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ORIGINAL PAPER

Ranibizumab versus aflibercept for the treatment of vascularized pigment epithelium detachment due to age-related macular degeneration

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Abstract

Purpose To compare the efficacy and safety of two intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents, ranibizumab and aflibercept, for the treatment of vascularized pigment epithelium detachment (vPED) due to age-related macular degeneration (AMD) in a follow-up time of 12 months.

Methods Participants in this study were 71 patients (71 eyes) with vPED due to AMD, who were treated with intravitreal 0.5 mg ranibizumab ($n = 38$) or 2.0 mg aflibercept ($n = 33$) and had at least 12-month follow-up. All patients underwent best-corrected visual acuity (BCVA) measurement and optical coherence tomography at baseline and at every visit. The PED height, the presence of subretinal fluid (SRF), intraretinal fluid and diffuse macular edema (DME) were recorded at each visit.

Results There was a statistically significant difference in BCVA between the two groups at month 12 in favor of aflibercept. However, both agents were found to improve or stabilize BCVA in the majority of patients at the end of the follow-up. The change in PED height did not differ significantly between the two groups at the end of the follow-up with similar number of injections. At month 12, there was a significant improvement in SRF presence in both groups compared to baseline.

Conclusions Although aflibercept was found to be superior to ranibizumab regarding BCVA improvement, both agents showed anatomical effectiveness with significant reduction in PED height and SRF absorption in patients with vPED due to AMD.

Keywords Aflibercept · Age-related macular degeneration · Pigment epithelium detachment · Ranibizumab · Treatment

Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness in adults older than 65 years in the developed world [1, 2]. Visual impairment is caused by geographic atrophy in dry AMD and by the development of choroidal neovascularization (CNV) in wet AMD [3, 4]. Pigment epithelium detachment (PED) is a well-known complication of AMD, occurring when the retinal pigment epithelium (RPE) detaches from the underlying Bruch membrane, and it is commonly associated with CNV

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[5, 6]. The term "vascularized PED" (vPED) has been used by Yannuzzi et al. to describe a subset of occult CNV, which represents a form of wet AMD and behaves in a unique manner. Specifically, it is a sub-pigment epithelial neovascularization associated with a serous detachment of the RPE, which is confirmed by indocyanine green angiography (ICGA) [7]. Vascularized PEDs can progress to form disciform scars, resulting in poor visual outcomes, but they may be also complicated by RPE rips and tears [8, 9].

Vascular endothelial growth factor (VEGF) is implicated in the pathogenesis of neovascular AMD, and anti-VEGF agents are considered the standard care for neovascular AMD. The MARINA, ANCHOR and VIEW studies have shown high efficacy of anti-VEGF agents in the treatment of CNV due to AMD [10–12]. However, analysis of the results based on the lesion subtypes (i.e., PED) was not performed. Previous studies have shown suboptimal outcome for the treatment of vPED. In fact, although anti-VEGF agents may reduce intraretinal or subretinal fluid, the vPED typically remains stable without resolution, leading usually to visual impairment [13–21].

In light of the above, the purpose of this study was to compare the efficacy and safety of two anti-VEGF agents, ranibizumab (Lucentis®, Novartis, Basel, Switzerland) and aflibercept (Eylea®, Bayer Healthcare, Germany), for the treatment of vPED due to AMD in a follow-up time of 12 months.

Materials and methods

This is a retrospective study, in which consecutive patients with vPED were enrolled from January 2013 to January 2015 in our department. The study was in accordance with the tenets of the Declaration of Helsinki and was approved by the institutional review board of our department. Written informed consent was obtained from all participants.

Participants in the study were 71 patients (71 eyes) with vPED in the context of AMD, who were treated with intravitreal 0.5 mg ranibizumab ($n = 38$) or 2.0 mg aflibercept ($n = 33$). Inclusion criteria consisted of age more than 55 years with documented vPED and minimum 12-month follow-up period. Switch of treatment was not permitted during the follow-up period. Patients with CNV from other causes than AMD, serous PED, retinal angiomatous proliferation (RAP), polypoidal choroidal vasculopathy (PCV), RPE tear, fibrosis more than 50% of the total lesion and prior vitrectomy were excluded from the study. Patients, who had been previously treated with anti-VEGF injections, should continue the same anti-VEGF agent and be at least 4 months free of injections, so as to be included in the study. Therefore, patients treated with aflibercept were not previously in ranibizumab and vice versa.

All patients underwent best-corrected visual acuity (BCVA) measurement by means of Snellen charts at each monthly visit. The visual acuity measurements were converted to logarithm of the minimum angle of resolution (logMAR) units for statistical reasons. Spectral domain-optical coherence tomography (SD-OCT), fluorescein angiography (FA) and ICGA were performed at baseline using Spectralis (Heidelberg Engineering, Heidelberg, Germany), while SD-OCT was done monthly thereafter. Central foveal thickness was not used, as it is considered to be unreliable in cases of PED, whereas PED height was measured. PED height was determined manually in SD-OCT scans and was defined as the maximum vertical distance between Bruch membrane and RPE border. In addition, the presence of subretinal fluid (SRF), intraretinal fluid (IRF) and diffuse macular edema (DME) were recorded at each visit. Specifically, SRF was diagnosed in areas, where a non-reflective space was present between the posterior boundary of the neurosensory retina and the RPE, while IRF was defined as diffuse non-reflective space within the neurosensory retina and DME as retinal thickening more than 320 μm without cystoid spaces. Apart from baseline, FA and ICGA were also performed, at the discretion of the physician, in cases refractory to treatment, so as to exclude other causes of PED and especially PCV.

Patients in both groups have received three monthly intravitreal injections (loading dose) and then pro re nata (PRN) regimen, according to specific criteria. Retreatment was performed if: (1) there was reduction in BCVA $\geq$ one Snellen line, (2) there was increase in PED height $\geq$ 50 μm or (3) there was persistence or recurrence of SRF, IRF or DME on SD-OCT. All injections were performed under local anesthesia (0.5% proparacaine) and under standard sterile conditions. Topical antibiotics were administered to all patients four times a day for five days after the injection. All patients were examined monthly.

Statistical analysis was performed using SPSS 22.0 statistical software (SPSS Inc, Chicago, IL. USA). For the description of patients' characteristics at baseline, mean ± standard deviation (SD) was used for continuous variables and counts with percentages for categorical variables. All variables were tested for normal distribution with the Kolmogorov–Smirnov test. For comparison of nominal variables between the two groups, the Student's t test for independent samples or Mann–Whitney–Wilcoxon test was used, as appropriate. Accordingly, for categorical variables, Chi-square test or Fisher's exact test was performed. For the longitudinal comparisons regarding BCVA and PED height between baseline and each time point, the Wilcoxon matched-pairs signed-ranks test was used; given that three comparisons were done, the level of statistical significance was set at $0.05/3 = 0.017$, according to the Bonferroni correction. The McNemar test was also used for the comparison of categorical binary variables (SRF, IRF, DME) at each time point versus baseline. A p value of < 0.05 was considered as significant, apart from cases where the Bonferroni correction was adopted, as declared above.

Results

Table 1 shows the demographic and clinical characteristics of our study sample at baseline. The mean age of patients was 72.2 ± 7.2 years in the ranibizumab group and 71.2 ± 6.5 years in the aflibercept group ($p = 0.560$). 47.4 and 51.5% of patients were males in the ranibizumab and aflibercept group, respectively ($p = 0.814$). The BCVA was 0.50 ± 0.21 and 0.54 ± 0.24 logMAR in the ranibizumab and aflibercept group, respectively, at baseline and did not differ between the two groups ($p = 0.658$). There was no statistically significant difference regarding the height of PED at baseline (366.1 ± 74.0 versus 382.5 ± 85.8 μm in ranibizumab and aflibercept group, respectively, $p = 0.196$). All patients in the ranibizumab group and 97% of patients in the aflibercept group had SRF at baseline ($p = 0.465$). 2.6 and 12.1% of patients in ranibizumab and aflibercept group, respectively, had IRF ($p = 0.176$), while DME was present in 18.4 and 15.2% of patients in ranibizumab and aflibercept group, respectively ($p = 0.761$). 5 out of 38 patients (13.2%) in the ranibizumab group and 7 out of 33 patients (21.2%) in the aflibercept group had received anti-VEGF injections previously ($p = 0.527$).

Figure 1 illustrates the change in BCVA over time in the two groups. In ranibizumab group, there was no statistically significant difference in BCVA at all time points compared to baseline ($p = 0.121$, $p = 0.194$ and $p = 0.290$ for months 3, 6 and 12, respectively). In aflibercept group, BCVA differs significantly at all time points in comparison with baseline ($p = 0.005$, $p = 0.001$ and $p < 0.001$ for months 3, 6 and 12, respectively). BCVA did not differ between the two groups at month 3 (0.46 ± 0.17 vs. 0.44 ± 0.17 logMAR for ranibizumab and aflibercept, respectively, $p = 0.492$) and month 6 (0.46 ± 0.15 vs. 0.43 ± 0.18 logMAR for ranibizumab and aflibercept, respectively, $p = 0.356$), while there was a statistically significant difference at month 12 (0.47 ± 0.20 vs. 0.37 ± 0.20 logMAR for ranibizumab and aflibercept, respectively, $p = 0.005$). At month 12, 14 out of 38 patients (36.8%) in ranibizumab group and 24 out of 33 patients (72.7%) in aflibercept group presented improvement in BCVA of ≥ 1 Snellen line, while 34.2 and 18.2% in ranibizumab and aflibercept group, respectively, had stabilization in BCVA at the 12-month follow-up.

Accordingly, Fig. 2 depicts the change in PED height in the two groups over time. There was a statistically significant difference in PED height at all time points compared to baseline for both groups ($p < 0.001$ for all comparisons at months 3, 6 and 12). PED height did not differ between ranibizumab and aflibercept group at month 3 ($p = 0.529$) and month 6 ($p = 0.514$), while at month 12 there was a statistically significant difference between the two groups regarding PED height ($p = 0.020$). The number of injections did not differ significantly between the two groups at month 12 (6.1 ± 0.9 vs. 5.3 ± 0.8 in ranibizumab and aflibercept groups, respectively, $p = 0.058$).

The progression of SRF, IRF and DME is shown in Table 2. Regarding the presence of SRF, 26.3% of patients in ranibizumab group and 9.1% of patients in aflibercept group had SRF at month 3 ($p = 0.073$ between the two groups) and the difference was statistically significant compared to baseline for both groups ($p < 0.001$). At month 6, 18.4% of patients in ranibizumab group and 9.1% of patients in aflibercept group had SRF ($p = 0.320$ between the two groups), and the difference was statistically significant

Table 1 Baseline characteristics of our study sample

	Ranibizumab group ($n = 38$)	Aflibercept group ($n = 33$)	p value
	Mean ± SD		
Age (years)	72.2 ± 7.2	71.2 ± 6.5	0.560
Visual acuity (logMAR)	0.50 ± 0.21	0.54 ± 0.24	0.658
PED height (μm)	366.1 ± 74.0	382.5 ± 85.8	0.196
	N (%)		
Gender			
Male	18 (47.4)	17 (51.5)	0.814
Female	20 (52.6)	16 (48.5)	
Subretinal fluid			
Yes	38 (100)	32 (97)	0.465
No	0 (0)	1 (3)	
Intraretinal fluid			
Yes	1 (2.6)	4 (12.1)	0.176
No	37 (97.4)	29 (87.9)	
Diffuse macular edema			
Yes	7 (18.4)	5 (15.2)	0.761
No	31 (81.6)	28 (84.8)	
Previous anti-VEGF injections			
Yes	5 (13.2)	7 (21.2)	0.527
No	33 (86.8)	26 (78.8)	

PED pigment epithelium detachment, *VEGF* vascular endothelial growth factor

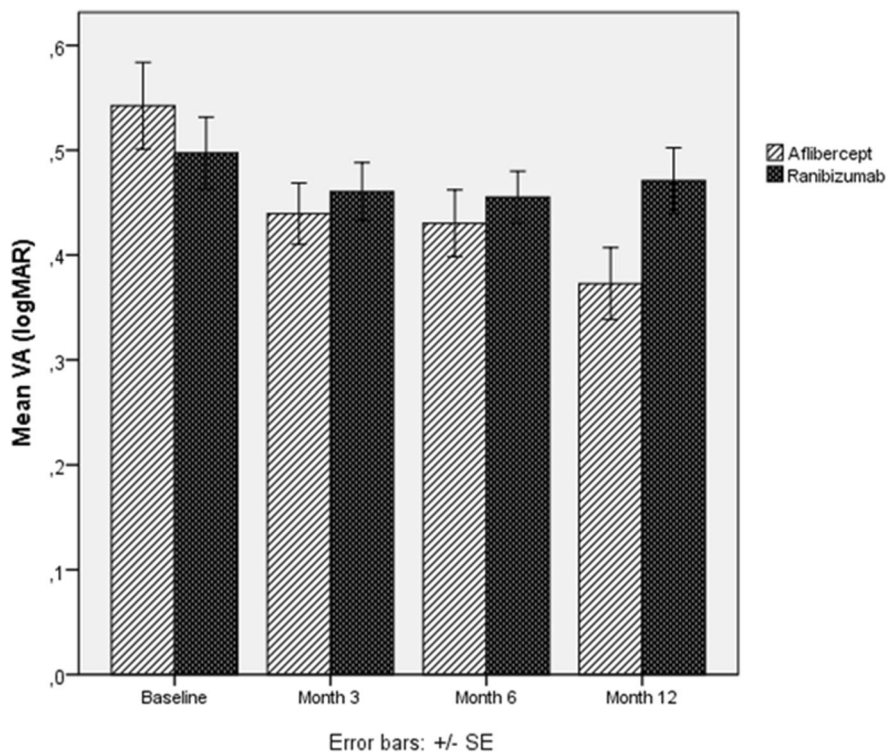


Fig. 1 Evaluation of best-corrected visual acuity over time in patients receiving ranibizumab and aflibercept

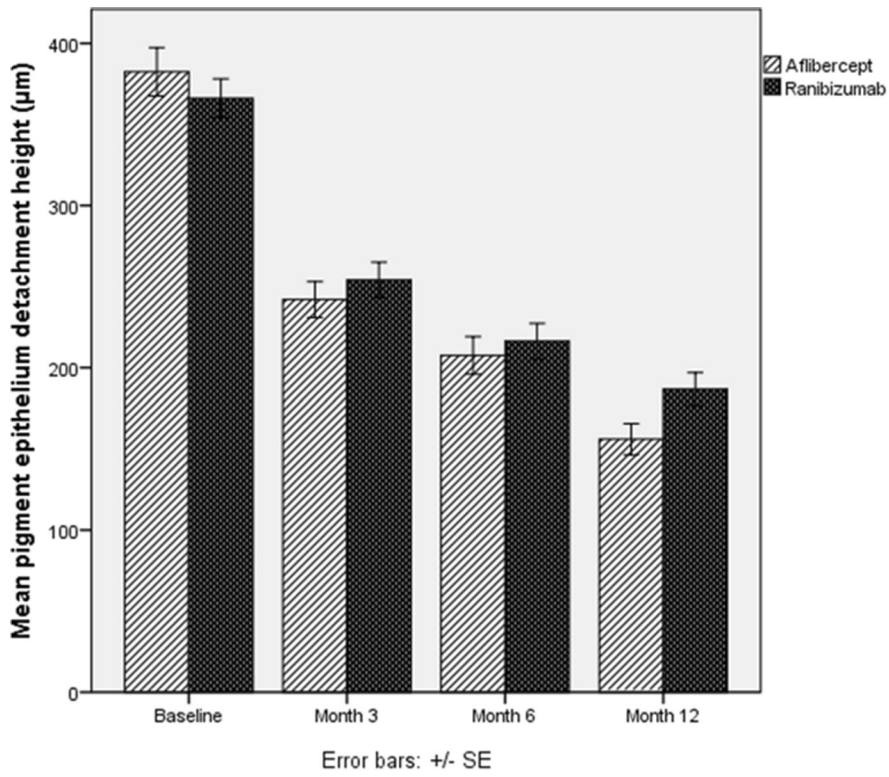


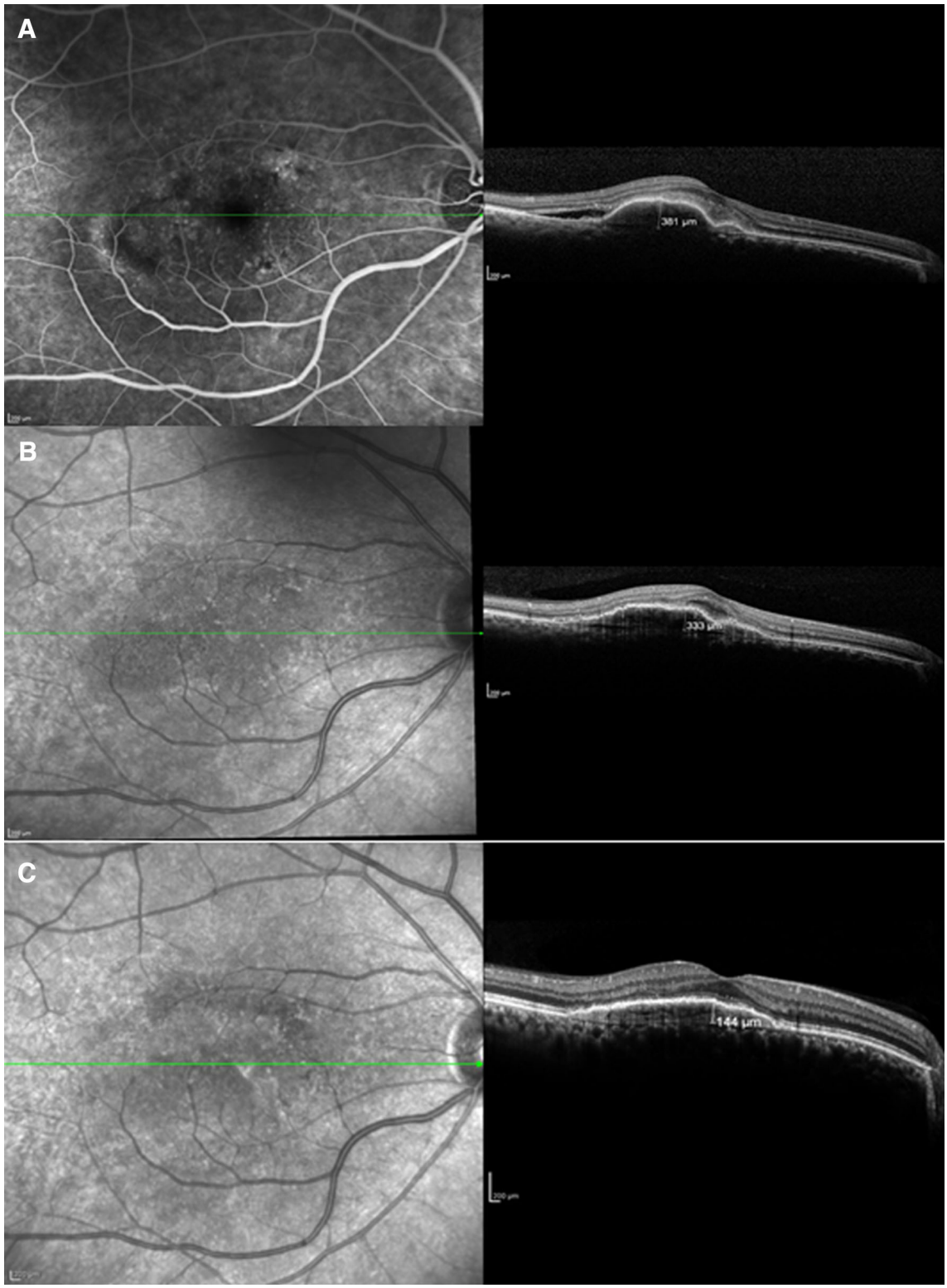
Fig. 2 Evaluation of pigment epithelium detachment height over time in patients receiving ranibizumab and aflibercept

Table 2 Progression of subretinal fluid, intraretinal fluid and diffuse macular edema over time in ranibizumab and aflibercept group

	Subretinal fluid, *n* (%)		Intraretinal fluid, *n* (%)		Diffuse macular edema, *n* (%)	
	Ranibizumab	Aflibercept	Ranibizumab	Aflibercept	Ranibizumab	Aflibercept
Baseline	38 (100)	32 (97)	1 (2.6)	4 (12.1)	7 (18.4)	5 (15.2)
Month 3	10 (26.3)	3 (9.1)	0 (0)	0 (0)	0 (0)	2 (6.1)
Month 6	7 (18.4)	3 (9.1)	0 (0)	0 (0)	0 (0)	1 (3%)
Month 12	7 (18.4)	4 (12.1)	0 (0)	0 (0)	0 (0)	1 (3%)

Bold cells denote a statistically significant difference at any time point compared to baseline

compared to baseline for both groups ($p < 0.001$). At month 12, one patient in aflibercept group had recurrence of SRF, but still there was a statistically significant difference compared to baseline for both groups ($p < 0.001$). None of patients in both groups presented IRF at months 3, 6 and 12, although the difference in IRF presence was not statistically significant compared to baseline for both groups ($p > 0.999$ and $p = 0.125$ for ranibizumab and aflibercept group, respectively, in all comparisons). As far as DME is concerned, none of patients in ranibizumab group presented DME at months 3, 6 and 12 and the difference was statistically significant compared to baseline ($p = 0.016$ in all comparisons). In aflibercept group, 6.1% of patients had DME at month 3, while at months 6 and 12 only one patient (3%) presented DME. However, the difference in DME presence was not statistically significant compared to baseline ($p = 0.375$, $p = 0.125$ and $p = 0.219$ for months 3, 6 and 12, respectively). Between the two groups, the presence of DME did not differ at any time point ($p = 0.212$, $p = 0.465$ and $p = 0.465$ for months 3, 6 and 12, respectively). Figures 3 and 4 show one case in each group and their progression over time.


A
381 µm
B
333 µm
C
144 µm

◀**Fig. 3** **a** Fluorescein angiography and optical coherence tomography in a 72-year-old male patient with vascularized pigment epithelium detachment at baseline; **b** infrared fundus photography and optical coherence tomography of the same patient at month 3 after three consecutive aflibercept injections; **c** Infrared fundus photography and optical coherence tomography of the same patient 12 months after baseline and 4 aflibercept injections, showing improvement in pigment epithelium detachment height and absorption of subretinal fluid

Concerning the adverse events, one patient in each group presented RPE tear during the 12-month follow-up. Specifically, one patient in ranibizumab group having high PED (480 μm) and one patient in aflibercept group with high PED (468 μm) and SRF presence developed RPE tear at months 6 and 9, respectively. No systemic adverse events attributable to ranibizumab or aflibercept use were reported.

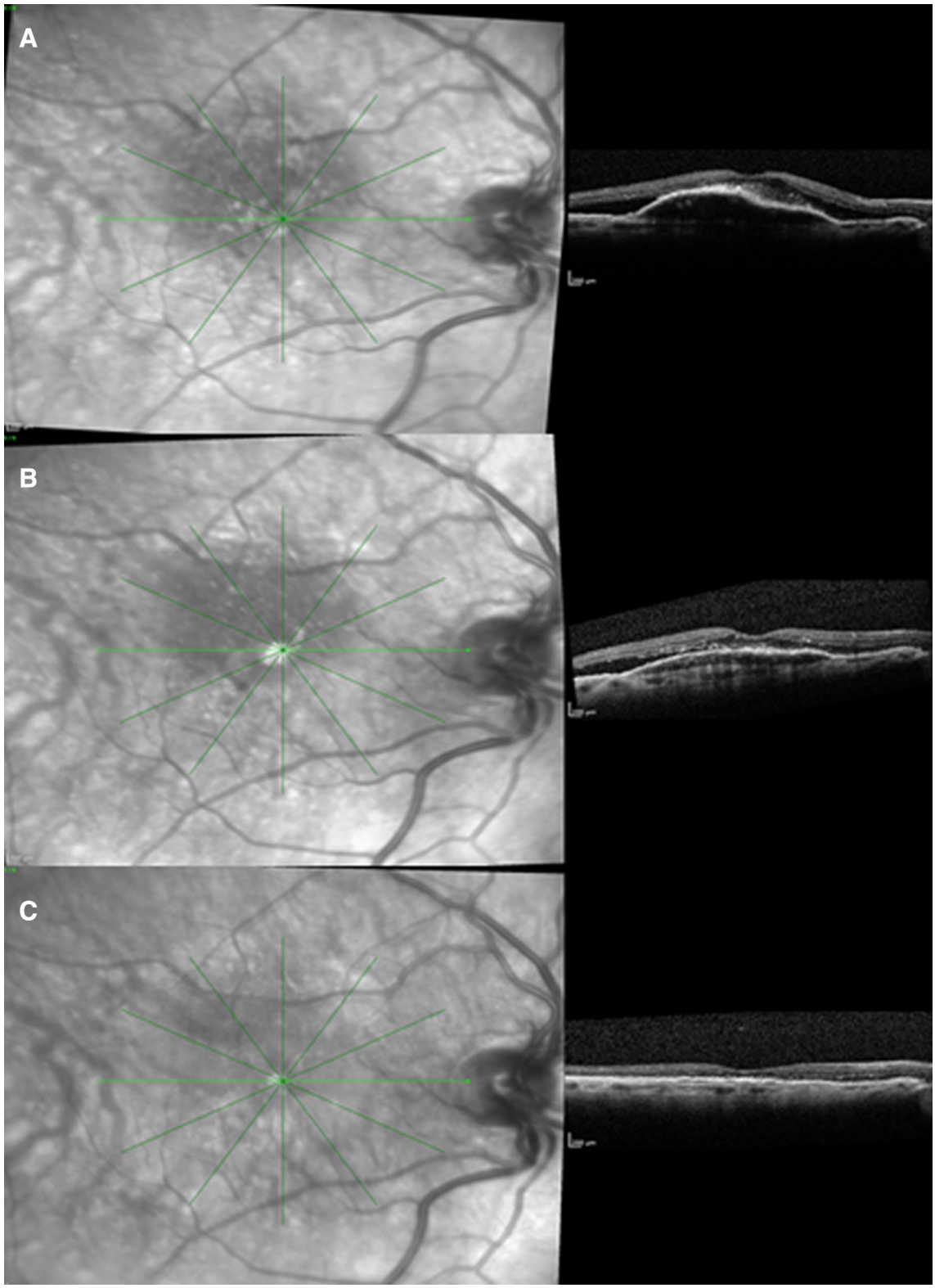
Discussion

The principal message of the study was that aflibercept presented a statistically significant improvement in BCVA from 0.54 ± 0.24 to 0.37 ± 0.20 logMAR at the one-year follow-up in patients with vPED secondary to AMD, with about 73% of patients gaining ≥ 1 Snellen line. Ranibizumab also showed an improvement in BCVA from 0.50 ± 0.21 to 0.47 ± 0.20 logMAR, which failed to reach statistical significance at the end of the follow-up, with about 37% of patients showing gain of ≥ 1 Snellen line. However, anatomically both groups exhibited statistically significant reduction in PED height and in SRF presence at the end of the 12-month follow-up. Of note, only one patient in each group had RPE tear during the follow-up period.

According to the current understanding, PED is caused by age-related changes at the level of the Bruch membrane. In elderly patients, Bruch membrane thickens due to the accumulation of lipids and abnormal materials. This accumulation results in reduced hydraulic conductivity of the Bruch membrane-choroid complex, leading to a decreased capacity for fluid exchange between the choroidal and RPE compartments [22]. Although VEGF is relevant for the development of the underlying CNV and its hyperpermeability, its contribution to the progression of PED remains controversial. Rapid flattening of the PED with high-dose anti-VEGF therapy could be attributed to the greater concentration of anti-VEGF that generates the RPE barrier, resulting in CNV regression and fluid absorption [19].

Several authors have investigated the impact of anti-VEGF treatment on PED with variable results. There are reports showing complete PED flattening even with a variability in functional outcomes, while other studies have found little morphologic response or progression of the lesion with poor visual outcomes [15–21]. Ach et al. [17], who retrospectively examined 28 eyes with vPED treated with intravitreal bevacizumab, found stabilization of visual acuity and nonsignificant reduction in PED height in 54%, although the PED response to treatment did not correlate with the visual acuity outcomes. Accordingly, Clemens et al. [20] observed a change in the mean PED height of -242.1 μm after monthly ranibizumab for 12 months, which was accompanied by BCVA improvement, being significant in a borderline trend. On the other hand, Chen et al. [16] reported stable or increased visual acuity in PED patients treated with intravitreal bevacizumab in a mean follow-up period of 30 weeks, despite the persistence of PED. This was in line with Ritter et al. [23], who found a significant reduction of PED height at the 6-month follow-up after ranibizumab treatment, which was not maintained at the 12-month follow-up. The discrepancy between the anatomical and functional outcome in vPED could be explained by the loss of function in the photoreceptors due to the presence of long-term RPE detachment [19, 24]. However, the exact mechanism of the inconsistent response of vPED to anti-VEGF treatment remains elusive.

Another interesting finding of our study was the superiority of aflibercept in the visual acuity improvement compared to ranibizumab, although the two agents were found to be similar in anatomical terms. Ranibizumab is a recombinant antigen-binding fragment that neutralizes all isoforms of VEGF-A, while aflibercept is a recombinant fusion protein consisting of key human VEGF receptor extracellular domains from receptors 1 and 2 (VEGFR1 and VEGFR2) fused to the Fc domain of the human IgG backbone. It has a much higher binding affinity for VEGF compared to ranibizumab, and apart from binding to all isomers of the VEGF-A family, it also binds VEGF-B and


A
B
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◀**Fig. 4** **a** Infrared fundus photography and optical coherence tomography in a 70-year-old female patient with vascularized pigment epithelium detachment at baseline; **b** infrared fundus photography and optical coherence tomography of the same patient at month 3 after three consecutive ranibizumab injections; **c** infrared fundus photography and optical coherence tomography of the same patient 12 months after baseline and 5 ranibizumab injections, showing improvement in pigment epithelium detachment height and total absorption of subretinal fluid

placental growth factor [10, 12, 25]. The higher potency of aflibercept could be a reasonable explanation for better visual outcomes compared to ranibizumab. However, since the duration of PED and the ultrastructural changes to photoreceptors were not known, this finding should be interpreted with caution.

Regarding the ocular adverse events, in our study, only one patient in each group developed RPE tear during the 12-month follow-up. It is known that RPE tears may complicate treatment of PEDs with intravitreal anti-VEGF therapy. Larger vascularized PEDs that have a higher intraluminal pressure are at a significantly greater risk of producing RPE tears after anti-VEGF therapy, with acute vision loss [9]. In addition, according to Chan et al. [26] the PED height was found to be the most significant predictor for RPE tears after intravitreal anti-VEGF injections, reporting that a PED height more than 400 μm has been associated with a significant risk for RPE tear. In our study, the low incidence of RPE tear may be attributed to the chronicity of PED, as tears have been shown to be more likely to occur in PEDs during the initial stages of anti-VEGF treatment [27].

Potential limitation of the study pertains to its retrospective nature. In addition, the duration of PED before initiating treatment was not recorded. However, this study compares ranibizumab and aflibercept for the treatment of vPED in terms of anatomical and functional outcomes in a relatively long follow-up of 12-month. Further investigations are needed to establish the optimal therapeutic approach and dose regimen for vPED due to AMD.

In conclusion, aflibercept was found to be effective for the treatment of vPED, showing significant improvement of BCVA at the 12-month follow-up, while ranibizumab did not provide significant improvement in BCVA. Both agents showed a significant reduction in PED height and in SRF, with a mean number of about 6 injections. There were no systemic adverse events, and only one patient in each group developed RPE tear during the follow-up period. Our results suggest that although aflibercept was superior to ranibizumab regarding functional improvement, both anti-VEGF agents showed anatomical improvement and were safe for the treatment of vPED.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest and no financial disclosure.

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