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Switch de antiangiogénicos en pacientes con degeneración macular relacionada a la edad de tipo húmeda en la asociación para evitar la ceguera en México

Tesis

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Introduction

Age-related macular degeneration (AMD) is a leading cause of legal blindness among individuals 50 years or older in the developed world. Choroidal neovascularization (CNV) is responsible for the majority of cases of severe vision loss due to AMD. CNV is characterized by the abnormal growth of blood vessels from the choroid into the subretinal space which may cause vision loss secondary to subretinal fluid, hemorrhage, intraretinal edema, or scarring.

The annual years of healthy life lost per 100,000 people from macular degeneration in Mexico has increased by 59.7% since 1990, an average of 2.6% a year.For men, the health burden of macular degeneration in Mexico, as measured in years of healthy life lost per 100,000 men, peaks at age 80+. It harms men at the lowest rate at age 45-49.

Women are harmed at the highest rate from macular degeneration in Mexico at age 80+. It was least harmful to women at age 45-49. At 194.3 years of healthy life lost per 100,000 women in 2013, the peak rate for women was higher than that of men, which was 143.6 per 100,000 men.

The 60% of the mexican population has AMD (13,3042 per 100,000).

The three most debilitating sense organ diseases in Mexico during 2013 were age-related and other hearing loss, uncorrected refractive error, and other sense organ diseases respectively.

It is established that vision loss, contrast sensitivity (CS) and central retinal thickness (CRT) secondary to CNV is reduced in eyes treated with intravitreal anti-vascular endothelial growth factor (VEGF) therapy, which is currently the standard of care for neovascular AMD.(Referencia 2 de articulo de Ricci).

The most commonly used agents are bevacizumab (IVB) and ranibizumab (IVR) which reduce exudative fluid and have been shown to improve best-corrected visual acuity (BCVA) in eyes with neovascular AMD. (Referencia 2 a 4 de articulo de Ricci). Although not approved for any intraocular disease, bevacizumab (Avastin; Genentech, first used off-

label in 2005), a nonselective anti-VEGF agent, has been widely used especially as a cost-effective alternative to the newer standard of care, ranibizumab (Lucentis; Genentech, introduced in 2006). (Referencia 22,23 de Katja)

As opposed to off-label bevacizumab, which is a VEGF-specific full-length antibody, ranibizumab is a VEGF-specific antibody fragment and aflibercept is a fusion protein that—aside from binding all VEGF-A isoforms—binds VEGF-B and placental growth factor (PGF).

Despite IVB is an off-label agent, without FDA aprovement, in Mexico is the most used agent for the price, although it has shown a limited response. 10,000 IVB have been applied in our center in the last two years (unpublished data).
Aflibercept (IVA) is a new anti-VEGF agent, it is a recombinant fusion protein of key domains VEGFR1 and VEGFR2 receptors to the constant region of human immunoglobulin G. This protein binds to all VEGF-A, VEGF-B and placental growth factor, thus inhibiting the binding and activation of VEGF receptors. Both VEGF-B and placental growth factor have been implicated in the neovascularization process of AMD (Referencia 5 y 6 de Ricci). IVA has a higher affinity for VEGF-A and a longer half-life when compared to IVB and IVR with equal effectiveness in improving BCVA, contrast sensitivity, and preventing visual loss (Referencia 16 de Massamba). The VIEW 1 and 2 studies evaluated aflibercept for the treatment of neovascular AMD, it demostrated that 2 mg of IVA administered every 8 weeks after a loading dose of 3 monthly injection was noninferior to 0.5 mg of IVR dosed monthly (Referencia 19 Heier).

Currently, three posologies are commonly used to treat CNV, irrespective of the anti-VEGF chosen: 1) fixed interval; 2) pro re nata (PRN); and treat-and- extend regimen (TER). (Referencia 27 de Katja). Following initiation of anti-VEGF therapy patients are followed at regular intervals to monitor the disease activity. Two parameters are used to assess response to anti-VEGF therapy at pre-determined intervals, VA and macular morphology on optical coherence tomography (OCT).

The 2015 American Society of Retinal Specialists found that 40.6% of European ophthalmologists and 11.8% of ophthalmologists in the United States use a PRN regimen, and 30.4% and 66.2%, respectively, use TER. (Referencia 28 de Prunte)

The comparison of treatment regimens for AMD demonstrated that patients under monthly or PRN dosing experience similar outcomes after 1 year and 2 years. (Referencia 13,29 de Katja).

Response to treatment is best determined at 1 month following the last initiation dose (that is, at month 4).

An optimal response is a absence of lesion activity (disappearance of the features of fluid in any of the macular tissue compartments), or reduction in 75% of the fluid at the end of the primary treatment phase. Suboptimal (‘partial’) response is a reduction in 25 to 75% of the fluid from baseline but still persistence of fluid . Poor response is defined as a reduction <25%- 0. Non-response is defined as unchanging or increasing CRT, SRF, IRF and/or PED compared with the baseline (Referencia Amoaku 27)

Morphological response takes into account the different lesion components including vascularised pigment epithelial detachment (PED), serous PED, Intraretinal fluid (IRF), Subretinal fluid (SRF), CRT, retinal or subretinal blood and the presence of vitreomacular interface changes. (Referencia 37 de Hanstrom).

Recent reports have shown that switching treatment from IVB or IVR to IVA led to an improved response with decreased exudation in patient’s refractory to their prior treatment with other anti-VEGF drugs. Dosing was reported by Ricci et al who concluded that in neovascular AMD the switch to aflibercept in PRN or fixed regimen enabled improvement in morphological parameters and stabilization of visual acuity, showing better results in the fixed regimen after 1 year. (Referencia a 4 de articulo de Ricci).

Kumar et al reported that after switching to IVA 17.6% of eyes had persistent subretinal fluid compared with more than 70% at baseline with IVR; and less that 25% had intraretinal fluid compared with 65% of eyes at baseline with IVR. (Referencia Kumar).

Purpose

The purpose of this investigation is to determine the effect achieved with a single dose of anti-angiogenic (AAG) treatment switch, in patients with persistent neovascular age-related macular degeneration (nAMD) unresponsive to intravitreal bevazicumab (IVB), switched to either intravitreal aflibercept (IVA) or ranibizumab (IVR), and to compare the response between these two drugs.

Methods

This is a retrospective, observational, and comparative study, designed to analyze the effect of switching from IVB to either IVA or IVR, in patients with unresponsive nAMD. The study was performed at the Asociación Para Evitar la Ceguera en México (Association to Prevent Blindness in Mexico [APEC]). The research had prior Institutional Review Board approval and was adherent to the tenants of the Declaration of Helsinki.
The clinical records and spectral-domain optical coherence tomography results of patients with nAMD were analyzed. Patients were included if they had the following: 1) nAMD; 2) treated exclusively with IVB; 3) were switch to either IVA or IVR during follow-up; 4) had complete clinical records, specially with SD-OCT performed before every intravitreal injection.

The patients were switched from IVB based on 2 criteria: A) If they were considered to have an un-responsive disease, defined as persistent intraretinal or subretinal fluid (IRF/SRF) after at least three monthly consecutive doses of IVB, or, B) if the treating clinician considered that a different AAG drug was more appropriate for treating the individual disease. Therefore, patients could be included if they at least had one initial dose of IVB and then were switched to IVA or IVR.

Study period was from January 2014 to December 2016. Primary outcome measure was the mean change in central macular thickness (CMT), considered to be an objective way to measure the effect of switching from IVB to IVA/IVR. CMT was obtained from SD-OCT automatic segmentation using the Cirrus 4000 HD-OCT system (Carl Zeiss Meditec AG. Jena, Germany). For every case, the automatic segmentation lines were observed to rule-out irregularities that could give false readings, and if so, they were corrected. A secondary outcome measure was mean change in macular volume (MV).

Patients were divided in two groups: Group 1, patients switched to IVA; Group 2, patients switched to IVR. Since every patient analyzed had complete measurements from baseline, previous from IVB switch to IVA/IVR (PreSwitch), and posterior to switch from IVB to IVA/IVR (Post Switch), a paired-samples t-test was selected as the statistical test to measure differences in CMT and MV. Also, to determine if there were differences in-between groups from PreSwitch to PostSwitch, a Mixed-Design (split-plot) ANOVA was used as a statistical test. The mixed-design analysis of variance is used to test for

differences between two independent groups (Group 1: IVA vs. Group 2: IVR), while the subjects in each group are tested for repeated measures (REF: WIKIPEDIA. PUBMED.)

All data was registered onto spreadsheets using Number for Mac (Ver. 3.6.2. Apple Inc. Cuppertino. USA.). Statistical analysis was performed with SPSS (Ver. 22. IBM Corp. Armonk, USA.)

Results

The analysis identified 85 patients fully satisfying inclusion and exclusion criteria. During the study period 49 eyes received IVA according to the PRN regimen (PRN group) and 36 eyes received IVR. There were two groups, group 1: IVB switched to IVA, and group 2: IVB switched to IVR.

Demographics and clinical characteristics of all cases are summarized in Table 1. In group 1, there were 63% (31) female cases.. In group 2, there were 75% (27) female cases. The median age was, 70.18 (58-84) and 69.46 (56-81), group 1 and group 2 respectively.

The median number of injections was, 6.04 and 5.75, group 1 and group 2 respectively. (Table 1)

Variable	Ranibizumab	Aflibercept	Total
Number	36	49	85
Median Age (range)	69.46 (81-56)	70.18 (84-58)	
Gender	27 F (75%)-9 M (25%)	31 F (63%)-18 M (36.7%)	
Median number of injections (range)	5.75 (18-1)	6.04 (18-1)	

In group 1, the mean baseline CMT was 308.18 (SD108.18) and post CMT was 259.27 (SD 65.27), the correlation between BL and POST CMT was 0.350, with a p= 0.015, with a mean of 48.916 (SD 104.97) and a IC (18.433 to 79.399), with a **p=0.002**

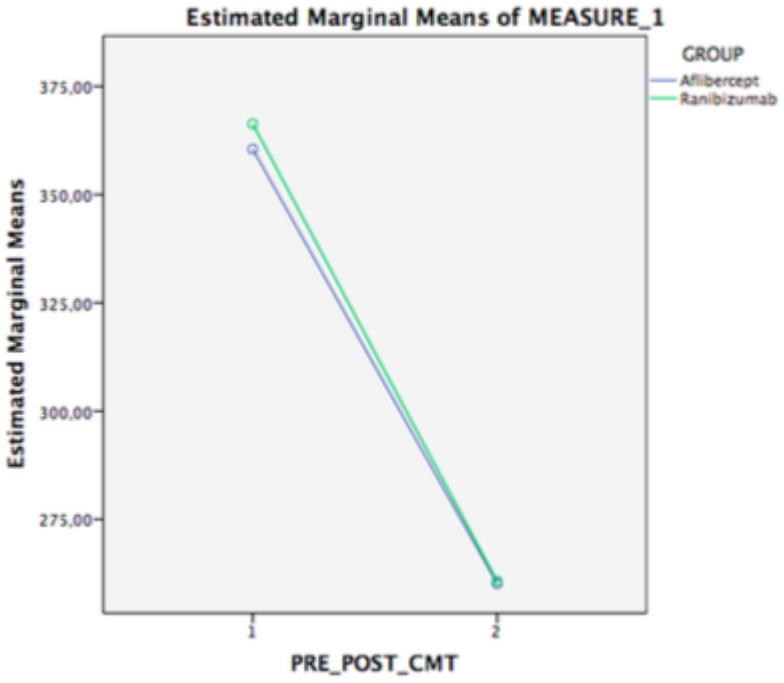
The mean Pre CMT was 360.51 (SD 207.16) and Post CMT of 260.16 (SD 64.89), the correlation between was 100.34 (SD 214.12), with a IC (38.844 to 161.849), with a **p=0.002, stadistically significant.**

The mean BL MV was 10.45 (SD 1.239) and Pre MV of 11.15 (SD 2.28), with a correlation of 0.792, and a **p=0.000**, with a mean of -0.702 (SD 1.507) IC (-1.140 to -2.644), with a **p= 0.002.**

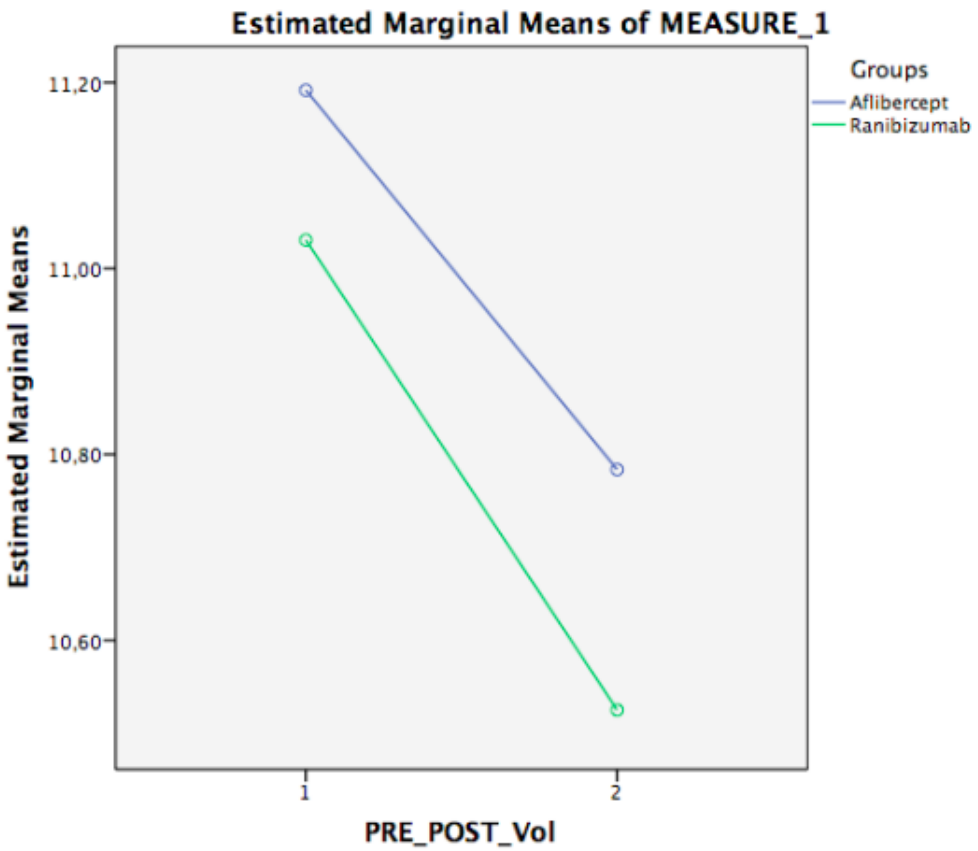
The mean baseline CMT was 366.00 (SD120.934) and post CMT was 260.72 (SD 60.157), the correlation between BL and POST CMT was 0.090, with a p= 0.603, with a mean of 105.277 (SD 130.147) and a IC (61.242 to 149.313), with a **p=0.000.**

The mean Pre CMT was 366.33 (SD 164.64) and Post CMT of 260.72 (SD 60.157), the correlation between was 0.380, p=0.22, with a mean paired sample test of 105.61 (SD 152.295), with a IC (54.081 to 157.140), with a **p=0.000.**

The mean BL MV was 10.60 (SD 1,666) and Pre MV of 11.03 (SD 1.694), with a correlation of 0.582, and a **p=0.000,** with a mean of -0.426 (SD 1.535) IC (-0.945 to 0.093), with a p= 0.105.



There is no difference between groups 1 and 2 in CMT.



Mean CMT (SD)	Group 1. IVA (N= 49)	Group 2. IVR (N= 36)
Baseline	308.18 (108.18)	366.00 (120.93)
PreSwitch	360.51 (207.16)	366.33 (164.64)
PostSwitch	260.16 (64.89)	260.72 (60.15)

Table 2. Mean CMT in group 1 and 2.

Mean MV (SD)	Group 1. IVA (N= 49)	Group 2. IVR (N= 36)
Baseline	10.45 (1.23)	10.60 (1.66)
PreSwitch	11.19 (2.27)	11.03 (1.69)
PostSwitch	10.78 (1.63)	10.52 (1.24)

Table 3. Mean MV in group 1 and 2.

Discussion

It has been well established that the efficacy of drugs blocking the increased level of intravitreal VEGF associated with nAMD may diminish over time. In addition to the mechanisms involving a change in the cellular composition of the neovascular membrane (pericyte coverage) and in the effects on the retinal architecture (fibrosis), the loss of activity has been partially attributed to tachyphylaxis or to increased tolerance. (Rosenfeld PG, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY et al. MARINA Study Group.)

At present the dilemma of when and how to change medications after their efficacy has diminished has not been addressed.

Aflibercept is the last anti-VEGF drug that has been approved for the treatment of CNV associated with AMD, based on the efficacy demonstrated in the VIEW trials. In recent studies, it has been considered as a treatment option for patients presenting with persistent/ resistant nAMD or with high recurrence rate. Moreover, aflibercept has also been used as alternative treatment in patients treated successfully with IVR and IVA.Additional activity of IVA may rely on higher binding affinity to VEGF-A and the ability to target VEGF-B and PlGF. (Singh RP, Srivastava S, Ehlers JP, Bedi R, Schachat AP, Kaiser PK.)

Different treatment regimens have been adopted for switching therapy, but no clear recommendation has been made due to the lack of direct comparisons between treatment strategies.

To the best of our knowledge, there are a few studies that compared the efficacy of IVA versus IVR treatment after initial IVB regimen. Several recent publications of mainly small, retrospective case series focused predominantly either on the switch to IVA for eyes non-responding to IVR and/or IVB, favouring the switch to IVA. Some other studies focused on the switch from IVB to IVR only. Nevertheless, it remains unclear whether a treatment with IVA is more effective e.g. due to a higher affinity to VEGF or possible cross tolerance effects between IVR and IVB. In addition, the question whether a switch of anti-VEGF drugs over time can also be a treatment option, has not finally been answered yet. (Papadopoulos N, Martin J, Ruan Q, Rafique A, Rosconi MP, Shi E et al.)

Our results are reflecting clinical reality outside randomized trials and confirm the efficacy of treatment with both IVA and IVR after initial IVB regimen.
Our results are in accordance with studies investigating both the outcome after switching from IVR and/or IVB to IVA and after switching from IVB to IVR . Bakall et al. found a statistical significant decrease in CMT in 36 eyes with exudative AMD but no significant change in visual acuity after a switch to IVA after initial treatment with IVR and/or IVB. (Bakall B, Folk JC, Boldt HC, Sohn EH, Stone EM, Russell SR et al.)
Comparison of anatomical results revealed that both switches from IVB to IVA and to IVR were accompanied by a statistical significant decrease in central macular thickness. (Pinheiro-Costa J, Costa JM, Beato JN, Freitas-da-Costa P, Brandão E, Falcão MS et al.) Meanwhile, comparing the CMT at pre to one -month-follow-up visit we found a statistically significant reduction of the mean Pre CMT was 360.51 (SD 207.16) and Post CMT of 260.16 (SD 64.89), the correlation between was 100.34 (SD 214.12), with a IC (38.844 to 161.849), with a p=0.002, in group 1 and in group 2 with a mean Pre CMT was 366.33 (SD 164.64) and Post CMT of 260.72 (SD 60.157), the correlation between was 0.380, p=0.22, with a mean paired sample test of 105.61 (SD 152.295), with a IC (54.081 to 157.140), with a p=0.000.
Our results are in accordance with studies investigating the anatomical outcome both after switching from IVR and/or IVB to IVA and after switching from IVB to IVR. Bakall et al. (Bakall B, Folk JC, Boldt HC, Sohn EH, Stone EM, Russell SR et al.) found a statistical significant decrease in CMT after a switch from IVR and/or IVB to IVA. Ehlken et al. (Ehlken C, Jungmann S, Böhringer D, Agostini HT, Junker B, Pielen A.) showed a statistically significant reduction of CMT after switching from IVB to IVR.

Therefore, our observations show comparable results for a switch either from bevacizumab to aflibercept or to ranibizumab. In summary, we identified a clinical benefit for both treatment options with ranibizumab and aflibercept after initial bevacizumab regimen, with a minimal advantage for aflibercept over ranibizumab.

Conclusions

The switch to aflibercept and ranibizumab, show an improvement in morphological parameters and in an important reductions in CMT and MV.

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