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ORIGINAL PAPER

Anti-VEGF treatment switch in neovascular age-related macular degeneration: a comparison of aflibercept versus ranibizumab after a single-dose switch

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Abstract

Purpose To determine the effect achieved from a single dose of anti-VEGF treatment switch, in patients with nAMD previously treated with bevacizumab, switched to either aflibercept or ranibizumab, and to compare the response between aflibercept and ranibizumab.

Methods In retrospective, observational, and comparative study, patients were divided into two groups: Group 1, patients switched to aflibercept; Group 2, patients switched to ranibizumab. Paired samples *t* test was performed to measure differences in central macular thickness (CMT). To compare whether there were differences between groups mixed-design ANOVA was used.

Results In Group 1, CMT changed from 360.51 to 260.16 µm, presenting a significant mean difference from PreSwitch to PostSwitch of 100.34 µm ($p = 0.002$, paired samples *t* test). In Group 2, CMT changed from 366.33 to 260.72 µm, showing a significant difference from PreSwitch to PostSwitch of 105.61 µm ($p \leq 0.000$, paired samples *t* test). The mixed-design ANOVA compared both groups and resulted in a nonsignificant value of 0.90.

Conclusion The effect achieved from a single dose in patients switched to aflibercept or ranibizumab reduced significantly CMT measurements. Comparing aflibercept and ranibizumab, the effect appears to be similar in both drugs, in terms of reduction of CMT.

Keywords Aflibercept · Bevacizumab · Choroidal neovascularization · Macular degeneration · Ranibuzumab

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Introduction

Age-related macular degeneration (AMD) is a leading cause of legal blindness among individuals 50 years or older in developed countries [1]. 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. In neovascular AMD (nAMD), vision loss, contrast sensitivity (CS) and central retinal thickness (CRT) are improved in eyes treated with intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy. Therefore, anti-VEGF therapy has become the standard of care for nAMD [2, 3].

There are currently three anti-VEGF agents used for the treatment of nAMD: bevacizumab (Avastin®. Genentech, San Francisco. USA), a non-selective VEGF-specific full-length antibody; ranibizumab (Lucentis®. Novartis AG, Basel. Switzerland), a VEGF-specific antibody fragment; and aflibercept (Eylea®. Bayer Healthcare Pharmaceuticals, Berlin, Germany), a recombinant fusion protein that binds to all VEGF-A and VEGF-B isoforms, as well as placental growth factor. Several studies have demonstrated the safety and efficacy of all three drugs, including bevacizumab (used as an off-label drug to treat nCNV) [4–13].

Probably, the most commonly used drug for nAMD in the world is intravitreal bevacizumab (IVB). The 2017 Preferences and Trends (PAT) Survey from the American Society of Retina Specialists (ASRS) revealed that in the USA 67.7% of retina specialists would treat a new nAMD patient with IVB, compared to 19.5% that would use intravitreal aflibercept (IVA), and 11.4% intravitreal ranibizumab (IVR) (2017 Global Trends in Retina/PAT Survey presented at the ASRS Annual Meeting, Boston, 2017. Gourav K. Shah, MD. American Society of Retina Specialists). Similarly in Mexico, at our center, the Asociación Para Evitar la Ceguera en México (Association to Prevent Blindness in Mexico [APEC]), in a period of two years and including all indications for anti-VEGF use (nCNV, diabetic macular edema, retinal vein occlusions, myopic CNV, retinopathy of prematurity, etc.), a total of 9263 IVB injections were performed, versus 896 IVA injections, and 272 IVR injections (unpublished data from the Statistics Department, APEC. Mexico).

Despite the wide use of IVB, due mainly to the cost per injection, many patients may not respond adequately to this drug and might be good candidates to switch to another anti-VEGF drug. Eyes being treated for CNV with anti-VEGF drugs might develop a diminished therapeutic response over time which could be attributed to tachyphylaxis [14]. Few data are known on switching from IVB to IVA/IVR, regarding what is the response of only one dose of another drug in eyes previously treated, and which drug could be better to switch to. Therefore, the purpose of this investigation is to determine the effect achieved from a *single dose* of anti-VEGF treatment switch, in patients with nAMD previously treated with IVB, switched to either IVA or IVR, and hence, to compare the response between IVA and IVR in a single dose of anti-VEGF treatment switch from IVB.

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 nAMD, performed at APEC, Mexico City. 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 (SD-OCT) results of patients with nAMD were analyzed. Patients were included if they had the following: (1) nAMD; (2) treated exclusively with IVB; (3) were switched 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 two criteria: (A) If they were considered to have an unresponsive 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 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 Macular Cube 512 × 128 protocol from the Cirrus 5000 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 into two groups: Group 1, patients switched to IVA; Group 2, patients switched to IVR. Both groups were tested for normality distribution. 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 (PostSwitch), a paired samples *t* test was selected as the statistical test to measure differences in CMT and MV. Also, to determine and compare 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 [15]. Statistical significance was defined as < 0.05.

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

Results

A total of 85 eyes were included in the study, 49 in Group 1: IVA, and 36 in Group 2: IVR. Demographics for both groups are shown in Table 1. Mean age for Group 1: IVA was 70.18 years (Median 70, range: 58–84). Mean age for Group 2: IVR was 69.46 years (Median 69, range 56–81). Average number of IVB injections previous to the switch for Group 1 was 6.04 injections (Median 4, range 1–18). Average number of previous IVB injections for Group 2 was 5.75 (Median 5, range 1–18).

Central macular thickness (CMT) results

Group 1: IVA

Baseline CMT was 308.18 µm (standard deviation [SD] 108.18), PreSwitch CMT was 360.51 µm (SD: 207.16), and PostSwitch CMT was 260.16 µm (SD: 64.89) (Table 2).

Mean difference from Baseline to PreSwitch was − 52.33 µm (SD: 201.61). Paired samples *t* test (Table 3) from Baseline to PreSwitch resulted in a *t* score of − 1.639, two-tailed significance (Sig.) of 0.108 (95% confidence interval [CI] − 106.22 to 10.85).

Mean difference from Baseline to PostSwitch was 48.02 µm (SD: 104.97). Paired samples *t* test from Baseline to PostSwitch resulted in a *t* score of 3.228, Sig. 0.002 (95% CI: 18.43–79.39).

Mean difference from PreSwitch to PostSwitch was 100.34 µm (SD: 2014.12). Paired samples *t* test from PreSwitch to PostSwitch resulted in a *t* score of 3.281, Sig. 0.002 (95% CI: 38.84–161.84).

Group 2: IVR

Baseline CMT was 366.00 µm (SD: 120.93), PreSwitch CMT was 366.33 µm (SD: 164.64), and PostSwitch CMT was 260.72 µm (SD: 60.15) (Table 2).

Mean difference from Baseline to PreSwitch was − 0.33 µm (SD: 176.47). Paired samples *t* test (Table 3) from Baseline to PreSwitch resulted in a *t* score of − 0.11, Sig. 0.991 (95% CI: − 60.04 to 59.37).

Mean difference from Baseline to PostSwitch was 105.27 µm (SD: 130.14). Paired samples *t* test from Baseline to PostSwitch resulted in a *t* score of 4.853, Sig. < 0.000 (95% CI: 61.24–149.31).

Table 1 Demographics

	Group 1. IVA (*N* = 49)	Group 2. IVR (*N* = 36)
Gender	Women: 31 (63%); Men 18 (36%)	Women: 27 (75%); Men 9 (25%)
Age	70.18 years (*M*: 70, *R*: 58–84)	69.46 years (*M*: 69, *R*: 56–81)
Previous IVB injections	6.04 injections (*M*: 4, *R*: 1–18)	5.75 injections (*M*: 5, *R*: 1–18)

IVA intravitreal aflibercept, *IVR* intravitreal ranibizumab, *M* median, *R* range, *IVB* intravitreal bevacizumab

Table 2 CMT results

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

CMT central macular thickness, *IVA* intravitreal aflibercept, *IVR* intravitreal ranibizumab, *SD* standard deviation

Table 3 Paired samples t test CMT

	Mean	Mean difference (SD)	95% CI	t score	Significance (2-tailed)
Group l: IVA					
Baseline versus PreSwitch					
Baseline CMT	308.18	− 52.33 (201.61)	− 106.22 to 10.85	− 1.639	0.108
PreSwitch CMT	360.51				
Baseline versus PostSwitch					
Baseline CMT	308.18	48.02 (104.97)	18.43–79.39	3.228	0.002*
PostSwitch CMT	260.16				
PreSwitch versus PostSwitch					
PreSwitch CMT	360.51	100.34 (214.12)	38.84–161.84	3.281	0.002*
PostSwitch CMT	260.16				
Group 2: IVR					
Baseline versus PreSwitch					
Baseline CMT	366.00	− 0.33 (176.47)	− 60.04 to 59.37	− 0.11	0.991
PreSwitch CMT	366.33				
Baseline versus PostSwitch					
Baseline CMT	366.00	105.27 (130.14)	61.24–149.31	4.853	< 0.000*
PostSwitch CMT	260.72				
PreSwitch versus PostSwitch					
PreSwitch CMT	366.33	105.61 (152.29)	54.08–157.14	4.161	< 0.000*
PostSwitch CMT	260.72				

CMT central macular thickness, *CI* confidence interval, *IVA* intravitreal aflibercept, *IVR* intravitreal ranibizumab, *SD* standard deviation

*Statistically significant values

Mean difference from PreSwitch to PostSwitch was 105.61 μm (SD: 152.29). Paired samples t test from PreSwitch to PostSwitch resulted in a t score of 4.161, Sig. < 0.000 (95% CI: 54.08–157.14).

Macular volume results

Group 1: IVA

Baseline MV was 10.45 mm^3 (SD: 1.23), PreSwitch MV was 11.19 mm^3 (SD: 2.27), and PostSwitch MV was 10.78 mm^3 (SD: 1.63) (Table 4).

Mean difference from Baseline to PreSwitch was − 0.74 mm^3 (SD: 1.50). Paired samples t test

Table 4 MV results

	Group 1. IVA (N = 49)	Group 2. IVR (N = 36)
Baseline	10.45 mm^3 (SD: 1.23)	10.60 mm^3 (SD: 1.66)
PreSwitch	11.19 mm^3 (SD: 2.27)	11.03 mm^3 (SD: 1.69)
PostSwitch	10.78 mm^3 (SD: 1.63)	10.52 mm^3 (SD: 1.24)

MV macular volume, *IVA* intravitreal aflibercept, *IVR* intravitreal ranibizumab, *SD* standard deviation

(Table 5) from Baseline to PreSwitch resulted in a t score of − 3.227, Sig. 0.002 (95% CI: − 1.14 to − 0.26).

Mean difference from Baseline to PostSwitch was − 0.33 mm^3 (SD: 1.76). Paired samples t test from Baseline to PostSwitch resulted in a t score of − 1.225, Sig. 0.227 (95% CI: − 0.82 to 0.20).

Mean difference from PreSwitch to PostSwitch was 0.40 mm^3 (SD: 2.30). Paired samples t test from PreSwitch to PostSwitch resulted in a t score of 1.242, Sig. 0.220 (95% CI: − 0.25 to 1.06).

Group 2: IVR

Baseline MV was 10.60 mm^3 (SD: 1.66), PreSwitch MV was 11.03 mm^3 (SD: 1.69), and PostSwitch MV was 10.52 mm^3 (SD: 1.24) (Table 4).

Mean difference from Baseline to PreSwitch was − 0.42 mm^3 (SD: 1.53). Paired samples t test (Table 5) from Baseline to PreSwitch resulted in a t score of − 1.665, Sig. 0.105 (95% CI: − 0.94 to 0.09).

Mean difference from Baseline to PostSwitch was 0.07 mm^3 (SD: 1.90). Paired samples t test from Baseline to PostSwitch resulted in a t score of 0.250, Sig. 0.804 (95% CI: − 0.56 to 0.72).

Mean difference from PreSwitch to PostSwitch was 0.50 mm^3 (SD: 1.74). Paired samples t test from PreSwitch to PostSwitch resulted in a t score of 1.73, Sig. 0.091 (95% CI: − 0.08 to 1.09).

Table 5 Paired samples t test MV

	Mean MV mm^3	Mean difference (SD)	95% CI	t score	Significance (2-tailed)
Group l: IVA					
Baseline versus PreSwitch					
Baseline MV	10.45	− 0.7 (1.50)	− 1.14 to − 0.26	− 3.227	0.002*
PreSwitch MV	11.19				
Baseline versus PostSwitch					
Baseline MV	10.45	− 0.33 (1.76)	− 0.82 to 0.20	− 1.225	0.227
PostSwitch MV	10.78				
PreSwitch versus PostSwitch					
PreSwitch MV	11.19	0.40 (2.30)	− 0.25 to 1.06	1.242	0.220
PostSwitch MV	10.78				
Group 2: IVR					
Baseline versus PreSwitch					
Baseline MV	10.60	− 0.42 (1.53)	− 0.94 to 0.09	− 1.665	0.105
PreSwitch MV	11.03				
Baseline versus PostSwitch					
Baseline MV	10.60	0.07 (1.90)	− 0.56 to 0.72	0.250	0.804
PostSwitch MV	10.52				
PreSwitch versus PostSwitch					
PreSwitch MV	11.03	0.50 (1.74)	− 0.08 to 1.09	1.73	0.091
PostSwitch MV	10.52				

MV macular volume, *CI* confidence interval, *IVA* intravitreal aflibercept, *IVR* intravitreal ranibizumab, *SD* standard deviation

*Statistically significant values

Mixed-design (split-plot) ANOVA for changes in CMT and MV

The change in CMT from PreSwitch to PostSwitch resulted in a statistical significant difference in both groups (Group 1: IVA: 100.34 µm [SD: 214.12]; Group 2: IVR: 105.61 µm [SD: 152.29]). To determine if the change in CMT was different between groups, a mixed-design (split-plot) ANOVA was performed (Fig. 1), which resulted in a sig. value of 0.90, considered non-statistical significant.

For MV, change from PreSwitch to PostSwitch resulted in a non-statistical significant difference in both groups (Group 1: IVA: 0.40 [SD: 2.30]; Group 2: IVR: 0.50 [SD:1.74]). To determine if the change in MV was different between groups, the same mixed-design (split-plot) ANOVA was performed (Fig. 2), which resulted in a sig. value of 0.832, considered non-statistical significant.

Discussion

This study shows that the effect achieved from a single dose of anti-VEGF treatment switch, in patients with nAMD previously treated with IVB, switched to either IVA or IVR appears to be statistically and clinically significant in terms of reduction of CMT. Patients were obtained from a real-life scenario at an ophthalmological reference center in Mexico. This implies that most of the population treated at our institution will probably have low socioeconomic status, and therefore might not be able to afford a continuous treatment with other anti-VEGF drugs (IVA nor IVR). However, the results shown in the present study demonstrate that with a single dose of IVA or IVR, a significant reduction in CMT might me expected. These results are important because many patients and clinicians alike might believe that it is preferable to maintain a patient treated with IVB, based mainly on the low cost of the treatment, even if there is no response on CMT. However, it is important to provide a patient with alternatives such as IVA or IVR which will probably decrease significantly the CMT.

Interestingly, no significant difference was obtained with the MV results. This nonsignificant effect, in contrast to what was observed for CMT, might be due to the fact that the MV analysis comprises the full macular cube studied by the OCT. In other words, it not only analyzes the central

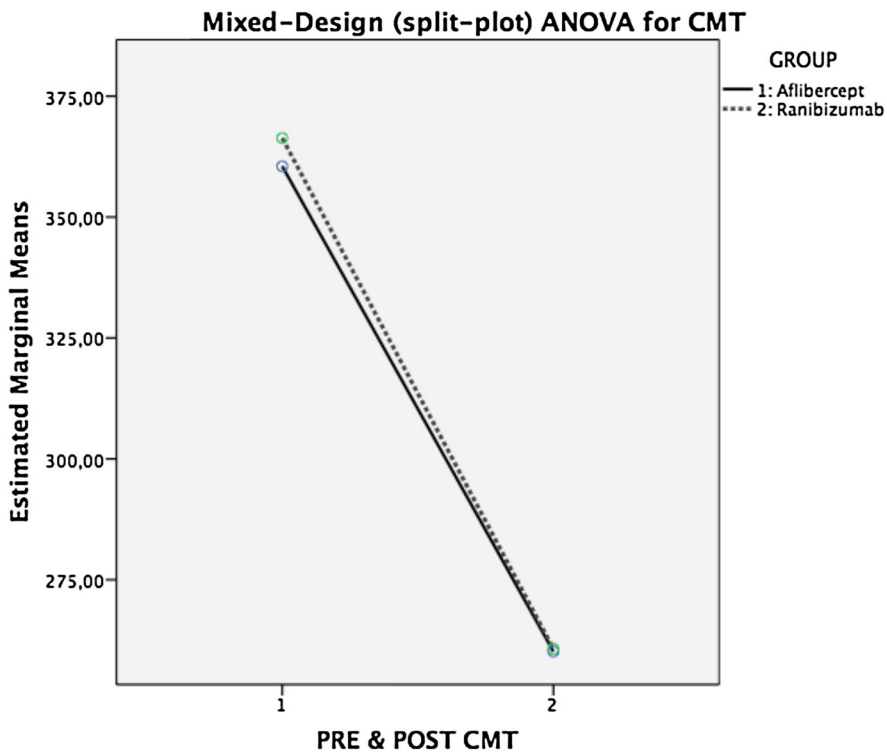

Fig. 1 Mixed-design ANOVA for central macular thickness (CMT) mean change. The *X*-axis presents PreSwitch (1) and PostSwitch (2). The *Y*-axis presents central macular thickness measurements in µm. Group 1, intravitreal aflibercept, had a mean difference of 100.34 µm (SD: 214.12 µm). It changed from 360.51 µm PreSwitch, to 260.16 µm PostSwitch. Group 2, intravitreal ranibizumab, had a mean difference of 105.61 µm (SD: 152.29 µm). It changed from 366.33 µm PreSwitch, to 260.72 µm PostSwitch. Mixed-design ANOVA resulted in a non-statistical difference between groups ($p = 0.90$)

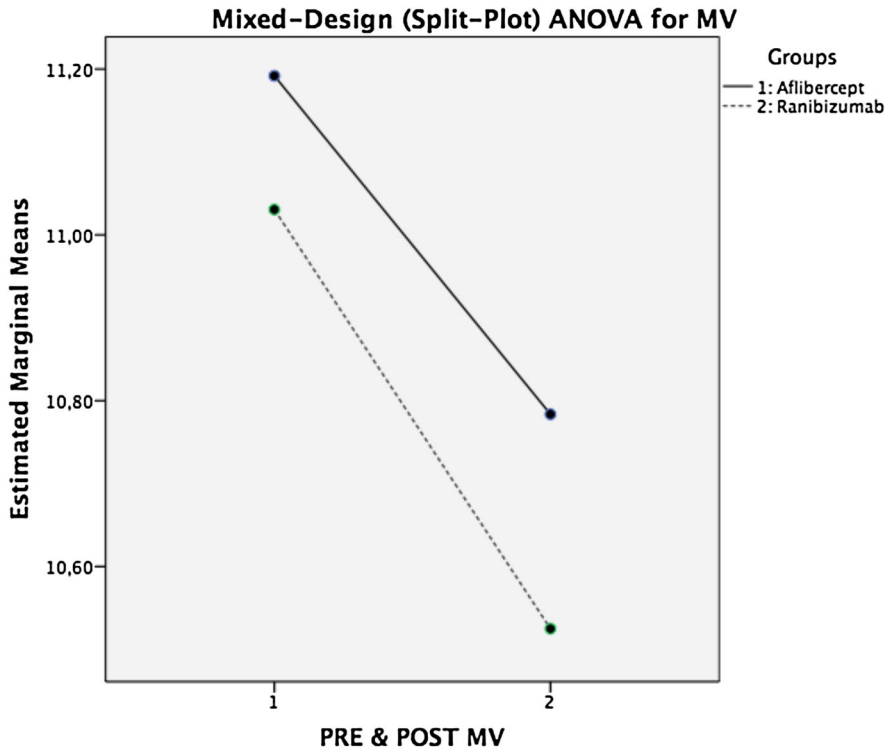

Fig. 2 Mixed-design ANOVA for macular volume (MV) mean change. The *X*-axis presents PreSwitch (1) and PostSwitch (2). The *Y*-axis presents macular volume measurements in mm^3. Group 1 had a mean difference of 0.40 mm^3 (SD: 2.30). It changed from 11.19 mm^3 PreSwitch, to 10.78 mm^3 PostSwitch. Group 2 had a mean difference of 0.50 mm^3 (SD: 1.74). It changed from 11.03 mm^3 PreSwitch, to 10.52 mm^3 PostSwitch. Mixed-design ANOVA resulted in a non-statistical difference between groups ($p = 0.832$)

subfield, but the full macula, therefore, a relatively small change in the foveal volume may not be sufficient to be statistically significant.

One of the main objectives of the present study was to compare the effect achieved from the two drugs, IVA versus IVR, in order to determine if an individual drug response is better than the other. Based on the design of the investigation, where each patient had a Baseline, PreSwitch and PostSwitch measurements in both groups, the mixed-design (split-plot) ANOVA was an adequate statistical test to determine if there was a difference between the response from each group. As shown in Fig. 1, no significant statistical difference ($p = 0.90$) was obtained when comparing the responses in CMT after the switch for both groups (Group 1: IVA: 100.34 µm [SD: 214.12]; Group 2: IVR: 105.61 µm [SD: 152.29]). This means that neither drug had a "better" effect decreasing CMT. Even if this is a small retrospective study, the results help determine that only one dose of a switch in anti-VEGF therapy, whether it is IVA or IVR will be significant, and that an adequate reduction in CMT could be expected. It is probable that a larger, randomized clinical trial that compares both drugs might show the presence of a more important difference in the response obtained from the first dose of switch between IVA and IVR, or in a longer follow-up.

To the authors' knowledge, there is only one other study that previously investigates the response from switching from IVB to IVA and IVR simultaneously. Waizel et al. studied a total of 96 eyes, under real-life conditions. Their primary end-point was reduction in CMT. In their IVA group, CMT decreased from 430 µm (SD: 220 µm) at baseline to 419 µm (SD: 212 µm) at switch, and decreased significantly to 318 µm (SD: 159 µm) at final follow-up visit ($p < 0.0001$). In their *IVR Group*, CMT increased from 396 µm (SD: 174 µm) at baseline to 499 µm (SD: 333 µm) at switch, and decreased significantly to 394 µm (SD: 202 µm) at final follow-up visit ($p = 0.007$) [16]. Their results contrast with our findings, where a significant reduction in CMT was observed in both groups. However, in their research, Waizel et al. did not report the CMT previous to the switch, which could have been a similar response as in our study. There are important differences in the baseline results for CMT. Waizel et al. reported baseline measurements at 430 µm (SD: 220 µm) and 396 µm (SD: 174 µm) for IVA and IVR groups,

respectively, versus our results at 308.18 μm (SD: 108.18) and 366.00 μm (SD: 120.93 μm) for IVA and IVR groups, respectively. Probably the most important difference is the response obtained from one dose of switch; Waizel et al. reported a difference after switch (from Baseline to Switch) of 11 μm of difference in their IVA group, versus 48.02 μm in our IVA group, from Baseline to PostSwitch ($p = 0.002$). In their IVR group, the response from Baseline to Switch was − 103 μm (an increase in CMT after the switch), versus 105.27 μm in our IVR group ($p \leq 0.000$). Lastly, another important difference between the two studies is the previous number of IVB injections, where they present a range of 3–33 injections, and our results have a range of 1–18 injections. Their results probably represent a group of patients treated for a longer time with IVB and that could explain the difference as well in the results at the switch.

Most combinations of switching from one anti-VEGF drug to another in nAMD have previously been reported. In another study by Waizel et al. [17], the investigators analyzed the response in 19 eyes treated previously with IVA and switched to IVB. CMT decreased from 367 μm (SD: 198 μm) to 345 μm (SD: 184 μm) after the switch from IVA to IVB ($p = 0.0065$, Wilcoxon pairwise comparison). Pinheiro-Costa et al. [18] investigated 110 eyes switched from IVR to IVB. CMT changed from 359.6 μm at Baseline, to 286.8 μm at PreSwitch (i.e., after treatment with IVR), and changed to 305.9 μm PostSwitch of IVB, which was not statistically significant ($p = 0.103$), but showed an increase in CMT with IVB. Moisseiev et al. [19] studied the response in 114 eyes switch from IVB to IVR. CMT changed from 292 μm (SD: 85 μm) at PreSwitch, to 255 μm (SD: 65 μm) after PostSwitch of 3 IVR injections, which was significant ($p = 0.003$). Yonekawa et al. [20] studied the effect of switching from IVB or IVR to IVA. They found an overall change from PreSwitch at 305.07 μm (SD: 80.65 μm) to PostSwitch at 274.05 μm (SD: 68.98 μm).

From the information gathered by this and other reports it is understood that little is really known on which patients require a switch of drugs, what is the best time to switch and what is the best drug to switch to. It has been reported that the median time to develop tachyphylaxis to anti-VEGF drugs was 100 weeks, and the median number of IVB treatments (in a specific report by Forooghian et al.) prior to developing tachyphylaxis was eight [21], while Schaal et al. [22] reported that approximately three injections were required before the efficacy decreased to 50% of the initial OCT response. Moreover, the data from large clinical trials, such as that reported by the CATT Research Group may suggest that keeping a patient treated with the same anti-VEGF while presenting criteria for a switch will still show a decrease in CMT over time [23]. The present study has several limitations, the main one being a retrospective study with its natural drawbacks. However, we aimed to study our patients in a real-life scenario that would include patients with worse presentations of nAMD. The total studied population was 85 eyes (49 eyes in Group 1: IVA and 36 eyes in Group B: IVR), which allowed both groups to present a normal distribution, and therefore, to be analyzed with a parametric test, such as the paired samples *t* test. Both groups had similar demographics, with a balance number of patients, a mean and range of ages and previous number of injections. One of the main strengths from this report is the comparison of two available alternatives to IVB. And while no drug demonstrated a "better" effect than the other, the results are important because it shows the clinician what could be expected from only one dose of switching to IVA/IVR.

In conclusion, the effect achieved from a *single dose* of anti-VEGF treatment switch, in patients with nAMD previously treated with IVB, switched to either IVA or IVR reduced significantly CMT measurements. Comparing IVA and IVR, the effect appears to be similar in both drugs, in terms of reduction of CMT.

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