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ORIGINAL PAPER

Indocyanine green angiography findings in patients with neovascular age-related macular degeneration refractory to ranibizumab switched to aflibercept

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Abstract
Purpose To describe indocyanine green angiography (ICGA) and visual acuity (VA) results in patients with neovascular age-related macular degeneration (nAMD) refractory to ranibizumab switched to aflibercept.
Methods This study is a prospective interventional case series. Thirty-two eyes of 32 patients with nAMD showing a poor response after at least 24 months of ranibizumab were switched to aflibercept. Twenty eyes had type I choroidal neovascularization (CNV group), and 12 eyes had polypoidal choroidal vasculopathy (PCV group). After an initial loading dose of three monthly aflibercept injections, treatment was continued on a treat-and-extend basis. ICGA was performed just before the first aflibercept injection (baseline) and 12 and 24 months later. The variables recorded were: closure of polyps and lesion area, VA, number of aflibercept injections, dry macula, and pigment epithelium detachment.
Results The following means were recorded in the CNV and PCV groups, respectively: number of ranibizumab injections 20.4 ± 11.2 and 22.4 ± 12.9 ($p = 0.740$); baseline VA (before aflibercept) 73.2 ± 9.1 and 70.3 ± 13.7 letters ($p = 0.654$); and final VA 73.0 ± 7.6 and 69.3 ± 15.6 letters ($p = 0.509$). VA remained stable ($p = 0.761$ and 0.964) after 15.5 ± 3 and 15.1 ± 3.5 aflibercept injections ($p = 0.244$). At 24 months, dry macula was noted in 40 to 50% of the eyes ($p = 0.620$). Complete resolution of polyps was observed in 58% at 12 months and 92% at 24 months.
Conclusions In patients with nAMD refractory to ranibizumab, aflibercept was effective at maintaining VA and closing numerous polyps. In half of the patients, dry macula was observed at 24 months.

Keywords Indocyanine green angiography · Polypoidal choroidal vasculopathy · Age-related macular degeneration · Ranibizumab · Poor responders · Aflibercept

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Introduction

Neovascular age-related macular degeneration (nAMD) is a major cause of vision loss in developed countries. Intravitreal anti-vascular endothelial

growth factor (anti-VEGF) drugs slow down the progression of the choroidal neovascularization (CNV) that occurs in nAMD and are able to recover some of the visual acuity (VA) loss produced in many patients [1–3]. However, the initial enthusiasm about anti-VEGF therapy has been marred by much worse outcomes in the real-world setting [4].

Some lesions diagnosed as nAMD frequently show a lack of anatomic response to intense treatment with intravitreal ranibizumab injections (Lucentis; Novartis, Basel, Switzerland). In effect, lesions such as those observed in polypoidal choroidal vasculopathy (PCV) and type I CNV are often only detected following a lack of response to anti-VEGF therapy [5–9].

PCV is a subtype of nAMD in which aneurysmal polypoidal choroidal vascular lesions are present in the choroidal vasculature. PCV is more prevalent in Asians than in Caucasians, and this could explain its underdiagnosis in Western countries [2, 3, 5].

Many nAMD studies have shown beneficial effects of switching to aflibercept when there is resistance to another drug [10–13]. However, data regarding the efficacy of different anti-VEGF agents at treating PCV are scarce, and most studies have been conducted in Asian treatment-naïve patients [14–19]. PCV is characterized by resistance to monotherapy such as ranibizumab or bevacizumab intravitreal injections [20]. Alternatives to this therapy have included switching to aflibercept (Bayer HealthCare, Berlin, Germany) or therapy combined with photodynamic therapy (PDT) [21, 22]. In Asian patients with PCV, ranibizumab was the first anti-VEGF agent found to be more effective at inducing polyp regression when combined with PDT compared to PDT or anti-VEGF monotherapy alone [19].

To diagnose PCV, some optical coherence tomography (OCT) findings are actually quite reliable, showing highly protruded retinal pigment epithelium (RPE) with underlying moderate reflectivity, double sign layer, and notched pigment epithelial detachment (PED) [23, 24]. However, PCV is frequently underdiagnosed in an OCT and fluorescein angiography (FA) examination. Nowadays, this situation is improving because of the increased use of indocyanine green angiography (ICGA), the gold standard for PCV diagnosis, especially in poor responders [2, 25, 26].

Several recent studies have assessed the efficacy of anti-VEGF agents used to treat PCV in Caucasian individuals including those refractory to prior anti-VEGF monotherapy [20, 26, 27]. However, there is still a need for many more data on this issue. So the present study was designed to describe ICGA and VA results over 24 months of follow-up in patients with nAMD refractory to ranibizumab switched to aflibercept.

Methods

This was a prospective interventional case series analysis of 32 eyes of 32 patients. Inclusion criteria was patients with a diagnosis of nAMD showing a poor anatomic response to at least 24 months of ranibizumab treatment. A poor response was defined as the presence of intraretinal or subretinal fluid determined by optical coherence tomography (OCT).

Exclusion criteria were the presence of CNV secondary to a disease other than nAMD, a concomitant disease in the study eye that could compromise the patient's vision or fixation, previous PDT, and previous thromboembolic episodes. Participants were withdrawn if they did not complete a minimum follow-up of 24 months.

The study period was from October 1, 2015, to June 15, 2018. The study protocol adhered to the tenets of the Declaration of Helsinki and received Review Board approval from the Hospital Universitario Clínico San Carlos (Madrid, Spain). Written informed consent to participate in the study was obtained from each participant.

The subjects enrolled were first subjected to a complete ophthalmologic examination including best-corrected visual acuity (BCVA) using ETDRS (Early Treatment Diabetic Retinopathy Study) letter charts, anterior segment slit-lamp examination, intraocular pressure (IOP), a detailed dilated fundus examination with special attention paid to the macula area and retinal periphery, retinography, and OCT (Spectralis, Heidelberg Engineering Inc., Heidelberg, Germany). All tests were performed by a retina specialist (CCG).

Participants were first treated with a loading dose of aflibercept consisting of three monthly injections followed by a treat-and-extend regimen over 24 months. In this type of regimen, the interval between injections is extended gradually after the loading dose according to the patient's response to therapy. The efficacy of a treat-and-extend regimen in controlling disease activity and improving VA has

been reported in patients with AMD [16, 26–29]. This regimen has the benefits of fewer clinical visits and injections over others such as fixed dosing and pro re nata (PRN) regimens.

Retreatment consisted of a single aflibercept injection given when one or more of the following signs were detected in a follow-up visit: anatomic activity, defined as intraretinal edema or subretinal fluid or increased pigment epithelium detachment in an OCT, presence of polyps on ICGA, and BCVA loss of at least five letters.

Follow-up examinations were performed at baseline (before the first aflibercept injection) and at 12 and 24 months after aflibercept treatment onset. These examinations consisted of the same tests as in the initial examination along with FA and ICGA, which were also performed by the same ophthalmologist (CCG). The variables assessed by OCT were central retinal thickness, pigment epithelium detachment (PED), and dry macula defined as the absence of intraretinal or subretinal fluid. The ICGA criteria assessed were the presence of polyps and their closure and a greater linear dimension area of the CNV type I or PCV lesion. The number of aflibercept injections received was also recorded in each patient.

According to the lesions observed in the baseline ICGA, eyes were classified as having type I CNV or PCV (Fig. 1).

Statistical analysis

All statistical tests were performed using the SPSS package version 18.0 (SPSS Inc., Chicago, Illinois, USA). The Mann–Whitney U test or repeated measures MANOVA (multivariate analysis of variance) with Bonferroni correction was used to compare continuous variables expressed as their mean ± standard deviation (SD). Significance was set at $p < 0.05$.

Results

The study sample comprised 32 eyes of 32 patients: 20 eyes with type I CNV and 12 eyes with PCV.

The two groups of eyes (type I CNV and PCV) were well matched for baseline variables such as age, gender or central retinal thickness (Table 1). The number of ranibizumab injections received (20.4 ± 11.2 and 22.4 ± 12.9; $p = 0.740$) was similar over 27.9 months of follow-up (range 24–34 months).

After intense intravitreal ranibizumab treatment and before the aflibercept loading dose (baseline), VA was 73.2 ± 9.1 and 70.3 ± 13.7 letters ($p = 0.654$) for type I CNV and PCV groups, respectively. Neither were VA differences between groups observed in the 3-, 12- or 24-month visits: 73.0 ± 7.6 and 69.3 ± 15.6 letters ($p = 0.509$) in type I CNV and PCV, respectively. Thus, in both groups, VA remained stable when compared between the final visit and

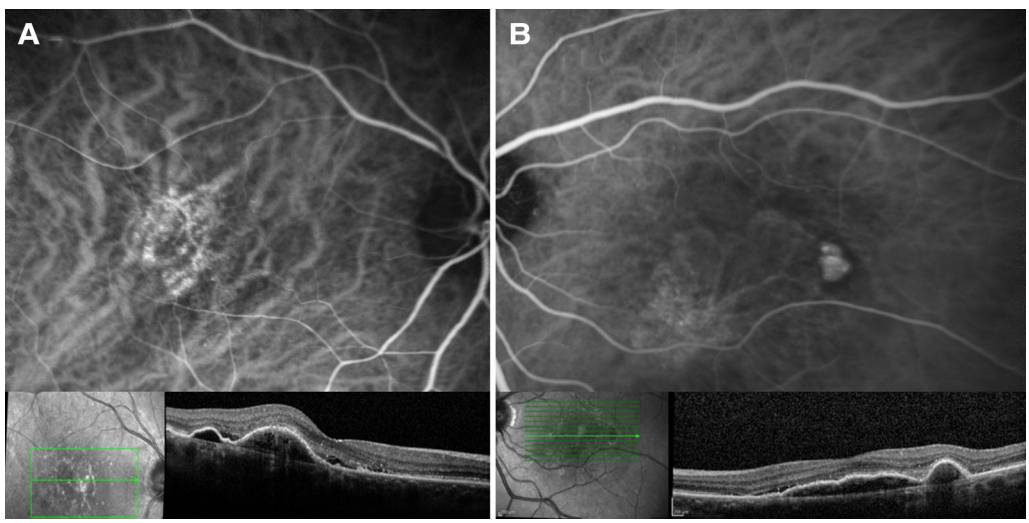

Fig. 1 Examples according to the lesions observed in the baseline ICGA, classified as having type I CNV (**a**) or PCV (**b**). Also the optical coherence tomography of each type is shown at the bottom

Table 1 Demographic and clinical variables recorded in patients with type I choroidal neovascularization (CNV group) and polypoidal choroidal vasculopathy (PCV group)

	Type I CNV $N = 20$	PCV $N = 12$	p Value between groups
Age (years)	77.8 ± 5.6	77.6 ± 5.1	$p = 0.876$
Sex (women)	60%	66.7%	$p = 0.647$
Prior ranibizumab injections (*n*)	20.4 ± 11.2	22.4 ± 12.9	$p = 0.740$
VA			
Baseline	73.2 ± 9.1	70.3 ± 13.7	$p = 0.654$
3 mo	73.0 ± 9.0	71.2 ± 13.6	$p = 0.861$
12 mo	72.9 ± 8.0	70.4 ± 12.9	$p = 0.612$
24 mo	73.0 ± 7.6	69.3 ± 15.6	$p = 0.509$
12 mo versus baseline	$p = 0.761$	$p = 0.964$	
24 mo versus baseline	$p = 0.231$	$p = 0.719$	
IVA no. injections			
12 mo	8.3 ± 1.6	8.1 ± 1.9	$p = 0.654$
24 mo	15.5 ± 3.0	15.1 ± 3.5	$p = 0.244$
Lesion area (mm^2)			
Baseline	10.5 ± 7.8	13.9 ± 8.2	$p = 0.284$
12 mo	10.6 ± 7.8	13.0 ± 6.6	$p = 0.259$
24 mo	9.7 ± 7.8	13.9 ± 8.1	$p = 0.087$
12 mo versus baseline	$p = 0.247$	$p = 0.248$	
24 mo versus baseline	$p = 0.222$	$p = 0.608$	
CRT (μm)			
Baseline	337.5 ± 47.4	320.7 ± 63.1	$p = 0.350$
3 mo	298.6 ± 82.1	269.2 ± 62.6	$p = 0.206$
12 mo	282.5 ± 86.4	280.4 ± 68.7	$p = 0.907$
24 mo	274.9 ± 51.3	266.5 ± 51.8	$p = 0.772$
12 mo versus baseline	$p = 0.004$	$p = 0.005$	
24 mo versus baseline	$p = 0.008$	$p = 0.011$	
Dry macula			
Baseline	0%	0%	$p = 1$
3 mo	45%	75%	$p = 0.098$
12 mo	60%	66.7%	$p = 0.710$
24 mo	40%	50%	$p = 0.620$
PED height			
Baseline	219 ± 120	189 ± 69	$p = 0.459$
3 mo	183 ± 119	137 ± 60	$p = 0.311$
12 mo	172 ± 124	146 ± 64	$p = 0.849$
24 mo	161 ± 85	135 ± 57	$p = 0.542$
12 mo versus baseline	$p = 0.006$	$p = 0.005$	
24 mo versus baseline	$p = 0.010$	$p = 0.007$	

IVA intravitreal aflibercept; *VA* visual acuity; *CRT* central retinal thickness; *PED* pigment epithelium detachment; *mo* month

baseline ($p = 0.761$ and 0.964, respectively) (Table 1).

The number of intravitreal aflibercept injections was 8.3 ± 1.6 and 8.1 ± 1.9, respectively, for type I CNV and PCV groups at 12 months and 15.5 ± 3 and 15.1 ± 3.5 at 24 months with no differences between groups ($p = 0.244$).

Our OCT observations indicated dry macula was achieved in 60 and 66.7% in the eyes with type I CNV and PCV, respectively, at 12 months and in 40 and 50%, respectively, at 24 months ($p = 0.620$). There were no differences between groups in central retinal thickness at 12 and 24 months. However, in both groups, this thickness was significantly reduced after aflibercept treatment compared with baseline (type I CNV, 337.5 ± 47.4 vs. 274.9 µm ± 51.3; $p = 0.008$ and PCV, 320.7 ± 63.1 vs. 266.5 ± 51.8 µm; $p = 0.110$). Also, while no differences were observed between groups at baseline in PED height ($p \geq 0.311$), this variable was effectively diminished after aflibercept treatment ($p \leq 0.01$) (Table 1).

In the ICGA examination, polyps were resolved in 58% of the whole study sample at 12 months and in 92% at 24 months. No polyp recurrences were produced. In both groups, lesion areas remained stable after aflibercept treatment ($p \geq 0.222$) (Table 1).

Discussion

Intravitreal anti-VEGF drugs have dramatically changed the visual prognosis for patients with nAMD [1–3]. However, patients not responding to conventional anti-VEGF therapy remain a challenge as a correct diagnosis and successful treatment could determine a better outcome [4].

For a good response to treatment, ICGA plays a key role in diagnosing and monitoring these non-responders [25, 26]. In our population, ICGA imaging was useful to classify patients into those with type I CNV and those with PCV. Both these forms of nAMD showed a poor response to 24 months or longer of intense intravitreal ranibizumab treatment. In patients with type I CNV and PCV, there is often a lack of anatomic response to ranibizumab monotherapy, as these forms are frequently detected according to ICGA findings indicating a failed response to anti-VEGF therapy. Ozkaya et al. [25] also highlighted the role of ICGA imaging in the differential diagnosis of patients with nAMD who are morphologically poor responders to ranibizumab in a real-life setting. In their study, 56% of patients had PCV and 26.5% had chronic central serous chorioretinopathy. As in our study, in the series of Caucasian patients with presumed nAMD examined by Hatz and Prünte, PCV prevalence was found by ICGA to be improved in eyes that responded poorly to ranibizumab monotherapy [26].

In our patients with type I CNV and PCV, respectively, VA was maintained after intense aflibercept monotherapy (8.3 ± 1.6 and 8.1 ± 1.9 injections at 12 months and 15.5 ± 3 and 15.1 ± 3.5 injections at 24 months) at 73.0 ± 7.6 and 69.3 ± 15.6 letters ($p = 0.761$ and 0.964 versus baseline, respectively, for group 1 and 2). In both groups, central retinal thickness fell significantly from 337.5 ± 47.4 to 274.9 µm ± 51.3 and from 320.7 ± 63.1 to 266.5 ± 51.8 µm, respectively.

In 90 eyes of 87 Asian patients with treatment-naïve PCV, Yamamoto et al. reported that intravitreal aflibercept administered over 1 year improved both VA (0.31 to 0.17 logMAR) and macular morphology. Mean central retinal thickness also fell from 315 µm at baseline to 204 µm at 12 months ($p < 0.001$) [15]. Wolff et al. followed 34 eyes with a mean baseline BCVA of 55 letters for 6 months and noted a significant improvement in BCVA of + 13 letters [14]. Other authors such as Hosokawa et al. [16] also observed in eyes with PCV that intravitreal aflibercept given as a treat-and-extend regimen was effective at improving BCVA (from 0.37 to 0.21 logMAR) and central retinal thickness (from 342 to 196 µm). In these studies, an improvement in VA was produced, possibly because they were treatment-naïve patients, rather than refractory, as our patients.

Hara et al. also showed in 29 eyes with treatment-naive PCV that aflibercept was effective in terms of resolving polypoidal lesions. Over 12 months, these authors administered a mean of 3.9 ± 1.9 injections (range 1–8) [14], while Yamamoto et al. administered 7.1 ± 0.3 aflibercept injections, both numbers being significantly lower than in the present study [16]. In 34 eyes followed for 6 months by Wolff et al. [20], the mean number of aflibercept injections was five, which is closer to our figure.

In the present series, dry macula was achieved in 40 and 50% of patients at 24 months. In the Yamamoto et al. [15] study, 71.1% of the eyes showed a dry macula at 12 months. Hara et al. [14] reported dry macula in 48% of eyes after the first aflibercept loading dose, with no additional injections needed. Wolff et al. [20] observed a dry macula on OCT images in all patients on a fixed-dose regimen (bimonthly) examined at 6 months.

In our ICGA images, complete resolution of polyps was observed in 58% of eyes at 12 months and in 92% at 24 months. No lesion area changes were produced after aflibercept treatment ($p \geq 0.222$) in both groups of eyes with type I CNV or PCV. At 12 months, Yamamoto et al. observed polypoidal lesion resolution in 55.4% of their participants and partial resolution in 32.5% [15]. These authors also observed that 13.4% of the lesions showed reduced branching choroidal vascular network dimensions. Hara et al. [14] found resolved polypoidal lesions at 3 months in 66% of eyes and further resolution at 1 year in 4 out of 10 eyes with persistent polypoidal lesions at 3 months. However, it should be underscored that in their study, 26% of polypoidal lesions that had resolved at 3 months recurred at 1 year. In the Wolff et al. [20] study, polyp disappearance was observed by ICGA in 62% of cases at 6 months.

Evidence regarding the effectiveness of aflibercept in patients refractory to other anti-VEGF agents is scarce and has mostly arisen from studies conducted in Asian populations. The EPIC study [18] included 11 patients with PCV (52%) previously treated with ranibizumab or bevacizumab, in whom aflibercept monotherapy markedly improved retinal pigment epithelium detachment and persistent polyps at 6 months of follow-up.

Thus, the efficacy and safety of aflibercept monotherapy in patients with PCV have been established in several studies that have revealed visual improvements and effective regression of polypoid lesions. These findings suggest that aflibercept may be more effective at achieving polypoidal lesion closure than other anti-VEGF therapies [2, 30, 31]. This could be because aflibercept offers another way of targeting neovascular lesions as it shows a higher binding affinity to VEGF A and B and a longer intravitreal half-life compared to other anti-VEGF agents. Aflibercept also has the capacity to antagonize growth factors other than VEGF, such as placental growth factor, which is believed to play a role in PCV [16].

Kawashima et al. compared the response to treatment conversion to aflibercept in patients with PCV ($n = 26$) and nAMD ($n = 15$) who were refractory to ranibizumab [9]. In this study, PCV patients gained about 1 line of vision ($p = 0.003$), while nAMD patients showed no significant improvement ($p = 0.699$) despite a decrease in central retinal thickness (202.1 ± 113.7 to 131.2 ± 55.7 μm; $p = 0.003$). In our study, VA remained stable in both patient groups, but there was no improvement. Unlike our study, in the study by Kawashima et al., the prevalence of dry macula after treatment was higher among PCV patients (80.8 vs. 46.7%; $p = 0.024$) [9]. The authors concluded that, although the underlying mechanism remains to be determined, when a refractory response to ranibizumab is produced, patients with PCV may benefit more from switching to aflibercept than those with nAMD. Our observations do not support this recommendation, as no differences in dry macula or the number of injections needed were observed between groups.

Several recent studies have focused on Caucasian patients with PCV. Agorogiannis et al. reported on the largest series to date of Caucasian patients (48 eyes of 45 patients) with PCV [27]. In their study, it was found that anti-VEGF monotherapy, PDT, or their combination preserved VA and improved subfoveal exudative changes. Interestingly, however, combination treatment was not superior to monotherapy. Wolff et al. [20] suggested that the use of aflibercept monotherapy in Caucasian subjects could avoid the risk of bleeding and atrophy linked to PDT. On the contrary, Hazt et al. [26] proposed that combination therapy may be beneficial for eyes with PCV.

Several studies have reported that in most patients with AMD, intravitreal aflibercept is effective at treating their eye pathology. However, non-responsiveness to aflibercept may occur in a small subset of patients with choroidal vascular hyperpermeability observed on ICGA, as described by Hara et al. [32].

The limitations of our study are its relatively small sample size and short follow-up. As argued by Medina et al. [31], given the lack of adequate studies assessing the use of aflibercept in Caucasian PCV patients, it is still unknown whether adding PDT to such treatment would reduce the number of injections needed or improve visual and anatomic outcomes. These issues need to be addressed in future investigations.

In conclusion, aflibercept proved effective in patients with nAMD refractory to ranibizumab, including those with PCV and type I CNV. The improvements produced were preserved VA, closure of a significant number of polyps, and dry macula observed by OCT at 24 months in half of the patients.

Compliance with ethical standards

Conflicts of interest There are no known conflicts of interest by the authors associated with this publication.

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