retinal pigment epithelium (RPE) and Bruch's membrane increase with the age. These deposits, known as drusen, appear as yellow spots on the macula and peripheral retina. The RPE is responsible for the correct maintenance of the photoreceptors.

With the age, RPE becomes less efficient and there is an accumulation of residual bodies, which can determine the loss of EPR cells. Changes in the thickness or composition of the Bruch membrane associated with age cause a significant reduction in the transport of fluids and nutrients that are vital for the proper functioning of the photoreceptors (13).

Age also causes a reduction of 50% in the thickness of the choroidal vessels and an alteration of its sinusoidal structure, which, together with the thickening of Bruch's membrane, results in a hypoxia that triggers, among other processes, the secretion of vascular endothelial growth factor that contributes to the development of neo-vessels (14).

GENETICS

More than 50 genes have been associated with common and rare variants of AMD (15). The most important are those related with the inflammation and immune response like CFH, C3, C2, CFHR4, CFHR5 and with the cell stress response like ARMS2 or F13B (16).

SEX

Female gender is considered a weak risk factor, with inconsistent association for late AMD. Women 75 years of age or older had a significantly higher frequency of neovascular AMD and this difference remainded after controlling for age (17). In other studies, no sex differences were observed for these lesions (18).

SMOKING

Smoking is the modifiable risk factor most consistently associated with AMD (19). Current smokers are exposed to a two to three times higher risk of AMD than non-smokers and the risk increases with intensity of smoking (20). Smoking is also associated with an increased risk of transitioning from minimal to moderate early AMD (21). Chronic cigarette smoke exposure

may be associated with decreased choroidal thickness (22). These facts reinforce recommendations to quit smoking even for older individuals.

SUNLIGHT EXPOISURE

The relation between sunlight exposure and the incidence of AMD remains uncertain. There are studies where the exposure to sunlight seems that increase the risk of AMD (20), while, in others, the sunlight exposure is not detected as a risk factor (23).

ETHNICITY

There is substantial evidence for higher prevalence of early disease in people of European ancestry than in Asians, and early and late disease in people of European ancestry than in those of African ancestry, in North American people (12).

CATARACTS AND CATARACTS SURGERY

Opinions remain divided about the role of cataract and, more specifically, cataract surgery (24,25) and its effect on the progression of AMD (26). In the published studies, there is also often a lack of details about the cataract procedures performed and the type of lens implanted.

HYPERTENSION

Systemic hypertension has been shown to be associate with decreased choroidal blood flow, which in turn is associated with the development of AMD, further suggesting that AMD development and/or progression have systemic contributions (27,28). A number of studies have found significant associations between AMD and blood pressure measures (19,29,30). Other studies have not observed significant associations between AMD and blood pressure (31,32). More studies have to be done, also controlling the adherence to the treatment for hypertension, to determinate if there is a real connection with the physiopathology.

OTHERS

Metabolic syndrome, obesity, diabetes, high glucose and high triglycerides were predictors of progression to late AMD (33) and may be related with the AMD appearance (34–36).

3.4 CLASSIFICATION

There are several classification schemes of AMD in the literature. In 2013 members of the Beckman Initiative for Macular Research Classification Committee proposed a 5-stage AMD classification scale (37). This classification system start from "no apparent aging changes" to "normal aging changes" further to "early" and "intermediate AMD" and finally "late AMD". However, in daily work AMD is most often referred to as "dry or wet" (37).

Table 1- Classification of AMD. Extracted from (37).

Classification		Definition
Without pathology	***Without aging changes***	No visible drusen or pigmentary abnormalities
	Aging changes	Small drusen (<63 µm), also termed *drupelets,* and ausence of pigmentary changes related with AMD
AMD	***Early AMD***	Medium drusen (≥63 – <125 µm), but without pigmentary abnormalities thought to be related to AMD
	Intermediate AMD	Large drusen (≥125 µm)* or pigmentary abnormalities associated with at least medium drusen
	Late AMD	Lesions associated with neovascular AMD or geographic atrophy**

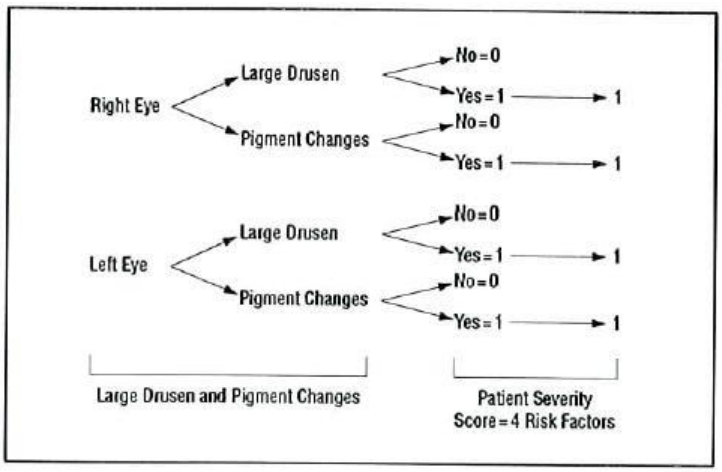
*It is recommended to use as reference the approximate size of the main retinal vein at the level of margin of the optic disc (125 µm).

**Lesions associated can be: Geographic atrophy of the RPE involving the foveal center; Neovascular maculopathy that includes: Choroidal neovascularization (CNV) defined as pathologic angiogenesis originated from the choroidal vasculature that extends through a defect in Bruch's membrane; Serous and/or hemorrhagic detachment of the neurosensory retina or RPE; Retinal hard exudates (a secondary phenomenon resulting from chronic

intravascular leakage); Subretinal and sub-RPE fibrovascular proliferation, Disciform scar/subretinal fibrosis (23).

In relation to the pigmentary alterations, they are defined as hyperpigmentation or hypopigmentation present in two disc diameters with respect to the center of the macula, without any other associated disease (5).

A simplified scale presented in the AREDS study (38) provides convenient risk categories for development of advanced AMD. The scoring system developed for patients assigns to each eye 1 risk factor for the presence of 1 or more large (≥125 µm) drusen and 1 risk factor for the presence of any pigment abnormality. Risk factors are summed across both eyes, resulting in a 5-step scale (0–4), on which the approximate 5-year risk of developing advanced AMD in at least one eye increases in this easily remembered sequence: 0 factors, 0.5%; 1 factor, 3%; 2 factors, 12%; 3 factors, 25%; and 4 factors, 50%. For persons with no large drusen, presence of intermediate drusen in both eyes is counted as 1 risk factor.



Graphic 2-Patient Severity Score for developing advanced AMD. Extracted from (38)**.**

Other scales, like the macular risk scoring system (MRSS)(39), and algorithms have been developed and may be useful for identifying and monitoring high-risk patients, selecting appropriate therapies, and designing clinical trials but most of them are not used in the daily practice.

3.5 DIAGNOSTIC METHODS AND FINDINGS

Early changes in the fundus, especially yellowish deposits (drusen), along with abnormalities of pigmentation and patchy atrophy of the retinal pigment epithelium are found in the older population but are not usually associated with vision loss (1).

In AMD, the common symptoms are the progressive loss of VA, difficulty reading and metamorphopsia (which was defined by Amsler in 1953 as the deviation of either vertical or horizontal lines, reported by the patient in the grid (40)). Sometimes, metamorphopsia is perceived by the patient as an 'instability' of vision, instead of precise deformation of objects.

Other visual symptoms like photopsias (the false perception of sparks or flashes), central scotoma (an area of depressed vision) or the abrupt and progressive loss of the VA are less common and often appear in the neovascular forms.

AMD is a complex process whose diagnosis and follow-up requires, in addition to retinal examination, the use of other diagnostic devices such as fluorescein angiography (FA) or OCT(41).

FUNDUS EXAMINATION

Indirect slit-lamp ophthalmoscopy uses high-power convex lenses designed to provide a wide field of view of the fundus that is seen inverted and laterally reversed.

OPTICAL COHERENCE TOMOGRAPHY

OCT is a non-invasive, non-contact imaging system providing high resolution cross-sectional images of the posterior segment. OCT uses infrared light interferometry to create digital images of the tissue.

Normal reflectivity can be depicted in a pseudo-colour images as red, intermediate as green-yellow and low reflectivity as blue-black. Fine retinal structures such as the external limiting membrane and ganglion cell layer can be defined. Detailed quantitative information on retinal thickness can be displayed numerically an in false-colour tomographical maps; three-dimensional images can be constructed and different retinal layers studied in relief (1,42).

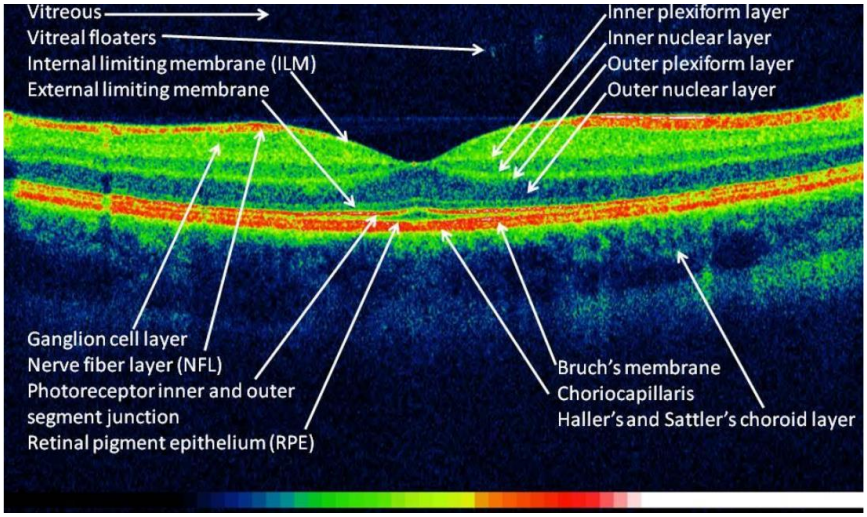


Image 1-OCT of the retinal layers in the macula. Extracted from (42).

FLUORESCEIN ANGIOGRAPHY (FA)

Fluorescence is the property of certain molecules to emit light of a higher wavelength when they are stimulated by a light of shorter wavelength. Sodium fluorescein is a water-soluble orange dye that when injected intravenously remains largely intravascular and circulates through the bloodstream. It has a renal and hepatic metabolism and is excreted in the urine for 24-48h. The angiography consists in monitoring through pictures the passage of the fluorescein through the retinal and choroidal circulations after an intravenous injection.

The first picture is taken previously to the fluorescein injection. The florescein is introduced into the eye through the ophthalmic artery and passes to the choroideal circulation trough the short posterior ciliar arteries and to the retinal circulation trough the central artery of the retina (42).

There are four phases of the angiography:

-The prearterial or choroideal: the way to the retineal circulation is slightly longer than the choroideal circulation that is fulled aproximately 1 second earlier. This phase appears 9-15 seconds after the injection and is characterized by the irregular filling of the choroides .

-The arterial phase: it starts aproximately 1 second later and shows the retina arteries.

-The arteriovenous or capilar phase: an intermediate phase between the arterial and venous phases.

-The venous phase: the venous laminar flow progress until the late venous phase which appears 30 seconds later.

FINDINGS OF AMD

DRUSEN

Drusen are extracellular deposits located at the interface between the RPE and Bruch's membrane. The material of which they are composed has a broad range of constituents, and is thought to be derived from immune mediated and metabolic process in the RPE. The precise role in the pathogenesis of AMD is unclear, but is positively associated with the size of the lesions and the presence or absence of associated pigmentary abnormalities. Age-related drusen are rare prior to the age of 40, but are common by the sixth decade (13). The distribution is highly variable and they may be confined to the fovea, may encircle it or form a band around the macular periphery. They may also be seen in the peripheral and mind-peripheral fundus (10). The situation of the drusen determine the VA loss.

The latest and most used classification divides drusen in three categories (37):

-*Small drusen(drupets)*: sometimes termed "hard drusen"; measure <63 µm in diameter.

-*Intermediate drusen*: well-defined yellow-white focal deposits at the level of the RPE measuring between 63µm and 125µm.

-*Large drusen*: less well delineated yellow-white deep retinal lesions measuring over 125µm in diameter; the term "soft drusen" is sometimes used synonymously. As they enlarge and becomes more numerous, they may coalesce giving a localized elevation of the RPE, a "drusenoid RPE detachment".

Dystrophic calcification may develop in all types of drusen.

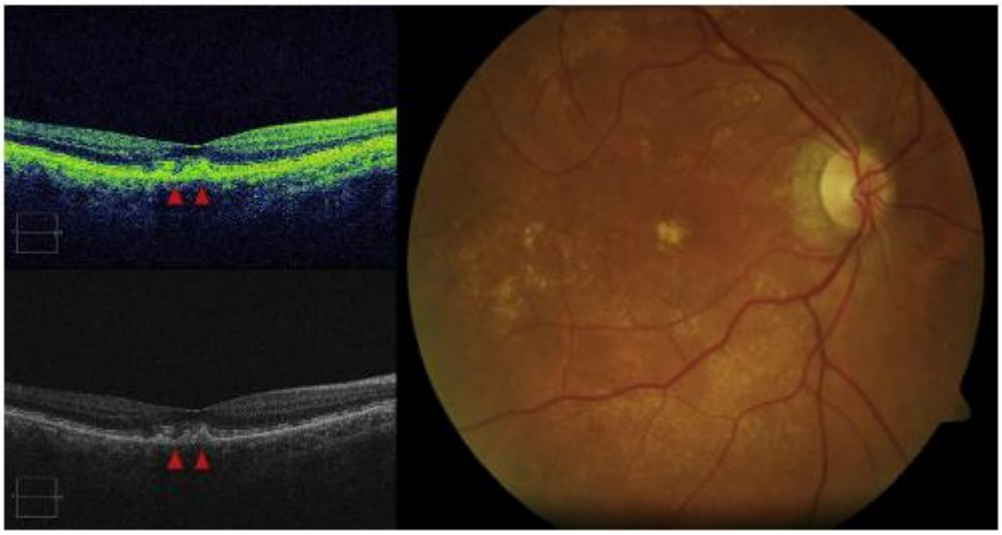


Image 2- Image of hard drusen seen in the color and black and white OCT and in the fundus photography. Extracted from (43).

OCT- Medium-sized and large drusen are seen as hyper-reflective irregular nodules beneath the RPE, located on or within the Bruch membrane.

Fluorescein angiography- FA findings depend on the state of the overlying RPE and on affinity of the drussen for fluorescein. Hyperfluorescence can be caused by a window defect due to atrophy of the overlying RPE, or by late staining. Hypofluorescent drusen masking background fluorescence are hydrophobic, with high lipid content, and tend not to stain.

CHOROIDAL NEOVASCULARIZATION

CNV consists of a blood vessel complex that extends through Bruch membrane from choriocapilars into the sub-RPE (type 1) or subretinal (type2) space. It occurs in many different disorders, usually when Bruch membrane and/or RPE function has been compromised by a degenerative, inflammatory, traumatic or neoplasic process. AMD is the most common causative association, followed by myopic degeneration (42). The common symptoms are acute or subacute painless blurring of vision, usually with metamorphopsia.

OCT- OCT is critical in quantitative monitoring of the response to CNV. Typically, CNV is shown as a thickening and fragmentation of the RPE and choriocapilars. Subretinal and sub-RPE fluid, blood and scarring are demonstrated.

FA- There are two types of CNV according to FA (44): Classic CNV is graded as present when there was an area of choroidal hyperfluorescence with well-demarcated boundaries that could

be discerned in the early phase of the angiogram. In later phases of the angiogram, there is aprogressive pooling of dye lekage in the overlying subsensory retinal space that usually obscures the boundaries of the CNV. Occult CNV is graded as present when an area of stippled hyperfluorescence appear within 5 minutes of fluorescein injection with persistent staining or poolinf of dye in the overlying subsensory retinal space by 10 minutes.

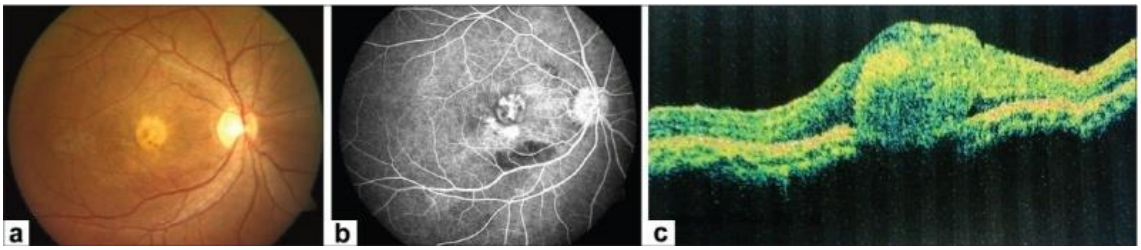


Image 3-(a) Right eye fundus (b) Fundus fluorescein angiography shows reduced leakage from choroidal neovascular membrane in right eye. (c) Optical coherence tomography shows involuting choroidal neovascular membrane. Extracted from (45)**.**

3.6 TREATMENT OPTIONS

ANTIANGIOGENIC FACTORS: Anti-VEGF

Anti-VEGF treatments are given by an injection into the eye and work by reducing the growth of new blood vesels and the oedema. There are several anti-VEGF drugs available that are currently used to treat AMD, but three are most commonly used for this condition: Aflibercept, Ranibizumab and Bevacizumab. Two of these, Ranibizumab (brand name Lucentis®) and Aflibercept (brand name Eylea®), were designed specifically for the treatment of AMD. A third drug, Bevacizumab (brand name Avastin®), was originally developed to treat various types of cancer, but is commonly used "off-label" in patients with AMD.

PEGAPTINIB (MACUGEN®)

It was the first anti-VEGF drug to obtain the indication for the treatment of neovascular AMD. It was approved by the Food and Drug Administration (FDA) on December 2004 and later by the European Medicines Agency (EMA) on January 2006 (46). The molecule was developed by Eyetech (New York, USA) and marketed worldwide by Pfizer.

The isoform VEGF-165 has been particulary implicated in blood-retinal barrier breakdown and pathological intraocular neovascularization. Pegatinib sodium is a short RNA oligonucleotide, an aptamer that binds with high specificity and affinity only to the isoform VEGF165 (47).

Therefore, due to its poorer efficacy compared with other currently available antiVEGF drugs, pegaptanib is no longer recommended for the treatment of exudative AMD (46).

RANIBIZUMAB (LUCENTIS®)

A drug synthesized by Genentech and marketed outside the United States by Novartis. It was approved by the FDA on July 2006 and by the EMA on January 2007 (46).

Lucentis is indicated in adults for the treatment of: neovascular AMD, choroidal neovascularisation, diabetic macular oedema and macular oedema secondary to retinal vein occlusion.

Ranibizumab is an humanised recombinant monoclonal antibody fragment targeted against human vascular endothelial growth factor A (VEGF-A). It blinds with high affinity to the VEGF-A isoforms, thereby preventing binding of VEGF-A to its receptors VEGFR-1 and VEGFR-2. Binding of VEGF-A to its receptors leads to endothelial cell proliferation and neovascularization, as well as vascular leakage, all of wich are thout to contribute to the progression of the neovascular form of AMD (48).

The official product label in Europe recommends monthly intravitreal injections continued until maximum VA is achieved for three consecutive monthly assessments. Thereafter, patients should be monitored monthly for VA. Treatment is to be resumed when monitoring indicates loss of VA due to wet AMD. Monthly injections should then continue until stable VA is reached again for three consecutive monthly assessment (46).

AFLIBERCEPT (EYLEA®)

Aflibercept was developed in 2011 by the Regeneron Biopharmaceutical Company and FDA and EMA approval for the treatment of neovascular AMD at a recommended intravitreal dose of 2.0mg was granted in 2012. The marketing-authorization is Bayer Pharma.

Eylea is indicated for adults for the treatment of: neovascular AMD, diabetic macular oedema, macular oedema secondary to retinal vein occlusion and CNV.

Aflibercept is a recombinant fusion protein consisting of portions of human VEGF receptor 1 and 2 extracellular domains fused to the Fc portion of human IgG1.

VEGF-A and placental growth factor (PlGF) are members of the VEGF family of angiogenic factors that can act as potent mitogenic, chemotactic, and vascular permeability factors for endothelial cells VEGF acts via two receptor tyrosine kinases: VEGFR-1 and VEGFR-2, present on the surface of endothelial cells. PlGF binds only to VEGFR-1, which is also present on the surface of leucocytes. Excessive activation of these receptors by VEGF-A can result in pathological neovascularization and excessive vascular permeability. PlGF can synergize with

VEGF-A in these processes, and is also known to promote leucocyte infiltration and vascular inflammation.

Aflibercept acts as a soluble decoy receptor that binds VEGF-A and PlGF with higher affinity than their natural receptors, and thereby can inhibit the binding and activation of these cognate VEGF receptors (49).

The EU label recommends three initial injections at monthly intervals, followed by eight weekly injections without any subsequent monitoring. After 12 months of treatment, the injection intervals may be prolonged, depending on the functional and anatomical condition of the individual patient. Control intervals for evaluation may be adjusted at the treating ophthalmologist's discretion (46).

BEVACIZUMAB (AVASTIN®)

Bevacizumab is a full-length recombinant monoclonal antibody that binds all VEGF isoforms. It was developed to inhibit pathological angiogenesis in tumours and tumour growth and is approbed by the FDA and EMA for the intravenous treatment of metastatic colorectal cancer and other cancer types (46).

Since 2005, many retrospective case series have indicated that bevacizumab has a beneficial effect in the treatment of neovascular AMD (50).

In the last years several studies have been published indicating that Ranibizumab and Bevacizumab both confer solid visual function benefits with similar safety results (51–53).

Bevacizumab is substantially less expensive, but each treatment decision is, legally and medically, based on an individual agreement between treating physician and patient, and must be the consequence of a comprehensive discussion of treatment alternatives and risks. Informed consent after discussing the optimal benefit, comfort and risks and the off-label status of the drug is mandatory (46).

SIDE EFECTS OF ANTI VEGFs

Anti-VEGF, when used intravitreally, are associated with ocular adverse events. These events include hiposfagma, endophthalmitis, intraocular inflammation, increase of intraocular pressure, vitreous hemorrhage, retinal detachment, retinal pigment epithelial tears and cataract.

The systemic events, which are less common compared with the ocular adverse events, are: arterial-thrombotic events, venous-thrombotic events, hypertension, cardiac disorder, infection, transient ischemic attack, nervous system disorder (54).

The relatively high frequency of injections required, increases the risk of endophthalmitis, rhegmatogenous retinal detachment, retinal tear, uveitis and vitreous hemorrhage. However, ocular complications in anti-VEGF treatment are still rather rare and are actually lower than those reported after other types of intravitreal injections.

There is no sufficient evidence to prove that there is a difference in rates of adverse events (ocular and systemic) between these anti-VEGF drugs (Bevacizumab, Ranibizumab and Aflibercept) (46,54,55).

PHOTODYNAMIC THERAPY (PDT)

Verteporfin is a light-activated compound preferentially taken up by dividing cells including neovascular tissue. It is infused intravenously and then activated by diode laser to cause thrombosis (42). Severe adverse effects are rare. With the advent of anti-VEGF treatment, PDT is now rarely used for CNV, but combination therapy and refusal of intravitreal treatment remain indications.

4.JUSTIFICATION

Age-related macular degeneration is the leading cause vision loss and non reversible blindness in the elderly in first world countries. Althoungh dry AMD accounts 85% of AMD causes, counting from early to late stages, wet or neovascular AMD causes 90% of severe vision loss (7,9,56).

The evolution of the illness and the patients prognosis has changed during the last decade due to the introduction of new treatments, the anti-VEGFs. Neovascular AMD is still a chronic degenerative disease that needs periodical controls and treatments.

The great major number of studies published about treating modalities with anti-VEGF analyzes the results obtained without separating those patients who receive a double doses treatment, one injection for each eye.

Actually, there are two reference treatments that are being used in Catalonia: Eylea and Lucentis. As no different results have been recorded in the published studies that compare them, the election for the study is going to be Aflibercept, because its treatment regimen is more strict during the 12 first months.

It is advertised in the *Summary of product characteristics* of the EMA for Eylea that "the safety and efficacy of Eylea therapy administrated to both eyes concurrently have not been systematically studied" (49), and for Lucentis that "there is limited data on bilateral treatment with Lucentis" (48). If bilateral treatment is performed at the same time this could lead to an increased systemic exposure, which could increase the risk of systemic adverse events. Following this reasoning, is possible that the systemic levels of the drug also have an effect in the evolution of the neovascular AMD.

Generally, the injection of anti-VEGF is done the same day for both eyes because it represents only one visit instead of two. There is no data available about if there are clinical differences between these two treatment regimens. If a patient prefers to be treated with one week of separation between the injections, it is normally accepted by the ophthalmologist.

Due to all this, if there is a significant difference when both eyes are treated concurrently, an evidence based recommendation should be done to these patients and the number of injections needed during the treatment could be lower, decreasing the cost of the treatment and the adverse effects derived from this.

5. HYPOTESIS AND OBJECTIVES

QUESTION

Does the treatment of both eyes with the anti-VEGF Aflibercept (Eylea®) in the same intervention has better results than treating each eye with one week of separation between injections, according to the % of reduction of fovea's thickness measured with OCT, for the bilateral neovascular AMD?

HYPOTHESIS

Treating both eyes the same day has better results (>5% of reduction of fovea's thickness measured with OCT) than treating each eye in different days.

OBJECTIVES

Main objective

-Evaluate and compare the thickness reduction of the retina measured with OCT in both treatment regimens (both eyes in the same intervention vs. treating one eye first and the other 7 days later) with Aflibercept in Girona's patients with 50 years old or older with bilateral neovascular AMD.

Secondary objective

-Evaluate and compare the effect of the treatments on visual acuity measured with measured using Snellen Charts system in Girona's patients with 50 years old or older with bilateral neovascular AMD.

-Evaluate and compare the incidence of ocular and systemic side effects of the anti-VEGF Aflibercept used in Girona's patients with 50 years old or older with bilateral neovascular AMD.

-Evaluate and compare the life's quality in Girona's patients with 50 years old or older with bilateral neovascular AMD treated with each pattern, using the National Eye Institute standardized Visual Function Questionnaire (NEI VFQ-25).

6.METHODOLOGY

6.1STUDY DESIGN

This study is designed as a prospective, cohorts, multi-centric study, with the purpose of comparing two treatment regimens with Aflibercept: both eyes in the same intervention vs. treating one eye first and the other 7 days later. It will be performed in the Ophthalmology Department of Hospital Universitari de Girona Doctor Josep Trueta (Girona), Hospital Santa Caterina (Salt), Hospital de Figueres (Figueres), Hospital Comarcal de Blanes (Blanes), Hospital de Palamós (Palamós) and Hospital d'Olot I Comarcal de la Garrotxa (Olot) in a period of time of 38 months.

6.2POPULATION OF INTEREST

The study population will be patients older than 50 years with bilateral neovascular AMD diagnosed by OCT and FA, who arrive to one of the hospitals mentioned previously to receive the anti-VEGF treatment.

INCLUSION CRITERIA: We only can include in this clinical trial patients who meet all criteria:

-Men and women of Girona's population with 50 years old or older.

-Patients with previous or new diagnosis of neovascular AMD by angiography and OCT.

-Patients who have signed the informed consent form to participate in the study.

EXCLUSION CRITERIA: The patients will not be included in the study if they meet one or more of these:

-Patients who have received treatments with intravitreal anti-VEGF or photodynamic therapy in the previous 6 months for neovascular AMD or other ocular pathologies.

-Patients who are receiving or have received in the 3 previous months treatments with anti-VEGF.

-Patients with other retinopathies.

-Patients with an ocular or periocular surgery in the previous 6 months.

-Patients with active ocular or periocular infection.

-Patients with active intraocular inflammation.

-Patients with glaucoma without a good control of the intraocular pressure.

-Patients with cataracts that makes impossible the visualization of the fundus with a slit lamp.

-Patients that are taking part in other studies.

- Hypersensitivity to any component of the treatment.

6.3 Sampling

The sample selection will be consecutive and non-probabilistic. Every patient that attend to one of the previously mentioned hospitals or referred to us meeting inclusion criteria and not exclusion will be offered to be enrolled in this trial. Interested patients will be informed about the study with an information sheet (Annex 1). Afterwards they will have to sign the informed consent (Annex 2) if they want to participate in the study. Each cohort is going to be formed by those patients who want to receive both injections the same day and, the other, with those who prefer being treated of each eye in different days.

6.4 Sample size

Accepting an alfa risk of 0,05 and a beta risk of 0,2 in a two sided test, with a expected ratio of 4:1, it is needed a sample of 17 patients treated the same day (pattern A) and 68 patients treated in different days (pattern B) for demonstrating the expected effect and rejecting the null hypothesis. It has been estimated a loss rate of 15% during the follow-up (protocol violations, drop outs, treatment failures...). All these measures have been done with the GRANMO (sample size and power calculator).

6.5 Variables and methods of measurement

Variables

INDEPENDENT

The two treatments will be given with the authorized indication, regimen and dose.

The decision of being treated with the regimen A or B will be done by the patients, who will receive the information about the processes.

Treatment regimen A: treating both eyes in the same day. Three initial injections at monthly intervals, followed by eight weekly injection until one year later since initiating the treatment.

Treatment regimen B: each eye is going to be treated following the same regimen but with 7 days of separation between each eye. Three initial injections at monthly intervals, followed by eight weekly injection until one year later since initiating the treatment.

DEPENDENT

- Subfovela choroidal thickness measured with OCT

Subfoveal choroidal thickness is defined as the distance between the hyperreflective line corresponding to Bruch's membrane beneath the RPE and the inner surface of the sclera at the foveal center and is measured manually using the OCT scaliper function.

All OCT measurements are going to be performed each month and at the end of the study by independent well-trained retina specialists. The average of the values measured by the investigators is going to be used for analysis. A macula is considered to be dry when there is complete resolution of subretinal and intraretinal fluid on OCT. The percentage decrease in subfoveal choroidal thickness at each time point compared with that at baseline is going to be calculated.

If no change in subfoveal choroidal thickness is observed during the 3 first months after initiating the treatment, the patient is going to be considered as "non-responder" and it will continue with another treatment defined by its ophthalmology outside the study.

-Visual acuity (VA) measured using Snellen Charts system.

The most widely adopted method of assessing visual acuity in clinical trials is by using Sellen Charts. The Snellen Eye Chart is commonly used in the Ophtalmology Departments of Catalonia. From a distance of 20 feet, the patient reads the letters on the wall-mounted chart, using one eye at a time. If a patient can read only down though the line marked 40 feet, sivion is 20/40, which indicates that from 20 feet the patient can read what someone with normal vision can read from 40 feet (57).

Distance visual acuity measurement is going to be performed by optometrists accredited for clinical trials work in a standardized protocol with Snellen Charts.

Optometrists are going to measure the best-corrected visual acuity, which means that the refraction problems of the patient are going to be corrected with lenses before the Snellen test.

-Adverse effects

All adverse effects observed during the clinical trial will be collected and will be perfomed as a descriptive analysis. They can be communicated directly by the patients, and confirmed later by an ophthalmologist, or observed by the investigators during periodic assessment.

If an adverse effect appears, it will be the investigator who decides if is necessary to move away the patient of the study.

Any unexpected adverse effect which happens during the study´s period must be informed by the main investigator to the Agencia Española de Medicamentos y Productos Sanitarios.

-Quality of life

It will be measured by the National Eye Institute Vision Function Questionnaire (NEI VFQ-25). It will be provided to all the patients at the beginning of the study and the last day (12 months after initiating the treatment). The objective is to evaluate the impact of CNV AMD in patient's life.

The VFQ-25 is the product of an item-reduction analysis of the longer field test version of the survey called NEI VFQ-51-item. This longer version contains 51 questions. However, the VFQ-25 consists of a base set of 25 vision-targeted questions, which also includes an appendix of additional items from the 51-item version. All items in the VFQ-25 are from the 51-item field test version; no new items are developed for use in the VFQ-25. VFQ-25 takes approximately 10 minutes on average to administer in the interviewer format. All items are scored; the lowers and highest possible scores are set at 0 and 100 points respectively. So a high score represents better functioning (Annex 4).

CoVariables

In order to avoid confusion in the study results, it is needed to introduce these variables because they could act as a confusing factor producing wrong interpretations or results in the trial.

-Age: expressed in years. Discrete quantitative variable

-Sex: male or female. Dichotomous nominal qualitative variable

-Race: Caucasian/European, Latin Americans, African, Others. Qualitative variable

-Hypertension: defined as a systolic pressure above 140mmHg or a diastolic pressure above 90mmHg at the begging of the treatment. Dichotomous nominal qualitative variable.

-Diabetis Mellitus diagnosed: yes or no. Dichotomous nominal qualitative variable

-Smoke habits: yes or not at the begging of the treatment. Dichotomous nominal qualitative variable.

-Previous cataract surgery: yes or not. Dichotomous nominal qualitative variable

-Obesity measured with Body Mass Index (BMI): obesity (≥30 BMI) or no obesity at the begging of the treatment. Dichotomous nominal qualitative variable

6.6 Description of the approaches

Both groups of patients are going to receive the recommended treatment for CNV AMD: three initial injections of Aflibercept (Eylea®) at monthly intervals, followed by eight weekly injections.

The difference between them is that the group A is going to receive the two injections the same day while in the group B each eye is going to be treated with 7 days of separation.

The gropu B is going to be formed by those patients who reject the concurrent treatment (treatment pattern A).

The duration of the treatment is twelve months since the first injection.

INTERVENTIONS EXPLAINED

REQUIREMENT TO DO BEFORE THE INJECTION:

a) Explain to the patient: what is the objective of the treatment, how is the procedure, calm down the patient, which are the possible side effects and explain that he/she can go out of the study when he/she wants or denies to participate in the study without following repercussions in medical care.

b) When the patient understands the points above. It will be necessary to facilitate the information sheet and to sing the informed consent for the injection (Annex3).

PREVENTIVE MEASURES TO KEEP THE DRUGS:

The anti-VEGF will be keep in a fridge between 2-8ºC, keeping the vial in the outer packing to protect its from the light. Before the use, 24 hours maximum, we can put the close vial in a room temperature (below 25 degrees).

PLACE WHERE WE WILL GIVE THE DRUG:

We put the intravitreal injection in a doctor´s office. The most important thing is that the place has to be enough comfort for the patient and for the ophthalmologist and allows doing a sterile technique.

VIAL´S CHARACTERISTICS:

It is important to inspect the vial before its administration to detect if there is some particles and/or colour's change or other physical aspect´s change; if we notice some alteration, we won´t use that drug. Each vial has only one use.

VIAL´S USE´S INSTRUCTIONS (49):

1. Move away the plastic capsule and disinfect the outside part of the rubber top of the vial.

2. Attach the 18 G, 5-micron filter needle supplied in the carton to a 1 ml sterile Luer-lock syringe.

3. Push the filter needle towards the centre of the vial´s top until obtain all the needle inside the vial. The inside extreme must be stay in contact with the bottom of the vial.

4. Using an aseptic technique put all the contents of the vial into the needle, putting the vial in a vertical position and inclining slightly to facilitate the complete extraction. To avoid the

introduction of air, we need to claim that the bevel of the needle is submerged in the solution totally. It is important to continue inclining the vial during the extraction putting the bevel of the needle submerged in the solution all the time.

5. Move away and throw the needle in a good way. This filter needle will not be used for the intravitreal injection.

6. Using an aseptic technique put the needle of the injection (30 or 32 G) in the top of the syringe with the Luer Lock adapter doing a rotatory movement.

7. After having everything ready to do the injection, move away the plastic cover of the needle, keeping the syringe with the needle pointing up and confirming that there aren´t bubbles inside, if there are, hit in a light way the syringe with one finger to get all the bubbles go to the top of the syringe which will be thrown out pushing the piston slowly.

PROPHYLAXIS BEFORE THE INJECTION:

If there is external ocular infection it must be done a previous treatment, because the ocular superficial bacterias are the most common microorganisms that cause the endophthalmitis.

It is necessary to use a topic anaesthetic eye drops (tetracaina) before the injection.

ADMINISTRATION OF THE DRUG:

To do intravitreal injection is necessary use sterile gloves and material (blefarostato, calibrator, needle (30 a 32 G), clothespin and cotton swab).

1. Administer anesthetic topic with sterile eye drops (1 or 2 drops of tetracaina).

2. Clean with yoded povidone at 10% the skin of the eyelids and eyelashes and at 5% the conjunctival sac where it will act during 3 minutes.

3. Put the blefarostato to separate the eyelashes and separate the eye from the eyelid border and from the secretions of the Meibomio glands.

4. Measures the correct distance from limbo until pars-plana using a compass or a similar tool. Normal distance between these two parts is 3,5mm in aphakic or pseudophakic eyes and 4 mm in phakic eyes.

5. Without help or with help by an assistant to hold the correct position of the patient´s head (the patient should be look up and opposite side of the injection). Usually the injection is in the inferior temporal quadrant.

6. We will inject the needle in a perpendicular way through the sclera with the tip towards the centre of the ocular glove to avoid damaging the crystalline lens. We will be specially careful in order to not pollute the needle by contact.

7. We will do a light extraction of the needle putting a sterile cotton swab; we do this to prevent the drug's recession and the subsequent bleeding.

8. We will give the patient antibiotic eye drops after the intravitreal injection (1 drop every 4 hours of Oftacilox each day during 5 days).

9. Finally we will explore the light perception and the vision of the objects.

After the first intravitreal injection, the Ophthalmologist will give to patient a document with:

a) Which eye has been injected.

b) Dosage and name of the antibiotic eye drops which is necessary to put during some days.

c) Instructions: don´t rub the eyes, don´t submerge and don´t put liquids during 3 days in the eyes which have been injected.

d) Alarm symptoms which are necessary to phone an ophthalmologist: loss of vision, ocular pain, blushing the eye by other cause different from the injection or purulent secretion of the eye.

e) Alarm symptoms which are necessary to phone a general physician or go to the emergency room: abdominal pain with gastric juices and constipation, abnormal bleeding, chest pain, problems in the speech, important head pain and weakness in some limb.

f) Contact number of the Hospital where has been injected and the name of the ophthalmologist who has put the injection.

g) Recommendations: the patient shouldn't drive and shouldn´t use machines until his or her visual function is completely recovered.

OTHER TREATMENTS

If any ocular adverse effect appears it is going to be treated by an ophthalmologist following the normal treatment patterns.

SUBJECTS REMOVAL/WITHDRAWAL

It must be necessary to register in the notebook the date and the reasons why the patient needs to interrupt the clinical trial. The meaning of interrupt is when the subject who is taking part of the study finishes his/her participation in the study before the clinical trial ends. The subjects should be move away for the clinical trial by the following reasons:

a) If the patient doesn´t participate in a good way.

b) If the investigators loss the following of the patient.

c) If appear some serious side effects which are associate with the treatment of study under investigator´s criteria.

d) If the patient needs other extra treatment which isn´t permitted in this study because it can affect in the study´s variables. So in this case, the patient will be excluded when he/she starts that treatment.

e) If the investigators see in the clinical assessments during the study, that the patient doesn´t answer for the treatment correctly defined as non macular reduction after the three first injections.

f) In any moment, when the patients will move away the informed consent form without affect his/her following medical assessment.

PATIENT'S CHRONOGRAM

	MONTHS												
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
TASKS													
Informed consent													
Variables and co-variables collection													
Intravitreal injection													
Control by OCT and VA													
Final control: OCT, VA and NEI VFQ-25													

6.7 Data collection

All the variables and co-variables (described in the point *6.7 Variables and methods of measurement*) are going to be collected the first day of the study, before the first injection.

The variables VA and Choroidal thickness by OCT are going to be measured for the eye that is going to be injected in that visit (since the third injection).

The last day of the study, 12 months later since the first injection (12 months + 1 week for those patients who receive the treatment pattern B), all the variables are going to be collected again: OCT, VA and VFQ.

If any adverse effect appears is going to be collected and registered the day of confirmation by an ophthalmologist.

All the data must be sent to the main researcher when the treatment pattern is concluded and the last measures will have been done.

7.STATISTICAL ANALYSISS

Statistical analysis will be performed with the Statistical Package for Social Sciences (SPSS) for Windows system.

Descriptive analysis:

On the one hand, categorical variables would be expressed in percentages; on the other hand, continuous variables would be represented in mean +/- standard, when we assume a normal distribution. However, if there is not a normal distribution, median will be the estimated measure.

Bivariate analysis

Considering that the treatment administered is a nominal qualitative outcome, the chi square test (x^2) will be performed to determine the differences between groups to evaluate qualitative variables. Student's T test will be applied to evaluation if the quantitative variables are normal, but if they are not normal Mann-Whitney test will be applied.

Multivariable

In order to avoid any possible confusion factor it is necessary a multivariate analysis adjusting for co-variables. Log-linear and general linear models will be used for the multivariable analysis.

For all analyses, a p values of <0.05 will be defined as statistically significant and highly significant for values <0.001. Confidence intervals will be expressed as 95%.

8.ETHICAL CONSIDERATION

As a cohort retrospective study, where the patients choose which treatment pattern prefer, where both treatment regimens are accepted and there is no published data about the superiority of one of them, there are not ethical problems.

The main investigators and collaborators guarantee that the study will be conducted in accordance to the human rights and the ethical consideration gathered in the World Medical Association Declaration of Helsinki of "Ethical Principles for Medical Research Involving Human Subjects revised in 2013"; as well as the Spanish law concerning medical investigations "Ley 14/2007, de 3 de Julio, de Investigación biomedica".

Concerning patients' autonomy and their right to decide, anyone included in the study will be very well informed by the physician. An information sheet (Annex 1) will be given to them where all the study will be explained, according to "Ley 41/2002 Básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica"; moreover they will have to sign an informed consent after comprehending all the information given (Annex 2).

As this research is an observational study involving authorized drugs, it will be conducted under the normative framework of these:

-Ley 29/2006, de 26 de Julio, de garantías y uso racional de los medicamentos y productos sanitarios.

-Real Decreto Legislativo1/2015, de 24 de julio, por el que se aprueba el texto refundido de la Ley de garantías y uso racional de medicamientos y productos sanitarios. Título III, artículo 58.2.

This study protocol will be presented to the Clinical Research Ethnics Commitee (CEIC, "Comitè Ètic d'Investigació Clínica") of Hospital Universitari Josep Trueta before the study begins in order to be evaluated and get its approval. Furthermore it will be presented to the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS).

All data collected from each patients will be treated and used with respect, following the right to confidentiality*: Articulo 5 de la Ley Organica 15/1999, de Regulación del Tratamiento Automatizado de los Datos de Carácter Personal.*

Every investigator will have to declare no conflict of interests.

9.STUDY LIMITATION

Analyzing our study, we detected and took into account some limitations which interfere in the research. The most relevant limitations are explained below:

-The main bias that must be considered in this study is the "selection bias". We will measure all covariates that could interfere in the treatment's efficacy. These covariates are age, sex, race, hypertension, Diabetes Mellitus, smoking habit, previous cataract surgery and obesity. The measure of these parameters will provide the study of a good external validity.

-Concerning the follow up of this prospective study, some patients could abandon the trial because of side effects or simple by their own will. Some conditions that could interfere in the following of the patient or the outcome of the treatment are reflected in our inclusion and exclusion criteria. Withdrawal bias was taken into account when sample size was calculated.

-Intravitreal injection is a dependent-technician treatment. If we want to do this study in more than one hospital, with different ophthalmologists, the solution is that one ophtamologist expert teaches to the other doctors how they must do the intravitreal injection or reserve this procedure to those ophthalmologists with experience in this kind of interventions.

10.WORK PLAN

The research team will be constituted by different specialists, who have long experience, not only in the research, but also in the use and interpretation of the diagnostic techniques in our study.

INVESTIGATORS: Flor Escalada Gutierrez, Oriol Borrull Ávila

COLLABORATORS: Ophthalmology Department, Nurseing staff and Optometrists of Hospital Dr Josep Trueta of Girona and Hospital de Figueres.

PHASE 0: PREPARATION AND COORDINATION

CONDUCTED BY: all investigators.

-Activity 1: Working out the protocol (M1-M2).

-Activity 2: Identification the problems and if it is necessary any change. Finally, elaboration and evaluation the final protocol (M3-M4).

-Activity 3: It is necessary the approval of the study by the ethic committee (M5-6).

PHASE 1: SAMPLE SELECTION AND INTERVENTIONS

CONDUCTED BY: all investigators, ophthalmologists, optometrists and nursing staff.

-Activity 1: The patients' selection will take place in Hospital Universitari Doctor Josep Trueta and XXX. . Investigators and collaborators will evaluate if the patients meet all inclusion an exclusion criteria. Patients will be informed about our study and will receive an information sheet, if they accept, the informed consent form must be signed (M7-M19).

-Activity 2: The treatment and the follow-up will start from the inclusion of the first patient in the study until twelve months after the last selected one. The data collection will be done with a centralized online data base (M7-31).

PHASE 2:DATA ANALYSIS AND FINAL EVALUATION

CONDUCTED BY: investigators and a statistical expert.

-Activity 1: Statistical analysis. A statistical expert will be hired to perform the analysis of the collected data (M32).

-Activity 2: Analysis and interpretation of the results and final report elaboration (M33).

PHASE 3: PUBLICATION AND DISSEMINATION OF RESULTS

CONDUCTED BY: investigators.

-Activity 1: The final article will be published in different medical journals in order to make a correct diffusion of the results. (M34-M38)

11.CHRONOGRAM

TASKS	Months																		STAFF
	1	2	3	4	5	6	7	…	19	…	31	32	33	34	35	36	37	38	
Phase 0: Preparation and coordination																			
-Protocol design																			Investigators
-Final protocol																			
-Ethic committee approval																			
Phase 1: Sample selection and interventions																			
-Sample selection																			Investigators Ophthalmologists Optometrists Nursing staff
-Treatment and follow-up																			
Phase 2: Data analysis and final evaluation																			
-Statistical analysis																			Statistician
-Results interpretation and final report																			Investigators
Phase 3: Publication and dissemination																			
-Scientific publications																			Investigators

12.STUDY BUDGET

Most of the stages in the study, such as bibliography research, redaction, information collection and publication, will be performed by the research team. The only extra personnel needed will be a statistician, quality controller and an English translator.

The costs attributable to the diagnostic methods, follow-up, treatments and coverage of possible side effects are included in routine clinical practice expenses.

We will hire a statistician specialist in order to do statistical analysis and an English translator to present the results obtained in English.

We will also hire a freelance clinical research professional with a master´s degree in Clinical Trial Monitoring and Management who will help with the quality control and final report preparation.

STAFF	Cost	N. persons	Time	Total
Statistician	35€/h	1	2h	70€
Freelance quality Controller	40€/h	1	12h	480€
English translator	25€/h	1	5h	125€
Investigators	20€/h	2	80h	1.600€
CONFERENCES	375€	2		750€
			TOTAL	3.025€

13.FEASIBILITY

The research study will be carried out at Hospital Universitari de Girona Doctor Josep Trueta (Girona), Hospital Santa Caterina (Salt), Hospital de Figueres (Figueres), Hospital Comarcal de Blanes (Blanes), Hospital de Palamós (Palamós) and Hospital d'Olot I Comarcal de la Garrotxa (Olot). The hospitals will provide all the necessary means such as personnel salaries, optical coherence tomography, ophthalmoscope, Snellen Charts to measure the visual acuity, cures, and also computer devices and programs to elaborate the database and to carry out the statistical analysis.

Only the freelance quality controller, the statistician and the English translator are going to be hired for the study.

It is estimated that in the six previous mentioned hospitals, about 400 patients per year will be diagnosed of bilateral CNV AMD, so they will be candidates for anti-VEGF treatment. So to find the main hypotheses relevant, it was estimated that the sample size should be 85 patients so we expected than in 12 months we will meet our goal.

14.IMPACT ON THE NATIONAL HEALTH SYSTEM

It is an easy way of standardization the quality and controls that this kind of patients receives. Nowadays, as more relevant data about this treatment is published, the decision of making more or less controls during the first year of treatment are made by the Ophthalmology Department and by the Ophthalmologist who treats the patient to evaluate its response.

If there is a difference between the responses of the two groups studied, a specific treatment guideline should be elaborated for them where, maybe, less injections or controls made by OCT were needed, helping saving interventions and/or controls for the patients, and money to the National Health System.

15.BIBLIOGRAPHY

1. Augood CA, Vingerling JR, Jong PTVM de, Chakravarthy U, Seland J, Soubrane G, et al. Prevalence of Age-Related Maculopathy in Older Europeans. Arch Ophthalmol [Internet]. 2006 Apr 1 [cited 2016 Dec 29];124(4):529. Available from: http://archopht.jamanetwork.com/article.aspx?doi=10.1001/archopht.124.4.529

2. Taylor DJ, Hobby AE, Binns AM, Crabb DP. How does age-related macular degeneration affect real-world visual ability and quality of life? A systematic review. BMJ Open [Internet]. 2016 Dec 2 [cited 2016 Dec 28];6(12):e011504. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27913556

3. Lamoureux EL, Pallant JF, Pesudovs K, Tennant A, Rees G, O'Connor PM, et al. Assessing Participation in Daily Living and the Effectiveness of Rehabiliation in Age Related Macular Degeneration Patients Using the Impact of Vision Impairment Scale. Ophthalmic Epidemiol [Internet]. 2008 Jan 8 [cited 2016 Dec 29];15(2):105–13. Available from: http://www.tandfonline.com/doi/full/10.1080/09286580701840354

4. Brandl C, Stark KJ, Wintergerst M, Heinemann M, Heid IM, Finger RP. Epidemiologie der altersbedingten Makuladegeneration. Der Ophthalmol [Internet]. 2016 Sep 19 [cited 2016 Dec 28];113(9):735–45. Available from: http://link.springer.com/10.1007/s00347-016-0341-6

5. Ruiz JM, Francisco M, López C, García A, José L, Arumí G, et al. Protocolo de diagnóstico, seguimiento y recomendaciones generales en la degeneración macular asociada a la edad (DMAE) precoz e intermedia: consenso de un panel de expertos [Internet]. Barcelona: Sociedad Española de Retina y Vitreo (SERV); 2016 [cited 2016 Dec 29]. Available from: https://serv.es/wp-content/descargasWP/documentacionMedica/consenso_DMAE.pdf

6. Stevens GA, White RA, Flaxman SR, Price H, Jonas JB, Keeffe J, et al. Global Prevalence of Vision Impairment and Blindness. Ophthalmology [Internet]. 2013 Dec [cited 2016 Dec 29];120(12):2377–84. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23850093

7. Jonas JB. Global prevalence of age-related macular degeneration. Lancet Glob Heal [Internet]. 2014 [cited 2016 Dec 29];2(2):e65–6. Available from: http://www.thelancet.com/pdfs/journals/langlo/PIIS2214-109X(13)70145-1.pdf

8. Klein R, Klein BEK, Knudtson MD, Meuer SM, Swift M, Gangnon RE. Fifteen-year cumulative incidence of age-related macular degeneration: the Beaver Dam Eye Study. Ophthalmology [Internet]. 2007 Feb [cited 2017 Jan 2];114(2):253–62. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0161642006014783

9. Klein R, Lee KE, Gangnon RE, Klein BEK. Incidence of Visual Impairment Over a 20-Year Period. Ophthalmology [Internet]. 2013 Jun [cited 2017 Jan 2];120(6):1210–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23466270

10. Augood CA, Vingerling JR, de Jong PTVM, Chakravarthy U, Seland J, Soubrane G, et al. Prevalence of Age-Related Maculopathy in Older Europeans. Arch Ophthalmol [Internet]. 2006 Apr 1 [cited 2016 Dec 29];124(4):529. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16606879

11. Spanish Eyes Epidemiological (SEE) Study Group. Prevalence of age-related macular degeneration in Spain. Br J Ophthalmol [Internet]. 2011 Jul 1 [cited 2016 Dec 16];95(7):931–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21216795

12. Wong WL, Su X, Li X, Cheung CMG, Klein R, Cheng C-Y, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. Lancet Glob Heal. 2014;2(2):e106–16.

13. Karampelas M, Sim DA, Keane PA, Papastefanou VP, Sadda SR, Tufail A, et al. Evaluation of retinal pigment epithelium–Bruch's membrane complex thickness in dry age-related macular degeneration using optical coherence tomography. Br J Ophthalmol [Internet]. 2013 Oct [cited 2017 Jan 2];97(10):1256–61. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23843264

14. Ablonczy Z, Dahrouj M, Marneros AG. Progressive dysfunction of the retinal pigment epithelium and retina due to increased VEGF-A levels. FASEB J [Internet]. 2014 May 1 [cited 2017 Jan 2];28(5):2369–79. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24558195

15. Fritsche LG, Igl W, Bailey JNC, Grassmann F, Sengupta S, Bragg-Gresham JL, et al. A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. Nat Genet [Internet]. 2016 Feb [cited 2017 Jan 2];48(2):134–43. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26691988

16. Tan PL, Bowes Rickman C, Katsanis N. AMD and the alternative complement pathway: genetics and functional implications. Hum Genomics [Internet]. 2016 Jun 21 [cited 2017 Jan 2];10(1):23. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27329102

17. Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy. The Beaver Dam Eye Study. Ophthalmology [Internet]. 1992 Jun [cited 2016 Dec 29];99(6):933–43. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1630784

18. Vingerling JR, Dielemans I, Hofman A, Grobbee DE, Hijmering M, Kramer CF, et al. The prevalence of age-related maculopathy in the Rotterdam Study. Ophthalmology [Internet]. 1995 Feb [cited 2016 Dec 29];102(2):205–10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7862408

19. Yang K, Wang F-H, Liang Y-B, Wong T-Y, Wang J-J, Zhan S-Y, et al. ASSOCIATIONS BETWEEN CARDIOVASCULAR RISK FACTORS AND EARLY AGE-RELATED MACULAR DEGENERATION IN A RURAL CHINESE ADULT POPULATION. Retina [Internet]. 2014 Aug [cited 2017 Jan 3];34(8):1539–53. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24978429

20. Armstrong RA, Mousavi M. Overview of Risk Factors for Age-Related Macular Degeneration (AMD). J Stem Cells [Internet]. 2015 [cited 2017 Jan 2];10(3):171–91. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27125062

21. Myers CE, Klein BEK, Gangnon R, Sivakumaran TA, Iyengar SK, Klein R. Cigarette Smoking and the Natural History of Age-Related Macular Degeneration. Ophthalmology [Internet]. 2014 Oct [cited 2017 Jan 2];121(10):1949–55. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24953792

22. Sigler EJ, Randolph JC, Calzada JI, Charles S. Smoking and choroidal thickness in patients over 65 with early-atrophic age-related macular degeneration and normals. Eye [Internet]. 2014 Jul 16 [cited 2017 Jan 2];28(7):838–46. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24833184

23. Age-Related Macular Degeneration Preferred Practice Pattern [Internet]. American Academy of Ophthalmology; 2015 [cited 2017 Jan 10]. p. 12–6. Available from: https://www.aao.org/preferred-practice-pattern/age-related-macular-degeneration-ppp-2015

24. Ho L, Boekhoorn SS, Liana, van Duijn CM, Uitterlinden AG, Hofman A, et al. Cataract Surgery and the Risk of Aging Macula Disorder: The Rotterdam Study. Investig Opthalmology Vis Sci [Internet]. 2008 Nov 1 [cited 2017 Jan 3];49(11):4795. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18599571

25. Kessel L, Erngaard D, Flesner P, Andresen J, Tendal B, Hjortdal J. Cataract surgery and age-related macular degeneration. An evidence-based update. Acta Ophthalmol [Internet]. 2015 Nov [cited 2017 Jan 3];93(7):593–600. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25601333

26. Qian CX, Young LH. The Impact of Cataract Surgery on AMD Development and Progression. Semin Ophthalmol [Internet]. 2014 Sep 17 [cited 2017 Jan 3];29(5–6):301–11. Available from: http://www.tandfonline.com/doi/full/10.3109/08820538.2014.962166

27. Grunwald JE, Metelitsina TI, DuPont JC, Ying G-S, Maguire MG. Reduced Foveolar Choroidal Blood Flow in Eyes with Increasing AMD Severity. Investig Opthalmology Vis Sci [Internet]. 2005 Mar 1 [cited 2017 Jan 3];46(3):1033. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15728562

28. Metelitsina TI, Grunwald JE, DuPont JC, Ying G-S. Effect of systemic hypertension on foveolar choroidal blood flow in age related macular degeneration. Br J Ophthalmol [Internet]. 2006 Mar 1 [cited 2017 Jan 3];90(3):342–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16488959

29. Thomas J, Mohammad S, Charnigo R, Baffi J, Abdel-Latif A, Ziada KM. Age-Related Macular Degeneration and Coronary Artery Disease in a VA Population. South Med J [Internet]. 2015 Aug [cited 2017 Jan 3];108(8):502–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26280780

30. Cougnard-Grégoire A, Delyfer M-N, Korobelnik J-F, Rougier M-B, Malet F, Le Goff M, et al. Long-Term Blood Pressure and Age-Related Macular Degeneration: The ALIENOR Study. Investig Opthalmology Vis Sci [Internet]. 2013 Mar 28 [cited 2017 Jan 3];54(3):1905. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23404120

31. Yip JLY, Khawaja AP, Chan MPY, Broadway DC, Peto T, Tufail A, et al. Cross Sectional and Longitudinal Associations between Cardiovascular Risk Factors and Age Related Macular Degeneration in the EPIC-Norfolk Eye Study. Lewin AS, editor. PLoS One

[Internet]. 2015 Jul 15 [cited 2017 Jan 3];10(7):e0132565. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26176222

32. Tan JSL, Mitchell P, Smith W, Wang JJ. Cardiovascular Risk Factors and the Long-term Incidence of Age-Related Macular Degeneration. Ophthalmology [Internet]. 2007 Jun [cited 2017 Jan 3];114(6):1143–50. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17275090

33. Ghaem Maralani H, Tai BC, Wong TY, Tai ES, Li J, Wang JJ, et al. METABOLIC SYNDROME AND RISK OF AGE-RELATED MACULAR DEGENERATION. Retina [Internet]. 2015 Mar [cited 2017 Jan 3];35(3):459–66. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25207946

34. Gemmy Cheung CM, Li X, Cheng C-Y, Zheng Y, Mitchell P, Wang JJ, et al. Prevalence and Risk Factors for Age-Related Macular Degeneration in Indians: A Comparative Study in Singapore and India. Am J Ophthalmol [Internet]. 2013 Apr [cited 2017 Jan 3];155(4):764–773.e3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23246273

35. Zhang Q-Y, Tie L-J, Wu S-S, Lv P-L, Huang H-W, Wang W-Q, et al. Overweight, Obesity, and Risk of Age-Related Macular Degeneration. Investig Opthalmology Vis Sci [Internet]. 2016 Mar 18 [cited 2017 Jan 3];57(3):1276. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26990164

36. Clemons TE, Milton RC, Klein R, Seddon JM, Ferris FL, Age-Related Eye Disease Study Research Group. Risk Factors for the Incidence of Advanced Age-Related Macular Degeneration in the Age-Related Eye Disease Study (AREDS)AREDS report no. 19. Ophthalmology [Internet]. 2005 Apr [cited 2017 Jan 3];112(4):533–539.e1. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15808240

37. Ferris FL, Wilkinson CP, Bird A, Chakravarthy U, Chew E, Csaky K, et al. Clinical classification of age-related macular degeneration. Ophthalmology [Internet]. 2013 Apr [cited 2016 Dec 28];120(4):844–51. Available from: http://linkinghub.elsevier.com/retrieve/pii/S016164201201055X

38. Ferris FL, Davis MD, Clemons TE, Lee L-Y, Chew EY, Lindblad AS, et al. A Simplified Severity Scale for Age-Related Macular Degeneration. Arch Ophthalmol [Internet]. 2005 Nov 1 [cited 2017 Jan 3];123(11):1570. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/16286620

39. Chiu C-J, Mitchell P, Klein R, Klein BE, Chang M-L, Gensler G, et al. A risk score for the prediction of advanced age-related macular degeneration: development and validation in 2 prospective cohorts. Ophthalmology [Internet]. 2014 Jul [cited 2017 Jan 3];121(7):1421–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24650555

40. AMSLER M. Earliest symptoms of diseases of the macula. Br J Ophthalmol [Internet]. 1953 Sep [cited 2017 Jan 3];37(9):521–37. Available from: http://www.ncbi.nlm.nih.gov/pubmed/13081950

41. Andonegui J, Serrano L, Eguzkiza A. eOphthalmology: current state and future tendencies. An Sist Sanit Navar. 2010;33(1):79–91.

42. Kasnki JJ, Bowling B, Nischal K, Pearson A. Clinical Ophtalmology. 7th ed. Barcelona: Elsevier; 2012.

43. Gallego-Pinazo R, Dolz-Marco R, Díaz-Llopis M. Hacia la nueva clasificación de la degeneración macular asociada a la edad basada en la tomografía de coherencia óptica de dominio espectral. Arch Soc Esp Oftalmol [Internet]. 2012 Aug [cited 2017 Jan 19];87(8):247–52. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0365669111005478

44. Maguire MG, Alexander J, Fine SL. Characteristics of Choroidal Neovascularization in the Complications of Age-Related Macular Degeneration Prevention Trial. Ophthalmology [Internet]. 2008 Sep [cited 2017 Jan 13];115(9):1468–1473.e2. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0161642008002224

45. Rishi E, Rishi P, Mahajan S. Intravitreal bevacizumab for choroidal neovascular membrane associated with Best's vitelliform dystrophy. Indian J Ophthalmol [Internet]. 2010 [cited 2017 Jan 19];58(2):160–2. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20195045

46. Schmidt-Erfurth U, Chong V, Loewenstein A, Larsen M, Souied E, Schlingemann R, et al. Guidelines for the management of neovascular age-related macular degeneration by the European Society of Retina Specialists (EURETINA). Br J Ophthalmol [Internet]. 2014 Sep [cited 2017 Jan 5];98(9):1144–67. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25136079

47. Macugen (Pegaptanib) [Internet]. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS); [cited 2017 Jan 5]. Available from: http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_-_Product_Information/human/000620/WC500026214.pdf

48. Lucentis (Ranibizumab) [Internet]. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS); [cited 2017 Jan 5]. Available from: http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_-_Product_Information/human/000715/WC500043546.pdf

49. Eylea (Aflibercept) [Internet]. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS); [cited 2017 Jan 5]. Available from: http://ec.europa.eu/health/documents/community-register/2012/20121122124535/anx_124535_es.pd

50. Leydolt C, Michels S, Prager F, Garhoefer G, Georgopoulos M, Polak K, et al. Effect of intravitreal bevacizumab (Avastin®) in neovascular age-related macular degeneration using a treatment regimen based on optical coherence tomography: 6- and 12-month results. Acta Ophthalmol [Internet]. 2009 May 22 [cited 2017 Jan 5];88(5):594–600. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19485959

51. Chen G, Li W, Tzekov R, Jiang F, Mao S, Tong Y. BEVACIZUMAB VERSUS RANIBIZUMAB FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION. Retina [Internet]. 2015 Feb [cited 2017 Jan 5];35(2):187–93. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25105318

52. Berg K, Hadzalic E, Gjertsen I, Forsaa V, Berger LH, Kinge B, et al. Ranibizumab or Bevacizumab for Neovascular Age-Related Macular Degeneration According to the Lucentis Compared to Avastin Study Treat-and-Extend Protocol. Ophthalmology [Internet]. 2016 Jan [cited 2017 Jan 5];123(1):51–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26477842

53. IVAN Study Investigators U, Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, et al. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. Ophthalmology [Internet]. 2012 Jul [cited 2017 Jan 5];119(7):1399–411. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0161642012003582

54. Ventrice P, Leporini C, Aloe JF, Greco E, Leuzzi G, Marrazzo G, et al. Anti-vascular endothelial growth factor drugs safety and efficacy in ophthalmic diseases. J Pharmacol Pharmacother [Internet]. 2013 Dec [cited 2017 Jan 6];4(Suppl 1):S38-42. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24347979

55. Yashkin AP, Hahn P, Sloan FA. Introducing Anti-Vascular Endothelial Growth Factor Therapies for AMD Did Not Raise Risk of Myocardial Infarction, Stroke, and Death. Ophthalmology [Internet]. 2016 Oct [cited 2017 Jan 4];123(10):2225–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27523614

56. Mehta S. Age-Related Macular Degeneration. Prim Care Clin Off Pract [Internet]. 2015 Sep [cited 2017 Jan 16];42(3):377–91. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0095454315000421

57. Miller KE, Zylstra RG, Standridge JB. The geriatric patient: a systematic approach to maintaining health. Am Fam Physician [Internet]. 2000 Feb 15 [cited 2017 Jan 20];61(4):1089–104. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10706161

16. ANNEXES

ANNEX 1- Information for the patient

Hospital Universitari de Girona
Doctor Josep Trueta

HOJA DE INFORMACIÓN PARA EL PACIENTE

INVESTIGADORES PRINCIPALES: FLOR ESCALADA, ORIOL BORRULL

La degeneración macular asociada a la edad (DMAE) es una afectación de la retina que suele afectar a las personas mayores de 50 años, quienes pueden notar una pérdida progresiva de la visión central. Existen dos formas de DMAE: la seca y la húmeda.

La neovascularización coroidea (NVC) es un tipo de DMAE húmeda en la que se empiezan a formar nuevos vasos en la retina. Estos vasos, de morfología anormal, pueden empeorar la calidad de visión de quien la padece, incluso llegar a la pérdida total de visión.

Para prevenir que la enfermedad progrese, incluso lograr que vuelva a estadíos anteriores, el tratamiento de elección son las sustancias antiangiogénicas, también conocidas como anti-VEGF. Su vía de administración es intraocular, con la previa utilización de un anestésico local, para facilitar que el fármaco actúe directamente en la retina. El fármaco que se utilizará es Aflibercept (Eylea®).

Algunos pacientes, cuando van a recibir el tratamiento en los dos ojos, prefieren ser tratados en días diferentes. No hay información publicada sobre si al tratar los dos ojos a la vez los resultados se obtienen con mayor brevedad. Por este motivo, se suele aceptar la decisión del paciente, adaptando la pauta a sus necesidades y preferencias.

Objetivos y finalidad del estudio: Para poder observar si hay diferencias entre las dos pautas de tratamiento y, así, poder aconsejar a los pacientes sobre ellas, se recogerán los datos que se obtengan durante el primer año de tratamiento y seguimiento.

Participación: Su participación en este estudio es totalmente voluntaria y gratuita. El participante es libre de dejar el estudio en cualquier momento. El tratamiento que recibirá será el mismo que si no participara en este. A los controles habituales se les añadirá la realización de un cuestionario al inicio y al final del estudio (12 meses después).

Confidencialidad y protección de datos: Se adoptarán las medidas para garantizar la confidencialidad de sus datos en cumplimiento de la Ley Orgánica 15/1999 y la información recogida será gestionada de forma anónima y sólo se utilizará en fines de investigación. También se garantizarán los principios establecidos por la Ley de Investigación Biomédica 14/2007.

Con su participación es este estudio podrá ayudar a personas que tengan una afectación semejante a suya en un futuro.

Gracias por particiar

ANNEX 2-Informed consent for the study

Hospital Universitari de Girona
Doctor Josep Trueta

CONSENTIMIENTO INFORMADO DEL ESTUDIO

·Yo,_____

con D.N.I._____.

·He leído la hoja de información sobre el estudio que se me ha entregado.

·He recibido suficiente información acerca del estudio.

·He podido hacer todas las preguntas necesarias respecto al estudio.

·He estado informado por el investigador _____ sobre las implicaciones y finalidades del estudio.

·Entiendo que mi participación es voluntaria.

·Entiendo que los datos facilitados por mi persona son totalmente confidenciales.

·Entiendo que puedo revocar mi consentimiento informado de participación en el estudio, sin tener que dar explicaciones y sin que ello afecte a mi asistencia sanitaria.

-¿Acepta que los investigadores del estudio puedan contactar con usted si en un futuro lo consideran oportuno?

Sí ◯ No ◯

-¿Da su consentimiento para que información de su persona sea utilizada en el estudio?

Sí ◯ No ◯

Firma del participante Firma del investigador

Fecha:___/___/___ Fecha:___/___/___

ANNEX 3-Informed consent for the intravitreal injections

Hospital Universitari de Girona
Doctor Josep Trueta

CONSENTIMIENTO INFORMADO SOBRE EL TRATAMIENTO CON INYECCIÓN INTRAVITREA: AFLIBERCEPT (EYLEA®)

INDICACIONES

Eylea (aflibercept) está aprobado por la Agencia Europea de Medicamentos para tratar la Degeneración Macular Asociada con la Edad (DAE) Húmeda Neovascular, que es la principal causa de ceguera en personas mayores de 50 años. Hay dos tipos de degeneración macular: seca y húmeda. En la forma "húmeda" de DMAE, se desarrollan vasos sanguíneos anormales en la parte posterior del ojo. A veces estos vasos presentan escapes de sangre o gotereo de líquido que conduce a visión borrosa o distorsionada en los pacientes. Si esta condición no es tratada, la pérdida de visión puede ser rápida y severa.

El objetivo del tratamiento es evitar pérdida adicional de visión. Aunque algunos pacientes han recuperado visión, el medicamento puede no restaurar la visión que ya se ha perdido y, en último caso, puede no evitar la pérdida adicional de visión producida por la enfermedad.

ADMINISTRACIÓN

Después de insensibilizar el ojo con anestesia, se inyecta el medicamento en le vítreo, es decir, en la sustancia gelatinosa de la cámara posterior del ojo. Su oftalmólogo le informará la frecuencia con la que deberá recibir la inyección y el tiempo que durará el tratamiento.

POSIBLES COMPLICACIONES

Las posibles complicaciones de la administración de Eylea (aflibercept) incluyen, eventos adversos relacionados con el ojo, como desprendimiento de retina, una infección severa (endoftalmitis), inflamación al interior del ojo, formación de cataratas (opacificación del cristalino), glaucoma (aumento de la presión intraocular), hipotonía (disminución de la presión intraocular), daño a la retina o a la córnea (estructuras del ojo) y sangrado. Los efectos secundarios más comunes en el ojo son: aumento de enrojecimiento en la parte blanca del ojo (hemorragia sub-conjuntival), dolor ocular, catarata, desprendimiento del vítreo, pequeñas manchas en la visión (flotadores), aumento de la presión intraocular y sensación de cuerpo extraño en el ojo.

Además hay un riesgo potencial de eventos arteriales tromboembólicos (EATEs), definidos como accidente cerebrovascular no fatal, infarto no fatal y muerte arterial, después del uso intravítreo de medicamentos anti-VEGF.

CONSENTIMIENTO DEL PACIENTE

He leído/me han leído la anterior explicación. La naturaleza de mi afección ocular me ha sido explicada y se me ha descrito el tratamiento propuesto. Se me han explicado los riesgos, beneficios, alternativas y limitaciones del tratamiento. He recibido respuesta a todas mis preguntas.

Por el presente documentos autorizo al Dr. _____ a administrar la inyección intravítrea de Eylea (aflibercept) a intervalos regulares, según sea necesario.

FIRMA DEL PACIENTE FIRMA DEL MÉDICO

ANNEX 4-National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25)

Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

1. In general, would you say your overall health is:

(Circle One)

Excellent **1**
Very Good **2**
Good **3**
Fair **4**
Poor **5**

2. At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?

(Circle One)

Excellent **1**
Good **2**
Fair **3**
Poor **4**
Very Poor **5**
Completely Blind **6**

3. How much of the time do you worry about your eyesight?

(Circle One)

None of the time **1**
A little of the time **2**
Some of the time **3**
Most of the time **4**
All of the time? **5**

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:

(Circle One)

None **1**
Mild **2**
Moderate **3**
Severe, or **4**
Very severe? 5

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have <u>reading ordinary print in newspapers</u>? Would you say you have:

(Circle One)

No difficulty at all **1**
A little difficulty **2**
Moderate difficulty **3**
Extreme difficulty **4**
Stopped doing this because of your eyesight **5**
Stopped doing this for other reasons or not interested in doing this **6**

6. How much difficulty do you have doing work or hobbies that require you to <u>see well up close</u>, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:

(Circle One)

No difficulty at all **1**
A little difficulty **2**
Moderate difficulty **3**
Extreme difficulty **4**
Stopped doing this because of your eyesight **5**
Stopped doing this for other reasons or not interested in doing this **6**

7. Because of your eyesight, how much difficulty do you have <u>finding something on a crowded shelf</u>?

(Circle One)

No difficulty at all **1**
A little difficulty **2**
Moderate difficulty **3**
Extreme difficulty **4**
Stopped doing this because of your eyesight **5**
Stopped doing this for other reasons or not interested in doing this **6**

8. How much difficulty do you have reading street signs or the names of stores?

(Circle One)

No difficulty at all **1**
A little difficulty **2**
Moderate difficulty **3**
Extreme difficulty **4**
Stopped doing this because of your eyesight **5**
Stopped doing this for other reasons or not interested in doing this **6**

9. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?

(Circle One)

No difficulty at all **1**
A little difficulty **2**
Moderate difficulty **3**
Extreme difficulty **4**
Stopped doing this because of your eyesight **5**
Stopped doing this for other reasons or not interested in doing this **6**

10. Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?

(Circle One)

No difficulty at all **1**
A little difficulty **2**
Moderate difficulty **3**
Extreme difficulty **4**
Stopped doing this because of your eyesight **5**
Stopped doing this for other reasons or not interested in doing this **6**

11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say?

(Circle One)

No difficulty at all **1**
A little difficulty **2**
Moderate difficulty **3**
Extreme difficulty **4**
Stopped doing this because of your eyesight **5**
Stopped doing this for other reasons or not interested in doing this **6**

12. Because of your eyesight, how much difficulty do you have <u>picking</u> <u>out and matching your own clothes</u>?

(Circle One)

No difficulty at all **1**
A little difficulty **2**
Moderate difficulty **3**
Extreme difficulty **4**
Stopped doing this because of your eyesight **5**
Stopped doing this for other reasons or not interested in doing this **6**

13. Because of your eyesight, how much difficulty do you have <u>visiting</u> <u>with people in their homes, at parties, or in restaurants</u> ?

(Circle One)

No difficulty at all **1**
A little difficulty **2**
Moderate difficulty **3**
Extreme difficulty **4**
Stopped doing this because of your eyesight **5**
Stopped doing this for other reasons or not interested in doing this **6**

14. Because of your eyesight, how much difficulty do you have <u>going out</u> <u>to see movies, plays, or sports events</u>?

(Circle One)

No difficulty at all **1**
A little difficulty **2**
Moderate difficulty **3**
Extreme difficulty **4**
Stopped doing this because of your eyesight **5**
Stopped doing this for other reasons or not interested in doing this **6**

15. Are you <u>currently driving</u>, at least once in a while?

(Circle One)

Yes ..... **1** *Skip To Q 15c*

No **2**

15a. IF NO: Have you never driven a car or have you given up driving?

(Circle One)

Never drove ..... **1** *Skip To Part 3, Q 17*

Gave up..... **2**

15b. IF YOU GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?

(Circle One)

Mainly eyesight ..... **1** *Skip To Part 3, Q 17*

Mainly other reasons ..... **2** *Skip To Part 3, Q 17*

Both eyesight and other reasons ... **3** *Skip To Part 3, Q 17*

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:

(Circle One)

No difficulty at all.....**1**

A little difficulty **2**

Moderate difficulty.....**3**

Extreme difficulty.....**4**

16. How much difficulty do you have driving at night? Would you say you have:

(Circle One)

No difficulty at all **1**

A little difficulty..... **2**

Moderate difficulty **3**

Extreme difficulty **4**

Have you stopped doing this because of your eyesight **5**

Have you stopped doing this for other reasons or are you not interested in doing this **6**

16A. How much difficulty do you have driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic? Would you say you have:

(Circle One)

No difficulty at all **1**
A little difficulty **2**
Moderate difficulty **3**
Extreme difficulty **4**
Have you stopped doing this because of your eyesight **5**
Have you stopped doing this for other reasons or are you not interested in doing this....**6**

PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, please circle the number to indicate whether for you the statement is true for you all, most, some, a little, or none of the time.

(Circle One On Each Line)

READ CATEGORIES:	**All of the time**	**Most of the time**	**Some of the time**	**A little of the time**	**None of the time**
17. Do you accomplish less than you would like because of your vision?	**1**	**2**	**3**	**4**	**5**
18. Are you limited in how long you can work or do other activities because of your vision?	**1**	**2**	**3**	**4**	**5**
19. How much does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:	**1**	**2**	**3**	**4**	**5**

For each of the following statements, please circle the number to indicate whether for you the statement is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
20. I stay home most of the time because of my eyesight.....	**1**	**2**	**3**	**4**	**5**
21. I feel frustrated a lot of the time because of my eyesight.....	**1**	**2**	**3**	**4**	**5**
22. I have much less control over what I do, because of my eyesight.	**1**	**2**	**3**	**4**	**5**
23. Because of my eyesight, I have to rely too much on what other people tell me. .	**1**	**2**	**3**	**4**	**5**
24. I need a lot of help from others because of my eyesight.....	**1**	**2**	**3**	**4**	**5**
25. I worry about doing things that will embarrass myself or others, because of my eyesight.....	**1**	**2**	**3**	**4**	**5**