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Anti-VEGF treatment in clinical practice: a retrospective study with RETINA.PT

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Anti-VEGF treatment in clinical practice: a retrospective study with RETINA.PT

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LIST OF ABRREVIATIONS

AMD age-related macular degeneration

AV acuidade visual

BCVA best corrected visual acuity

CHUC Centro Hospital e Universitário de Coimbra

CMT central macular thickness

CNPD Portuguese National Committee for Data Protection

CNV choroidal neovascularization

DMI degenerescência macular da idade

ETDRS early treatment diabetic retinopathy study

FMUC Faculty of Medicine, University of Coimbra, Portugal

IVI intravitreal injections

LOCF last observation carried forward

MT macular thickness

nAMD neovascular age-related macular degeneration

OCT optical coherence tomography

PCV polypoidal choroidal vasculopathy

PED pigmented epithelium detachment

RAP retinal angiomatous proliferation

RPE retinal pigmented epithelium

VA visual acuity

VEGF vascular endothelial growth factor

ABSTRACT

Purpose: to analyse clinical evolution and outcomes of anti-VEGF treatment in neovascular age-related macular degeneration (nAMD) in a real-world clinical setting, based on RETINA.PT database.

Materials and methods: database observational retrospective study of eyes diagnosed with nAMD, followed at the Centro Hospitalar e Universitario de Coimbra, that received at least 1 anti-VEGF intravitreal injection (IVI) since 2007 and had more than 1 year of follow-up. Outcomes were the mean change in visual acuity, number of IVI and visits, cases submitted to therapy switch and structural parameters.

Results: 494 eyes from 369 patients were included. Mean baseline BCVA was 55,11 ± 21,92 letters and improved a mean 1,35 ± 16,90 (p=0.08) after one year of follow-up, receiving an average 4,14 ± 1,97 IVI. By then, 14,2% of the eyes had gained ≥15 letters and 12,8% lost ≥15 letters. After 5, 7 and 10 years of follow-up, 38%, 44,3% and 56,7% eyes lost ≥15 letters. Patients starting treatment in 2018 improved a mean of 3,14 ± 18,17 letters (p=0,216) after one year, receiving a mean of 4,20 ± 1,28 IVI. We found a moderate positive correlation between the baseline and the 120-month VA (ρ=0,560, p<0,001). Furthermore, a final BCVA ≤35 letters was associated with a lower number of anti-VEGF injections and a larger interval between treatments (p<0,001). We did not find CNV type to have an influence on VA nor CMT variation, although occult and type 1 CNVs presented a better overall VA. Baseline CMT was 358,08 µm ± 136,41, improving in the first 18 months (-66,40 µm ± 169,67, p<0,001), followed by stabilization. During follow-up, the number of eyes with PED and subretinal fluid decreased. At the end of follow-up, legally blind patients presented intraretinal fluid, macular atrophy and fibrosis in 42,1%, 36,2% and 63,8%, respectively.

Conclusion: our results, obtained through RETINA.PT database, show that stable outcomes can be achieved and maintained in long-term with anti-VEGF therapy. Not only are they influenced by baseline VA, but also by the number of injections and the frequency of treatments, besides the natural disease progression towards the development of atrophy.

Keywords: age-related macular degeneration, anti-VEGF, database, real-world evidence

RESUMO

O tratamento com anti-VEGF na prática clínica diária: um estudo retrospetivo com a base de dados RETINA.PT

Objetivo: analisar a evolução e resultados clínicos do tratamento com anti-VEGF na degenerescência macular da idade exsudativa (DMI), em contexto de prática clínica, baseado em dados da base RETINA.PT.

Materiais e métodos: realizou-se um estudo retrospetivo observacional, a partir de uma base de dados, de doentes diagnosticados com DMI que receberam pelo menos 1 injeção intravítrea de anti-VEGF desde 2007 e com mais de 1 ano de follow-up. As variáveis em estudo foram a variação média da acuidade visual (AV), o número de injeções e visitas, casos submetidos a troca terapêutica e parâmetros estruturais.

Resultados: foram incluídos 494 olhos de 369 doentes. A AV média inicial foi 55,11 ± 21,92 letras e melhorou 1,35 ± 16,90 (p=0.08) após 1 ano de seguimento, recebendo uma média de 4,14 ± 1,97 injeções. Nesse período, 14,2% dos olhos ganharam ≥15 letras e 12,8% perderam ≥15 letras. Após 5, 7 e 10 anos de seguimento, 38%, 44,3% e 56,7% olhos perderam ≥15 letras. Doentes que começaram o tratamento em 2018 melhoraram uma média de 3,14 ± 18,17 letras (p=0,216) após 1 ano, recebendo uma média de 4,20 ± 1,28 injeções. No nosso estudo encontrámos uma correlação positiva entre a AV inicial e após 120 meses (ρ=0,560, p<0,001). A AV final ≤35 foi associada a um número mais baixo de injeções anti-VEGF e a um maior intervalo entre tratamentos (p<0,001). Não encontrámos relação entre o tipo de membrana e a variação de AV, apesar de as membranas ocultas e tipo 1 apresentarem uma melhor AV. A espessura macular inicial foi 358,08 µm ± 136,41, melhorando ao fim de 18 meses (-66,40 µm ± 169,67, p<0,001), estabilizando. Ao longo do seguimento, registou-se menor presença de líquido subretiniano e de descolamento do epitélio pigmentar. No final do seguimento, 42,1% dos olhos com AV final ≤35 letras apresentaram líquido intraretiniano, 36,2% atrofia e 63,8% fibrose.

Conclusão: os nossos resultados, obtidos através da base RETINA.PT, mostram que com a terapêutica anti-VEGF pode ser alcançada uma AV estável e mantida a longo prazo. Este resultado é influenciado não só pela AV inicial, como pelo número de injeções e frequência de tratamentos, para além da progressão natural da doença.

Palavras-chave anti-VEGF, base de dados, degenerescência macular da idade, *real-world evidence*

INTRODUCTION

Intravitreal anti-vascular endothelial growth factor (VEGF) therapies have been emerging and becoming the first-line treatment in multiple retina pathologies, such as age-related macular degeneration (AMD)[1–3].

AMD is a leading cause of irreversible blindness in people over the age of 65 years in developed countries. In Portugal, its prevalence rises as the population ages, associated with risk factors such as obesity, smoking and arteriosclerosis[2]. Neovascular AMD (nAMD) is caused by the abnormal growth of choroidal vessels in the macula due to the increased expression of VEGF. Choroidal neovascularization (CNV) can lead to retinal fluid accumulation and haemorrhage, retinal neurosensorial or pigmented epithelium detachment (PED) and subretinal fibrosis, ultimately causing severe vision loss[4].

Early CNV detection is fundamental, and treatment must be initiated as soon as diagnosed. Current therapies include ranibizumab (Lucentis®), aflibercept (Eylea®) and, off-label, bevacizumab (Avastin®)[2]. By neutralizing VEGF isoforms, they inhibit neovascularization and decrease the permeability of abnormal vessels, leading to functional improvement or stabilization, as well as anatomical lesion recovery. The efficacy and safety of these treatments is proven by multiple randomized clinical trials. The randomized controlled trials ANCHOR[5] and MARINA[6] demonstrated the benefits of a ranibizumab fixed regimen regarding visual acuity (VA) and anatomical outcomes. The CATT trial[7] also validated the efficacy and safety for both ranibizumab and bevacizumab, considering different treatment regimens. Regarding aflibercept, the VIEW trial[8] demonstrated its non-inferiority concerning safety and visual and anatomical outcomes, when compared with ranibizumab.

However, clinical trials may not reflect the real-world experience regarding a progressive and chronic pathology such as nAMD, which requires long-term and continuous treatment and follow-up. These prolonged treatment schedules are often affected by a low therapeutic adhesion, making it impossible to recreate the exact trial conditions. In this regard, studies based on clinical practice have been emerging, aiming to optimize therapeutic strategies[9–11], compare the efficacy between different treatments[12], evaluate the results of therapeutic switch[13] and establish its long-term effectiveness[14]. Recently, we have been witnessing the creation of databases and the greater use of electronic clinical records in the area of ophthalmology, with the aim of facilitating large-scale registration and monitoring[15]. From these, real-world evidence can be quickly obtained, allowing to easily infer whether results from randomized controlled trials can be applied to the general population in the long-term[16].

The RETINA.PT database main goal is to facilitate patient's follow-up, regarding the perspective of a non-interventional study of the real-world clinical practice. It is pretended a simplified clinical data registry of each patient, its treatments and follow-up information, in a uniformized manner. This includes best corrected visual acuity (BCVA), central macular thickness (CMT), CNV activity and localization, presence of PED and fluid, haemorrhage, fibrosis and macular oedema. Systemic and ocular adverse effects, such as inflammation and endophthalmitis, retinal pigmented epithelium (RPE) rupture and thromboembolic events, are also considered. The obtained clinical data will support the efficacy and safety, in the long-term, of anti-VEGF treatments in our medical retina clinic.

The main goal of this study is to analyse the clinical evolution and outcomes of intravitreal anti-VEGF in nAMD patients, in a real-world clinical setting, based on RETINA.PT data.

MATERIALS AND METHODS

STUDY DESIGN

Single centre, retrospective, observational study conducted at the Ophthalmology Department of Centro Hospitalar e Universitário de Coimbra (CHUC). The RETINA.PT database and protocol was approved by CHUC Ethics Committee and by the Portuguese National Committee for Data Protection (CNPD) for data registry regarding clinical practice and development of non-interventional studies. This research study was also approved by the Faculty of Medicine, University of Coimbra (FMUC) Ethics Committee and adhered to the tenets of Declaration of Helsinki. All included participants provided written informed consent.

STUDY SUBJECTS

From August 2018 to December 2019, patients undergoing anti-VEGF treatment at the department of Ophthalmology of CHUC were identified and invited to participate, when going to their regular appointments and treatment sessions. Patients included in this study were previously diagnosed with nAMD and treated with anti-VEGF intra-vitreous injections (ranibizumab, bevacizumab and aflibercept), since 2007.

Exclusion criteria: no treatment sessions; less than 1 year of follow-up since diagnosis; choroidal neovascularization secondary to other diseases or other concomitant retinal diseases compromising main outcomes.

STUDY PROTOCOL

Medical records were reviewed, and the following data were collected: age; gender; systemic and ophthalmologic comorbidities and previous treatments; time since diagnosis and pathology. Data collected from clinical visits included: BCVA based on the number of letters read using the ETDRS (Early Treatment Diabetic Retinopathy Study) scale; intraocular pressure; biomicroscopy; fundoscopy findings. Registered morphological parameters from fluorescein angiography and OCT imaging were also collected: presence, type and location of CNV; CMT and macular oedema; presence of PED, neurosensorial detachment, sub-RPE and intraretinal fluid; subretinal fibrosis and atrophy. Occurrence of systemic and ophthalmologic adverse effects, such as endophthalmitis and RPE rupture were also recorded.

All anti-VEGF intravitreal injections, including the agents used, were registered.

STUDY OUTCOMES

The main outcome was to evaluate the mean change in BCVA over time of follow-up, considering baseline and final BCVA, for the entire study group. Secondary outcomes included number of injections and visits after the start of treatment, number of cases submitted to therapy switch and effect, structural parameters variation with follow-up, and IVI's adverse effects.

STATISTICAL ANALYSIS

For this study, the collected data were extracted from RETINA.PT and analysed. Graphs were also imported from RETINA.PT, regarding the real number of patients at each time of follow-up but also using the last observation carried forward (LOCF) method.

Population demographics and clinical characteristics were presented with traditional descriptive methods: categorical and binary data were described as frequencies and percentages, and continuous variables as means and standard deviation. Normality was evaluated by Kolmogorov-Smirmov test and variance homogeneity by Levene's test, verifying the applicability of statistical tests and use of parametric or the nonparametric-equivalent tests. To correlate variables without a normal distribution, Spearman's correlation test was applied. Student *T*-test, Wilcoxon sign-rank and Mann-Whitney U tests were used for comparisons within continuous variables, as appropriate. Kruswall-Wallis H. test was performed to compare means between multiple groups. P-values of $< 0,05$ were considered statistically significant.

Statistical analyses were performed using IBM© SPSS® Statistics for Mac, version 26 (IBM Corp., Armonk, N.Y., USA).

RESULTS

A total of 1125 eyes were registered at RETINA.PT, of which 1108 treated with anti-VEGF. From those, 448 did not have neovascular AMD or had CNV related with another pathology. 660 eyes from patients with nAMD being treated with anti-VEGF were registered. According to the exclusion criteria, 165 were excluded due to insufficient number of injections or time of follow-up since diagnosis, at the time of data collection.

Thus, 494 eyes of 369 patients were included in this study, having at least 1 year of follow-up and submitted to 1 or more anti-VEFG injections. This group comprised 167 (45,3%) men and 202 (54,7%) women, with a mean age of 76,06 ± 8.49 years at their first visit.

CNV classification and general patient characteristics are summarized in table I.

Table I: Demographic and clinical characteristics of the study population included for analysis (adapted from *RETINA.PT*)

Eyes, nº	494
Right (%)	254 (51,4%)
Mean baseline **age,** ± SD	76,06 ± 8,49
Gender: female, n (%)	202 (54,7%)
Mean **follow-up time (years),** ± SD; (min-max)	4,45 ± 2,99; (1-12,3)
Choroidal neovascularization: **lesion type**	
Occult	157 (31,8%)
Minimally classic	19 (3,8%)
Predominantly classic	31 (6,3%)
Classic	13 (2,6%)
RAP	67 (13,6%)
PCV	102 (20,6%)
Type 1 (OCT)	46 (9,3%)
Type 2 (OCT)	35 (7,1%)
Disciform	8 (1,6%)
Not recorded	16
Mean **baseline VA (letters)**, ± SD	55,11 ± 21,92
Mean **final VA (letters)**, ± SD	49,11 ± 22,75
Mean **baseline macular thickness (µm)**, ± SD	358,08 ± 136,41
Mean **final macular thickness**, ± SD	259,91 ± 110,40

OCT: optical coherence tomography; PCV: polypoidal choroidal vasculopathy; RAP: retinal angiomatous proliferation; SD: standard deviation.

FUNCTIONAL OUTCOME

The mean baseline BCVA was 55,11 ± 21,92 letters and the mean final BCVA was 49,11 ± 22,75 letters, with a mean BCVA variation between these time-points of -6,00 ± 20,96 letters. The mean VA at each year of follow-up is shown in figure 1 and its corresponding values in table I, considering the real number of eyes at each time.

VA was classified in terms of vision required to drive (≥70 letters, 20/40), read (≥60 letters, 20/63), as low vision (36-59 letters) and to be considered legally blind (≤35 letters, 20/200). The mean VA evolution regarding each group and eyes at each timepoint is represented in figure 2 and in table II.

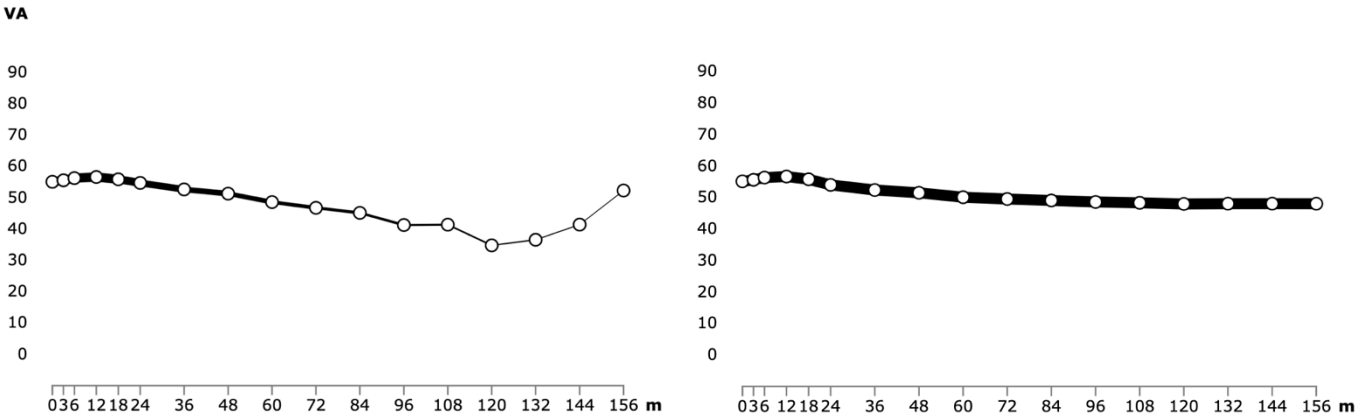

Figure 1: mean VA evolution during follow-up (months), all eyes considered (left) and as last observation carried forward (LOCF, right), with corresponding values in table I. (*from RETINA.PT*.)

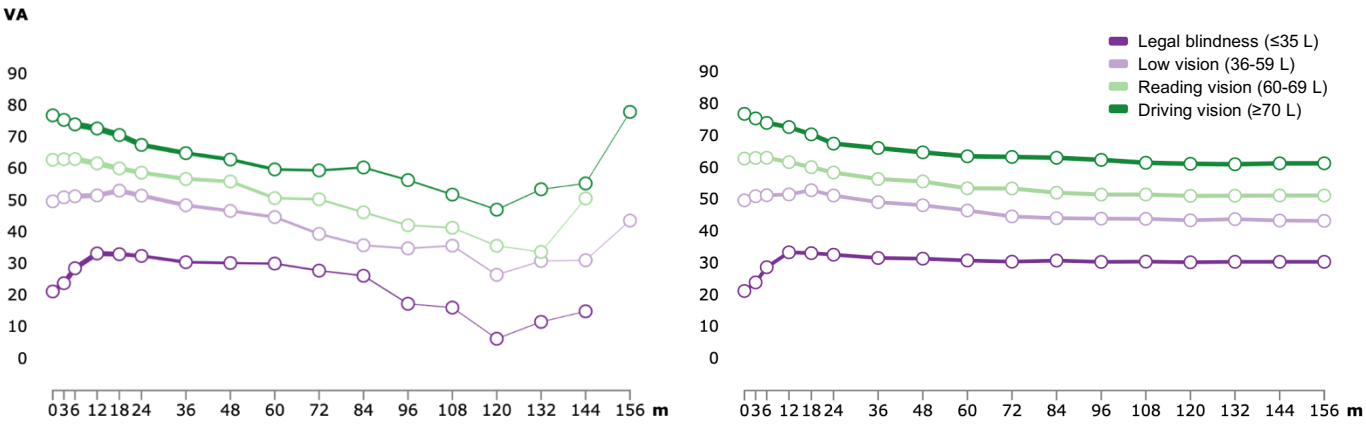

Figure 2: VA progression according to the initial VA subgroups (in months), all eyes considered (left) and as LOCF (right), with corresponding values in table II. (*from RETINA.PT*)

Table II: VA (letters) and CMT (µm) mean progression during follow-up (months), all eyes considered. (*from RETINA.PT*)

		0	3	6	12	18	24	36	48	60	72	84	96	108	120	132	144	156
All Patients	**N**	494	494	494	494	491	422	347	283	229	173	132	104	79	53	30	16	4
	N MT	375	414	440	460	466	406	340	278	227	171	130	103	78	53	30	16	4
	VA	55,11	55,60	56,30	56,65	55,93	54,79	52,74	51,41	48,70	46,91	45,34	41,49	41,35	34,75	36,53	41,38	52,25
	MT	369,05	356,70	322,76	295,78	285,85	286,41	274,56	272,60	262,48	270,31	277,15	295,12	280,94	262,83	257,70	238,75	250,00

Table III: VA (letters) and CMT (µm) mean progression during follow-up (months), according to initial VA. (*from RETINA.PT*)

		0	3	6	12	18	24	36	48	60	72	84	96	108	120	132	144	156
Legal Blindness (≤35 L)	**N**	109	109	109	109	108	81	62	50	37	26	17	12	6	3	3	1	
	N MT	76	88	96	100	101	77	62	50	37	26	17	12	6	3	3	1	
	VA	21,28	23,96	28,73	33,42	33,29	32,78	30,94	30,66	30,43	28,35	26,88	17,58	16,17	6,33	11,67	15,00	
	MT	442,47	442,41	381,29	315,72	300,57	292,26	270,45	280,12	268,38	270,62	307,59	355,25	529,50	311,67	271,67	144,00	
Low vision (36-59 L)	**N**	108	108	108	108	107	102	85	69	59	46	36	30	22	17	10	7	3
	N MT	84	92	99	102	102	97	83	69	59	46	36	30	22	17	10	7	3
	VA	49,74	51,03	51,34	51,61	53,13	51,55	48,49	46,72	44,76	39,46	35,86	34,87	35,73	26,53	30,90	31,14	43,67
	MT	378,13	364,93	329,25	308,80	285,19	281,39	274,17	274,90	276,56	282,63	309,11	344,17	258,41	239,53	246,30	200,14	213,00
Reading Vision (60-69 L)	**N**	126	126	126	126	126	107	90	77	63	49	38	31	25	16	8	3	
	N MT	103	111	115	122	123	105	89	76	63	49	38	31	25	16	8	3	
	VA	62,87	63,06	63,10	61,75	60,14	58,79	56,82	56,03	50,75	50,39	46,29	42,19	41,40	35,69	33,75	50,67	
	MT	359,42	337,41	304,45	279,93	281,50	292,83	276,36	277,05	256,41	275,90	255,71	246,42	245,12	266,94	234,63	197,67	359,42
Driving Vision (≥70 L)	**N**	151	151	151	151	150	132	110	87	70	52	41	31	26	17	9	5	1
	N MT	112	123	130	136	140	127	106	83	68	50	39	30	25	17	9	5	1
	VA	76,91	75,47	74,06	72,75	70,70	67,57	64,97	62,97	59,83	59,52	60,44	56,45	51,88	47,12	53,56	55,40	78,00
	MT	321,28	306,62	290,78	285,58	279,54	281,38	275,75	262,07	252,66	253,34	255,28	272,33	276,92	273,65	286,22	336,40	361,00

N: number of patients; N MT: number of patients to whom was measured their macular thickness; VA: visual acuity mean values; MT: macular thickness mean values.

After the first year of treatment, VA improved a mean of 1,35 ± 16,90 letters, although not statistically significant (p=0,08), declining progressively over time of follow-up.

On the first visit, 151 (30,6%) eyes had a baseline driving vision, 126 (25,5%) reading vision, and 109 (22,1%) legal blindness (table III). After 12 months, 63 (12,8%) eyes lost more than 15 letters when compared to baseline VA, whereas 101 (20,4%) eyes gained between 5 to 14 (20,4%) and 70 (14,2%) more than 15 letters. After completing 60 months of follow-up, 30,1% eyes presented a driving vision, whereas 15.0% had legal blindness. After 72 and 120 months, 30,6% and 30,0% eyes, respectively, had driving vision, while 11,5% and 10% had legal blindness, respectively. BCVA differences after 60, 84 and 120 months are presented in table IV.

BCVA alteration (%) for each group is shown in figure 3. The subgroups with better initial VA (driving and reading vision) presented a mean VA variation of -15,54 and -11,60 letters, respectively. Regarding those groups, 38% and 37% of the eyes lost ≥15 letters, whereas 36% of the eyes starting as legally blind gained ≥15 letters.

We found a statistically significant variation between baseline and VA after 60 (-11,07 ± 20,60, p=0,004), 84 (-14,50 ± 20,96, p=0,001) and 120 (-23,34 ± 21,16, p<0,001) months of follow-up (table IV). There was a moderate positive correlation between baseline and 120-month BCVA (**ρ**=0,560, p<0,001). A lower final VA (≤35L) was shown by eyes with lower baseline BCVA (p<0,001). Likewise, a better final BCVA (≥70L) was related with a higher baseline BCVA (p<0,001). The same associations were found after 60 (**ρ**=0,454, p<0,001) and 84 months (**ρ**=0,499, p<0,001) of follow-up.

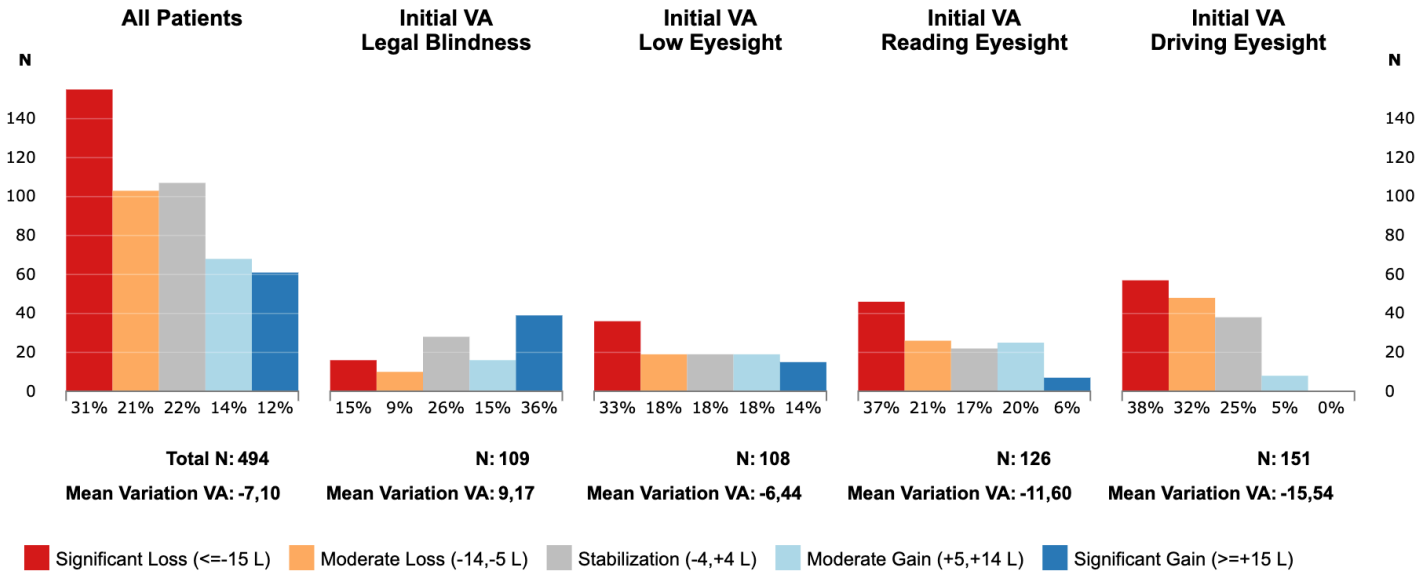

Figure 3: alteration of the initial BCVA, for all eyes, according to initial VA subgroup. (*from RETINA.PT*)

Table IV: VA difference and mean variation relative to baseline after 12, 60, 84 and 120 months [as number of eyes (%)]

	Loss of ≥15 letters	**Loss of -14 to -5 letters**	**Stabilization -4 to 4 letters**	**Gain of 5 to 14 letters**	**Gain of ≥15 letters**	**Mean VA variation**
12 months (n=494)	63 (12,8%)	77 (15,6%)	183 (37,0%)	101 (20,4%)	70 (14,2%)	1,35 ± 16,90, p=0,08
60 months (n=175)	66 (38,0%)	36 (20,7%)	38 (21,8%)	20 (11,7%)	15 (7,8%)	-11,07 ± 20,60, p=0,004
84 months (n=104)	46 (44,3%)	26 (25,0%)	15 (14,4%)	12 (11,5%)	5 (4,8%)	-14,50 ± 20,96, p=0,001
120 months (n=30)	17 (56,7%)	7 (23,3%)	5 (16,7%)	1 (3,3%)	0 (0,0%)	-23,34 ± 21,16, p<0,001

Baseline, 12-month and 60-month BCVA (table V) were statistically significant different across CNV types (p<0,001). Occult and type 1 CNVs had a better overall VA, being the baseline and 60-month VA significantly different when comparing with minimally classic and type 2 CNVs (p<0,05). Presence of disciform scar at baseline was related to a general lower VA, when comparing with any CNV type without a marked fibrotic component (p<0,01).

Mean VA variation regarding each group showed no other significant differences.

Table V: Baseline, 12 and 60-month mean BCVA, regarding CNV lesion type (n=494 at 12 months; n=175 at 60 months follow-up)

CNV: **lesion type**	**Baseline VA** (mean ± SD)	**12-month VA** (mean ± SD)	**60-month VA** (mean ± SD)
Occult	57,87 ± 20,02	58,96 ± 19,37	47,49 ± 21,76
Minimally classic	47,74 ± 22,76	43,53 ± 18,40	43,43 ± 24,68
Predominantly classic	56,84 ± 21,96	55,16 ± 21,96	47,65 ± 23,76
Classic	53,85 ± 20,56	58,62 ± 18,16	45,00 ± 17,07
RAP	52,27 ± 21,85	54,54 ± 20,37	45,24 ± 25,09
PCV	56,20 ± 21,05	57,86 ± 19,17	46,36 ± 20,92
Type 1 (OCT)	63,63 ± 16,98	62,50 ± 17,43	48,75 ± 22,22
Type 2 (OCT)	45.09 ± 27,27	50,23 ± 25,61	44,57 ± 23,18
Disciform	18,38 ± 26,66	22,00 ± 22,80	16,00 ± 22,42

CNV: choroidal neovascularization; OCT: optical coherence tomography; PCV: polypoidal choroidal vasculopathy; RAP: retinal angiomatous proliferation; VA: visual acuity

INJECTIONS AND TREATMENT PATTERNS

During a mean follow-up of 4,45 ± 2,99 years the mean number of visits was 22,31 ± 14,03. The mean time between nAMD diagnosis and treatment initiation was 2,08 ± 2,61 months. The highest number of IVI per year was recorded by the end of the first year of treatment, with a mean of 4,14 ± 1,97 injections, declining the following years, as pictured in figure 4 and table VII.

The number of IVI, clinic visits and mean time interval between each are presented in table VI.

Table VI: follow-up, number of treatments and consults, and mean interval between each (n= 494), *adapted RETINA.PT*

	Number of		Mean interval between (months)
	Total (%)	**Mean ± SD**	**Mean ± SD**
Follow-ups	11020 (100%)	22,31 ± 14,03	2,39 ± 1,51
Time until 1st treatment	-	-	2,08 ± 2,61
Treatments	6477 (58,8%)	13,11 ± 8,39	4,07 ± 5,62
anti-VEGF		12,87 ± 8,17	
Aflibercept	3231 (49,9%)	6,53 ± 6,09	
Ranibizumab	3141 (48,5%)	6,35 ± 7,63	
Bevacizumab	3 (0%)	0,01 ± 0,08	
PDT	96 (1,5%)	0,19 ± 0,80	
Others	9		
Consultations	4543 (41,2%)	9,20 ± 7,33	5,80 ± 6,51

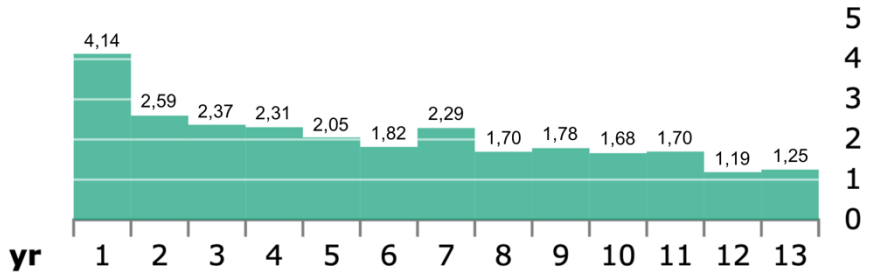

Figure 4: number of anti-VEGF injections at each year of follow-up, all eyes considered. Corresponding values in table VII. (*from RETINA.PT*)

Table VII: mean number of anti-VEGF injections at each year of follow-up, and the corresponding number of eyes still being followed and treated. *Adapted RETINA.PT. 1st f.: 1st follow-up*

year	1	2	3	4	5	6	7	8	9	10	11	12	13
nº injections	4,14	2,59	2,37	2,31	2,05	1,82	2,29	1,70	1,78	1,68	1,70	1,19	1,25
Real N	494	491	347	283	229	173	132	104	79	53	30	16	4
Real N still in treatment (%)	483 (97,8%)	382 (77,8%)	307 (88,5%)	249 (88,0%)	193 (84,3%)	138 (79,8%)	101 (76,5%)	73 (70,2%)	57 (72,2%)	35 (66,0%)	18 (60,0%)	10 (62,5%)	4 (100%)
N in treatment as LOCF (%)	97,8%	77,3%	62,1%	50,4%	39,1%	27,9%	20,4%	14,8%	11,5%	7,1%	3,6%	2,0%	0,8%

Statistically significant differences were found between BCVA subgroups regarding the number of injections during follow-up ($p<0,001$), as legally blind eyes received a lower number of anti-VEGF injections. Additionally, differences were found on the mean time interval between IVI ($p<0,001$). A worse final BCVA was related with a larger time interval, after 120 months of follow-up ($\boldsymbol{\rho}=0,645$, $p<0,001$).

Disciform lesions received less IVI during follow-up ($p=0,004$), but no other differences were reported regarding different CNV types.

A SUB-ANALYSIS

Since 2018, all anti-VEGF treatment protocols have been adjusted. Therefore, a sub-analysis was made considering the 104 eyes which started treatment during 2018, in order to explore the outcomes with the implemented protocol.

The mean baseline BCVA was 49,56 ± 26,10 letters and final mean BCVA was 50,58 ± 25,35 letters. The mean interval between diagnosis and first treatment was 2,30 ± 1,87 months. During a mean follow-up of 1,49 ± 0,72 years, each eye was submitted to 6,45 ± 1,92 IVI (table VIII). During the first year, eyes received a mean of 4,20 ± 1,28 injections. The mean number of injections for each period of follow-up is depicted in figure 5.

After the first year of treatment, VA improved a mean of 3,14 ± 18,17 letters (p=0,216), and 3,70 ± 23,51 letters (p=0,102) after 18 months. No statistically differences were found regarding the VA variation after 12 or 18 months (p>0,1). Furthermore, no differences were found between aflibercept and ranibizumab on VA variation nor number of injections (p>0,05).

Table VIII: follow-up, number of treatments and consults, and mean time intervals, for eyes starting treatment during 2018 (n = 104)

	Number of		Mean interval between (months)
	Total (%)	**Mean ± SD**	**Mean ± SD**
Follow-ups	978 (100%)	9,40 ± 2,32	1,78 ± 0,41
Time until 1st treatment	-	-	2,30 ± 1,87
Treatments	671 (68,6%)	6,45 ± 1,92	2,60 ± 0,87
Aflibercept	475 (70,8%)	4,57 ± 0,448	
Ranibizumab	195 (29,1%)	1,88 ± 0,184	
PDT	1 (0,1%)	0,01 ± 0,001	
Consultations	307 (31,4%)	2,95 ± 0,78	5,68 ± 1,62

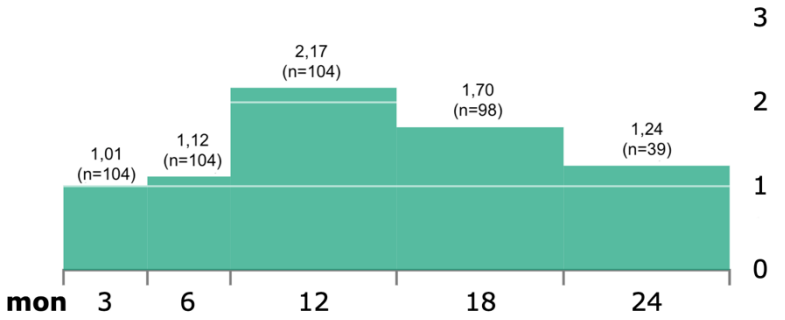

Figure 5: number of anti-VEGF injections for period of follow-up, since diagnosed — 0-3 months, 6-12 months, 12-18 months, 18-24 months — for eyes starting treatment in 2018 (*from RETINA.PT*)

TREATMENT SWITCH

On total, 145 eyes were submitted to the switch of anti-VEGF, due to maintained CNV activity or poor response to the drug used. This group presented a mean baseline BCVA of 59,84 ± 16,99 letters and final BCVA of 49,08 ± 19,04 letters, with a mean variation of -10,96 ± 20,29 letters.

During a mean follow-up of 5,94 ± 2,82 years, eyes with a higher baseline BCVA presented a greater variation, as 50% of the eyes starting with driving vision had a significant VA loss (figure 6). This group's mean number of injections during the first year was of 4,30, decreasing to 2,99 in the second year.

Of all treatments, 45,6% were of aflibercept and 52,5% of ranibizumab (table IX). 130 (89,6%) eyes switched from ranibizumab to aflibercept, 9 of which changed back. Of the remaining, 3 resumed treatment with aflibercept. No difference was found between eyes submitted to treatment switch or not on VA variation or number of IVI after 12 or 24 months (p>0,1).

Table IX: follow-up, treatments, consults and mean time intervals, for eyes submitted to protocol switch (aflibercept and ranibizumab) (n = 145)

	Number of	Mean interval between (months)
	Total (%)	**Mean ± SD**	**Mean ± SD**
Follow-ups	4745 (100%)	32.72 ± 16,14	2,17 ± 0,57
Treatments	2847 (60,0%)	19,63 ± 9,60	3,61 ± 1,58
Aflibercept	1299 (45,6%)	8,96 ± 0,74	
Ranibizumab	1495 (52,5%)	10,30 ± 0,86	
Bevacizumab	1 (0%)	0,01 ± 0,001	
PDT	51 (1,8%)	0,35 ± 0.03	
Laser	1 (0%)	0,01 ± 0,001	
Consultations	1898 (40,0%)	13,09 ± 8,31	5,42 ± 3,77

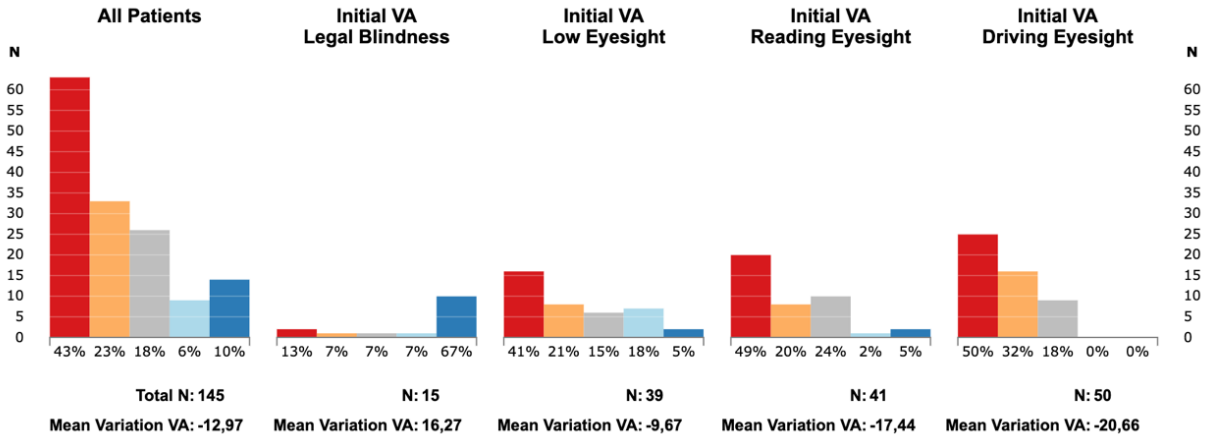

Figure 6: VA variation of eyes submitted to anti-VEGF protocol switch, according to initial VA subgroup. (*from RETINA.PT*)

CENTRAL MACULAR THICKNESS

Figure 7 and table II present CMT evolution for each year of follow-up. The mean baseline CMT was 358,08 µm ± 136,41. There was a significant decline during the first 18 months (285,85 µm, mean variation of -66,40 µm ± 169,67; p<0,001) followed by stabilization. The final mean CMT (259,91 µm ± 110,40) was significantly lower compared to baseline (p<0,001).

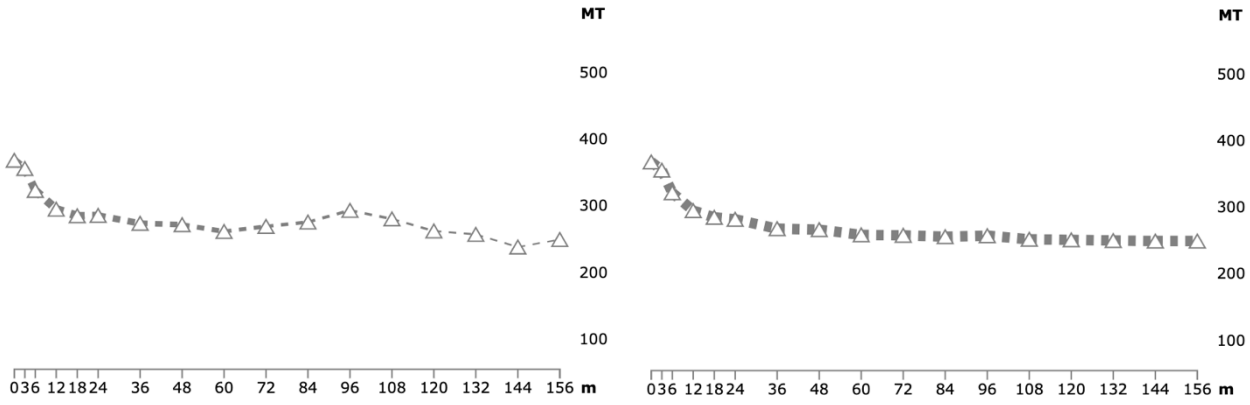

Figure 7: mean CMT variation during follow-up, all eyes considered, with corresponding values in table II; and LOCF. (*from RETINA.PT*) MT: macular thickness

A statistically significant but weak negative correlation was found between CMT and BCVA variations after 18 months of follow-up (**ρ**=-0,294, p<0,001). Eyes with a significant BCVA loss (≥15) presented a positive CMT variation (p<0,001), when comparing with BCVA stabilization (-4 to 4) or gain (≥4 letters).

After 60, 84 and 120 months of follow-up, eyes with lower vision presented lower CMT values, although not significant (p>0,05).

No differences were found regarding different CNV types and the final CMT (p=0,48).

STRUCTURAL PARAMETERS

Structural OCT parameters that were reported at baseline and at the end of follow-up are presented in table X.

Table X: structural parameters at the 1st and last visits (n = 494, NR: not recorded)

	1st follow-up (n, %)	NR	Final follow-up (n, %)	NR
Fibrovascular PED	254 (51,4%)	46 (9,3%)	222 (44,9%)	21 (4,3%)
Serous PED	55 (11,1%)		10 (2,0%)	
Subretinal fluid	202 (40,9%)	22 (4,5%)	69 (14,0%)	5 (1,0%)
Intraretinal fluid	155 (31,4%)		161 (32,6%)	
Atrophy			121 (24,5%)	6 (1,2%)
Fibrosis			162 (32,8%)	6 (1,2%)

PED: pigmented epithelium detachment

There was a decrease in the number of eyes with both fibrovascular and serous PED, being present in 44,9% and 2% by the final follow-up, respectively. There was also a decrease in eyes presenting subretinal fluid, from 40,9% to 14,0%.

During follow-up, 75 (15,2%) eyes ended treatment due to a disciform scar. They presented a significantly lower BCVA ($p<0,001$) and final CMT ($p=0,03$) when comparing with eyes still in treatment.

Considering all eyes with a final BCVA of ≤35 letters, 42,1% ended with fluid, 36,2% presented atrophy and 63,8% fibrosis.

By the end of follow-up, 391 eyes (79,3%) were still under treatment protocols.

ADVERSE EFFECTS

During follow-up, we observed 3 anti-VEGF IVI related endophthalmitis. Although one patient maintained its previous VA, the other two patients ended with a VA ≤35 letters.

No other major ocular or systemic drug-related adverse effects were recorded.

DISCUSSION

The efficacy and safety of anti-VEGF treatment for nAMD are well established by clinical trials. However, they do not replicate the real-world daily practice on treating such a prevalent and chronic pathology. Clinical databases in ophthalmology allow the large-scale follow-up and analysis of real-world evidence, supporting treatment efficacy and safety in clinical practice. This retrospective study is based on the results of the RETINA.PT database and aimed to evaluate the real evidence of clinical practice in the treatment of nAMD with anti-VEGF.

Our results showed an overall mean BCVA improvement (1,35 ± 16,90), although not significant, after the first year of treatment, followed by a progressive decline. By that timepoint, 87,3% of the eyes had lost ≤15 letters and 14,2% gained ≥15 letters, when compared with baseline. Our results are in agreement with both clinical trials and clinical practice-based studies. In both ANCHOR[5] and MARINA[6] trials, the majority of the sample had lost ≤15 letters after the first year of treatment (96,4% and 94,5%, respectively), 33-40% gaining ≥15 letters, with a mean VA improvement of 11,3 and 7,2 letters. Real-world based studies also report a BCVA improvement by the end of the 1st year of follow-up, although consistently lower than clinical trials[9,10,12,17–20]. In spite of the initial improvement observed in clinical trials, BCVA gains were not sustained in the long-term, as reported in CATT[7] and SEVEN-UP[21] studies. The same progressive loss was observed in our study. After 5, 7 and 10 years of follow-up, 38%, 44,3% and 56,7% (respectively) of eyes had loss ≥15 letters compared to baseline. Regardless of the follow-up period, eyes presenting a better initial BCVA had an important BCVA variation, tending to lose VA. In spite of that, those eyes were able to maintain a better VA in the long-term, as described in other studies[14,20,22,23]. We did not find CNV type to have an influence on VA variation, although occult CNVs were related with a better overall VA, as observed in similar studies[13,24].

Besides baseline VA, multiple reasons have been stated for the different VA variation between clinical trials and RWO, such as the number of injections and treatment protocols[25]. In our study, the first year of treatment was the one that recorded the highest number of injections (4,14 ± 1,97), declining the following years. Regarding patients submitted to the protocol implemented in 2018, in order to prevent undertreatment – loading dose of 3 monthly injections, followed by fixed bimonthly injections – BCVA improved a mean of 3,14 ± 18,17 letters after 12 months, receiving a mean of 4,20 ± 1,28 injections. No difference was found between drugs on mean VA variation or number of injections. Marques et al[9] reported a gain of 1,64 letters with a mean of 3,75 injections during the first year of follow-up, without loading dose. Hjelmqvist et al[18] reported a BCVA improvement (4.9 letters) after 3 initial injections, although by 12 months VA was closer to baseline (+1.0 letter). Likewise, Pedrosa et al[20] described a gain of 5.1 letters after the third injection, with VA returning to baseline throughout

follow-up. In the long term, the recent FIDO study[26] reported 70% of vision improvement, with mean a gain of 11.3 letters, after 10 years of continued therapy (mean of 10 injections per year). The FRB group also reported greater VA gains together with a higher number of injections[14,17], as did other real-world based studies[10,23,27]. It was also showed that a lower number and frequency of treatments lead to a worse final VA in long-term[14,16,28]. Although we reported better results since 2018, the number of injections were inferior to the intended 8 IVI during the first year, considering a loading dose, followed by at least 6 IVI per year. It would be interesting to further analyse this group of patients and understand why the IVI rate was lower than expected, as well as the longer time until first treatment (2,30 ± 1,87 months). A larger interval between injections and consultations and resulting undertreatment, that can be due to both patient and hospital burden and constraints, may have a significant impact in their clinical evolution.

Additionally, it is known that similar outcomes can be obtained with both ranibizumab and aflibercept[10,12,19]. Switching treatments is common when there is a poor response or CNV activity is maintained after prolonged therapy, seeking a favorable effect. In our study, although beginning with a better baseline BCVA, these eyes presented a larger VA variation throughout follow-up. Barthelmes and FRB! group[13] showed that after 1 year of switching treatments mean BCVA did not differ, but treatment intervals became larger and more CNVs were graded as inactive. Also, eyes treated for the longest time before switching had worse vision. Likewise, other studies showed that although improving anatomical features, VA improvement was very limited[29,30]. Interpretation of switch effects can be challenging, as most eyes have extensive follow-up periods, during which atrophy or fibrosis may been formed.

As presented in our study, a worst final BCVA is not only associated with a lower number of injections and a larger interval between treatments but also with a worse baseline BCVA[31,32]. Although it may be limited by structural impairment, a low baseline BCVA can have a potentially higher VA gain. As reported by both CATT[32] and VIEW[8] trials, a higher frequency of injections is expected to lead to a higher gain and sustained BCVA. Also, a better baseline BCVA is associated with a lower risk of VA loss. This reinforces the importance of an early disease detection and treatment, allowing patients to maintain a better VA and to improve as much as possible from a lower baseline VA.

Morphologic criteria evaluated during follow-up and considered for retreatment include CMT, the presence of PED and retinal fluid (intraretinal, subretinal and sub-RPE), which can be associated with VA variation. Our results showed an improvement in CMT evidenced by its decline during the first 18 months, followed by stabilization, being the CMT below the baseline the following years. We also reported a great decrease in the presence of PED and subretinal fluid during follow-up. The VIEW study[8,33] found OCT structural parameters such as intraretinal

fluid and PED to be correlated to a compromised initial VA, also limiting its possible outcome. Accordingly, in our study a large percentage of eyes with a final BCVA ≤35 letters ended follow-up with intraretinal fluid and presented atrophy and fibrosis. It is known that formation of subretinal atrophy during follow-up is related to the risk of vision loss and limits a possible VA improvement. The extended CATT[7] study concluded that long-term frequent treatments increased risk of atrophy development, stated as the most common cause of VA loss in clinical-based studies[14,23]. Nonetheless, it is also known that insufficient treatment is likely to lead to the development of atrophy and fibrosis in long-term[28], being detrimental to VA outcome. So, treatment protocols must consider not only the best frequency of IVI but also the negative effect that it may have in long-term.

Electronic databases in ophthalmology allow the large-scale registration and monitoring of a broader and more representative group of patients[15,16]. RETINA.PT is designed to collect real world data on retina pathologies. Intending to facilitate patient's follow-up in a simple and standardized way, layout alterations have been made, as suggested in Annex 1. It allows quick data entry, with 1 minute or less spent for each follow-up (retrospective data taking longer to register). The data analysis section allows the application of search filters such as pathology, follow-up time or number of treatments, as used in our study. It also allows the automatic exportation of graphs and tables, with BCVA and CMT progression for all patients or by baseline VA subgroups, or concerning number of treatments. As the population searched may not have the same follow-up time, it allows graph visualization as real numbers or LOCF, taking into account the last follow-up of each patient. Data can be exported as an excel file, useful for statistical analysis. However, data is exported considering each individual eye, disregarding a possible intereye correlation and consequent statistical effect[34]. An output report can be exported for electronic medical records, facilitating even more clinical registries. It would also be interesting the possibility of exporting treatment data as line graphs and its association with VA variation, including the comparison between different treatments. It is important to acknowledge the limitations associated to these databases, such as the possible selection bias (as it depends on voluntary report) and facultative submission data[16]. Furthermore, mandatory fields should be established, in order to avoid incomplete data entry, such as CNV activity and lesion type, morphological parameters and presence of atrophy, which restricts potential analysis. Complete records would allow further analysis such as optimum treatment regimens, time to inactivate CNV lesions and its impact in VA variation in long-term, or risk of reactivation.

This study has some limitations and eventual sources of bias. Eyes included lacked homogeneity, presenting not only different follow-up times, as we have also included both treatment-naïve and previously treated eyes (with IVI or other therapies, such as PDT).

Also, eyes were submitted to different IVI protocols and some patients participated in clinical trials, thereafter not all received an IVI loading dose or regular treatments. As in other real-world studies, it was not possible to implement a strict follow-up, and there are still missing values on BCVA, anatomical parameters and real number of injections. Furthermore, mild adverse effects were probably underreported, and should be taken into account as it may impact therapy adhesion. The vast majority of the eyes included were under treatment by the time of initial registration on RETINA.PT. Thus, there are still plenty of patients to register, including those who are no longer under IVI protocols due to untreatable conditions or do not want further treatment. It is known that patients having a better baseline VA are motivated to preserve it, and so more compliant to treatments and follow-up visits, whereas higher rates of dropout correlate with sustained BCVA loss[31,35]. This said, it would be important to include these patients as well and understand the reason for the dropout and its correlation with the improvement or not of the disease from the patient's perspective. An outcome to consider would be the patient's quality of life, reflecting not only changes in vision but also the impact on daily living and independence and emotional wellbeing.

CONCLUSION

Anti-VEGF treatments have the potential to stabilize the natural vision loss of nAMD, a chronic and progressive disease which requires long-term and continuous treatment. The RETINA.PT database aims to support clinical practice and, through the obtained real-world evidence, infer whether results from controlled trials can be applied in the long-term. Our study shows that stable outcomes can be achieved and maintained in long-term with anti-VEGF therapy. Not only they are influenced by baseline BCVA, but also by the number of injections and the frequency of treatments, besides the natural disease progression towards the development of atrophy. It is crucial to understand and account for the factors that lead to vision loss, in order to allow a rapid access to appropriate care and to overcome the current challenge that is the establishment of optimized treatment without causing significant constraints to our patients nor the healthcare system.

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ANNEX 1. RETINA.PT layout page

Personal Data (1st APPOINTMENT)

> Main Data

ID (NHS)*

Name*

Hospital/Clinic File Nbr

Sex* Male District

Birth Date*

Signed informed consent Retina.PT

Study(ies)

Studies	Participate	Signed consent.
RIVER STUDY		
FRB		

Medical Record

> Main Data > Additional Data > History

RIGHT EYE		LEFT EYE	
Date of Diagnosis*	Onset of symptoms	**Date of Diagnosis***	Onset of symptoms
Pathology*		**Pathology***	
Previous treatments		Previous treatments	
View Comparative Table of Visual Acuity		View Comparative Table of Visual Acuity	
Initial Visual Acuity 20/*		**Initial Visual Acuity 20/***	
VA Log		**VA Log**	
Letters*		**Letters***	
VA* 0		**VA*** 0	
CNV activity	Membr. Type	CNV activity	Membr. Type
PED	Location	PED	Location
Subretinal fibrosis		Subretinal fibrosis	
Geographic atrophy		Geographic atrophy	

Follow-up

> Main Data > Secondary Data > Images > Summary

RIGHT EYE

Date*

Visit treatment Visit consultation

Visual Ac.: 20/*

Letters*

VA* Biomicroscopy

Ocular tension 0 Fundoscopy

Adverse Events

Treatment

Previous procedures

Comments

> Main Data **> Secondary Data** > Images > Summary

CNV activity

PED

Subretinal fibrosis

Geographic atrophy Greasted linear dimension 0

Intraretinal or Subretinal Fluid

CMT

Neurosensory D.