Research Article

Journal of Ophthalmology and Eye Disorders (ISSN 2831-3216)

Effectiveness Of Intravitreal Bevacizumab In The Treatment Of Neovascular Age-Related Macular Degeneration: Visual And Anatomical Results - A Real-Life Retrospective Study.

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Received Date : December 27, 2024
Accepted Date : January 25, 2025
Published Date : February 04, 2025

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ABSTRACT

Objective: To evaluate the effectiveness intravitreal bevacizumab in the treatment of neovascular macular degeneration (n-ARMD) in a real-life scenario.

Method: Retrospective, longitudinal study that evaluated the medical records of 101 eyes (89 patients) with n-ARMD who received intravitreal bevacizumab, in a Pro Re Nata (PRN) treatment regimen, between July 2021 and March 2024.

Results: After one year of follow-up, 41 eyes (41.4%) showed improvement in VA, 32 (32.3%) showed a decline in VA, and 26 (26.3%) maintained stable VA. There was a significant reduction in median central macular thickness, with a decrease from 317 µm at baseline to 271 µm (p-value < 0.001; Δ = 46 µm). Of all variables evaluated, the number of visits was the only modulator significantly correlated with VA improvement (p = 0.008).

Conclusion: In our study, the majority of patients treated with Bevacizumab improved or maintained their CCVA status. Therefore, bevacizumab in a PRN regimen was effective in the treatment of n-ARMD, supporting its use in a high-throughput public service. Our study also reinforced the clinical application of OCT-based anatomical results to individualize and optimize therapeutic strategies and protocols for patients

Financial Disclosure(s): The author(s) have no commercial interest in any of the discussed subjects.

INTRODUCTION

Age-Related Macular Degeneration (ARMD) is a chronic degenerative disease currently ranked as the leading cause of irrevdersible blindness in patients over 50 years of age.[1] Worldwide, ARMD accounts for approximately 6% of blindness casse.[2] Nowadays, approximately 200 million individuals have moderate or severe visual acuity (VA) loss (impairment) as a result of the development of ARMD.[3] Mathematical projections estimates that by 2040, over 288 million individuals will be diagnose with ARMD. In Brazil, the estimated prevalence of ARMD is around 2.2% among patients aging 70 to 79 years and over 10.3% among patients older than 80 years.[4] Additionally, ARMD is commonly associated with functional disability, greater need for assistance in daily activities, elevated rates of institutionalization among the elderly, along with increased risk of depression and various mental health disorders.[5] Altogether, these factors cause a significant socioeconomic impact and burden for both patients, their formal and informal caregivers, and healthcare system.[6]

ARMD progression can be categorically divided into four stages based on clinical and pathological features. Firstly, based on the physiological aging process, ophthalmological changes (i.e., small drusen formation) occur and highlights the onset of the disease development.[7] At second, the ARMD is initially established, with the formation of intermediate drusen taking place associated with an unaltered retinal pigment epithelium (RPE).[7] The third stage is marked with a moderate ARMD, with at least one large drusen and remarkable epithelium modification.[7] Lastly, in an advanced ARMD stage, a geographic atrophy of the fovea or neovascular macular degeneration (n-ARMD) is observed, resulting in loss of VA.[7] As far as major biochemical modulators that contribute to ARMD development are concerned, it is well-known that the oxidative stress, altered choroidal circulation, Brunch's membrane degeneration, and long-term inflammation might

predispose patients to an impaired local homeostasis.[8–10] The combined disruptions between pro-inflammatory and angiogenic factors, synergically resulting in the in drusen accumulation, RPE changes and, ultimately, the development of a neovascular membrane.[11,12] To note, the main bioactive substance involved in the physiopathology of n-ARMD is the vascular endothelial growth factor A (VEGF-A).[13,14]

Over the last decades, multiple pharmacological interventions have positively transformed the area of ophthalmology, particularly those pharmacological advancements related to n-ARMD treatment.[15,16] Notably, injectable Anti-VEGF pharmacological interventions have demonstrated remarkable clinical results to patients who have received the diagnosed of this critically debilitating disease, either by mitigating n-ARMD progression or reversing its natural course.[15,16] Bevacizumab (Avastin®), a chimeric monoclonal antibody against VEGF-A, is utilized interventions against n-ARMD as an off-label medication.[17,18] Its administration has been associated with enhancement of VA, besides improvement in the contrast sensitivity test.[17,18] Following its prior exclusion from the Brazilian Clinical Protocol and Therapeutic Guidelines due to regulatory changes, bevacizumab became again available for the users of the Brazilian Unified Healthcare System (*Sistema Único de Saúde*), as a reflect of evidence-based health technologies assessments regarding effectiveness, cost-effectiveness, and safety features.[19] Despite governmental strategies and positive clinical results related to bevacizumab in countries with upper-income countries, its large-scaled utilization in low- and middle-income countries is yet limited, restricted, and challenging.[20–22] The treatment typically required monthly ocular injections, in which in limited-resourced populations might correlated with displacement from home, expenses with travels, and ultimately, lower therapeutical adhesion and poorer health and ophthalmological-related outcomes.

Despite multiple trials suggesting the clinical effective of bevacizumab for n-ARMD, the evaluation of optimal number of injections and follow-up visits to the specialists remains unclear, especially for those patients living in low- and middle-income countries (LMICs). V

Therefore, this study aimed to evaluate the efficacy of bevacizumab in a real-world setting (Belo Horizonte, Minas Gerais, Brazil), evaluating factors such as treatment regimens and their impacts on relevant clinical outcomes in resource-limited populations. The results obtained in this study aim to obtain a critical evaluation of international guidelines for the use of bevacizumab in patients with n-ARMD as a strategy to optimize the treatment of one of the leading causes of irreversible blindness globally.

METHODS

Study design and population

This is a single-center wide retrospective, observational analysis of individuals of 53-95-years old in Belo Horizonte, Brazil, admitted from July 2021 to March 2024. We included patients diagnosed with neovascular n-ARMD who had clinical indication for receiving intravitreal bevacizumab injection (1.25 mg/0.05 mL). Additionally, included patients had VA greater than 20/800 and had medical records registered for at least 12 months of follow-up. We utilized the definition endorsed in the Consensus on Neovascular Age-Related Macular Degeneration Nomenclature Study Group, which stated that n-ARMD is "a condition in patients, typically beyond 50 years of age, in which the structure and function of the macula deteriorates. A salient characteristic is the accumulation of extracellular deposits including subretinal drusenoid deposits, basal linear, and basal laminar deposit. These eyes may demonstrate neovascularization or atrophy".[23] We followed international guidelines in the management of neovascular n-ARMD.[24] In particular, in our cohort of patients, all included patients underwent a detailed assessment of patient's history, clinical examination (including standardized best corrected visual acuity [BCVA] testing and stereoscopic biomicroscopy and ophthalmoscopy of the macula of both eyes), in addition to optical coherence tomography (OCT). Moreover, whenever the conclusive diagnose of neovascular n-ARMD was not achieved, patients were submitted to fluorescein angiography (FA) to confirm the diagnostic hypothesis.

Enrolled patients were assisted in a secondary level of care medical center ("*Instituto de Olhos Ciências Médicas*", translated as Institute of Eyes and Medical Sciences) and waived consent for being part of the study. All individuals without a confirmed diagnose of neovascular n-ARMD (i.e., those medical records with inconsistent data or indefinite diagnostic hypothesis) or those without sufficient information (demographic, epidemiological, or clinical) were not included in the analysis. Moreover, we excluded those patients with permanent structural injury or damage to the central fovea, relevant media opacities harnessing retinal image quality, or concomitant retinal disorders. The clinical board who participated in the diagnose of neovascular n-ARMD is composed by medical residents in ophthalmology, fellows in retina and vitreous, as well as attending ophthalmologists, who whenever needed, discussed the clinical cases to better manage the evaluated cases.

The patient's data collection and management were authorized by the Institutional Review Board (CAAE 64571022.9.0000.5134/5.750.093) from the *Faculdade de Ciências Médicas de Minas Gerais* (Belo Horizonte, Brazil). Institutional Review Board final report of our submitted

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protocol and the final acceptance decision is available in Supplementary Material 1 (available in Portuguese). Unofficial translation is available by the corresponding author upon request. We hereby declare that we adhered to the principles of the Declaration of Helsinki. We ascertained the anonymity of each included participant by deanonymizing each evaluated medical record and solely identifying the enrolled individuals by their electronic medical record identifier. Therefore, we comprehensively complied with major national and international confidentiality and regulatory requirements, in special the Resolution 466/12 of the Brazilian National Health Council.

Procedures

Patients evaluated in our study received intravitreal injections of bevacizumab based on the "Pro Re Nata" (PRN) approach (whenever required), with subsequential reinjections determined by clinical and OCT findings. Potentially deterministic factors included (but were no limited to) recurrent or persistent fluid and worsening of VA. At each ophthalmological medical appointment, the on-call clinical body assessed the patient's BCVA, with further performance of OCT whenever the evaluation of the retinal status was necessitated. Follow-up schedule encompassed monthly medical visits at the designated secondar level of care ophthalmological center, though the timing of intravitreal injections was individualized based on diseases activity (appraised by the attending physician). Data associated with ocular and systemic adverse events were also recorded at each visit and classified in accordance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use.[25] We classified adverse events as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment", while serious adverse event, experience, or reaction as "any untoward medical occurrence that at any dose resulted in death, were considered life-threatening, requiring hospitalization or resulted in persistent or significant disability or incapacity".[26] All data collection and management were performed on Microsoft Excel Spreadsheets (Microsoft Corporation, United States of America).

Primary and Secondary Outcomes

We managed in our study both clinical and imaging data, collected through revision of electronic medical records and evaluation of OCT reports. With regards to demographic and clinical-related data, key extracted features included patient's age, gender, affected eye (right-, left-sided, or bilaterally), duration of symptoms, as well as baseline BVCA. Likewise, OCT-based anatomical outcomes comprised central macular thickness (CMT), expressed in microns (μm), presence of intraretinal cystoid spaces (ICS), subretinal fluid (SRF), retinal tubulation (RT), besides presence of serous pigment epithelial detachment (PED).

Sample Size Calculation

To ensure sufficient statistical power to detect relevant changes in both visual and anatomical outcomes over time, our statistical and epidemiological specialists carried out the minimal sample size determination. According to the body of the literature, our study was tailored to detect a clinically meaningful modification in BCVA and CMT with a significance level of 0.05% (α =5%) and a statistical power of 0.8 (β = 80%). Following the utilization of the G*Power software (version 3.1.9.4), our statistical team estimated that a minimum of 105 eyes would be required by the end of our observational study.

Statistical Analyses

Our primary statistical assessment focused on the evaluation of repeated and consecutive measures of BCVA and CMT, from baseline and after 12-months of follow-up. Initially, descriptive statistics were utilized to synthesize patient's baseline characteristics. Additionally, paired t-tests or Wilcoxon signed-rank test (based on data normality) were applied to assess alteration in BCVA and CMT measures. We further performed subgroup analyses evaluating the influence of baseline characteristics (i.e., patient's age, gender, and disease severity), frequency of injections, and number of hospital visits on both visual and anatomical outcomes.

Our study utilized a comprehensive approach to evaluate the potential relationship between baseline OCT-based anatomical outcomes (CMT, ICS, SRF, RT, and PED) and VA-related outcomes across multiple time points. We employed a complementary approach: a categorical assessment using Chi-square tests with Monte Carlo simulations. The Chi-square evaluation explored the potential association between the presence of a determined anatomical outcome and categorical VA outcomes at 12-months endpoint (improved VA, worsened VA, and unchanged VA). Those patients who were lost during follow-up were included in our analysis as non-responders (i.e., those individuals who presented no improvement or worsening in BCVA), following an intention-to-treat (ITT) pragmatic approach.

Statistical evaluations were conducted in IBM® Statistical Package for the Social Sciences (SPSS) (version 30.0.0), with a significance threshold established at $p < 0.05$.

RESULTS

Patient Characteristics

Throughout a 32-months span time, a total of 101 eyes (89 patients) with n-ARMD were identified among the electronic

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medical records and had their data extracted. Their demographic and clinical characteristics are displayed in **Table 1**. Overall, the median age of included were 75 years (Interquartile Range [IQR]: 70-83 years), with slightly more female (57.3%). Female to male ratio was 1,4. Across the different comorbidities registered within selected electronic medical records, most patients had previous diagnose of hypertension (69.7%), diabetes mellitus (21.3%), and were active smokers (11.4%). With regards to the number of ophthalmological care visits, patients attended a median of 8 visits (IQR: 7-10 visits) over the 12-months study period, with a range of 3 to 15 visits.

Table 1. Main baseline characteristics of included patients (n = 89).

Variable	**n (%)**
Demographic characteristics	
Gender	
Male	38 (42,7)
Female	51 (57.3)
Age (in years)	
Median (IQR)	75.0 (70 – 83)
Range (Minimum – Maximum)	53 – 95
Clinical characteristics	
Affected and Treated Eye	
Right (R)	43 (48.3)
Left (L)	46 (51.7)
Comorbidities	
Hypertension	62 (69.7)
Diabetes Mellitus	19 (21.3)
Active Smoker	10 (11.4)
Number of Ophthalmological Care Visits	
Median (IQR)	8.0 (7 – 10)
Range (Minimum – Maximum)	3 – 15

Legend:
n = Total number of observations
SD = Standard Deviation
IQR = Interquartile Range

Baseline OCT-based anatomical findings

All eyes were evaluated for the presence of retinal biomarkers across the cohort at baseline (as shown in **Table 2**). In sum, most biomarkers observed among included patients were SRF (75.2%), ICS (61.4%), PED (8.9%), and retinal tubulation (4.9%).

Table 2. Presence of retinal biomarkers among included eyes (n = 101).

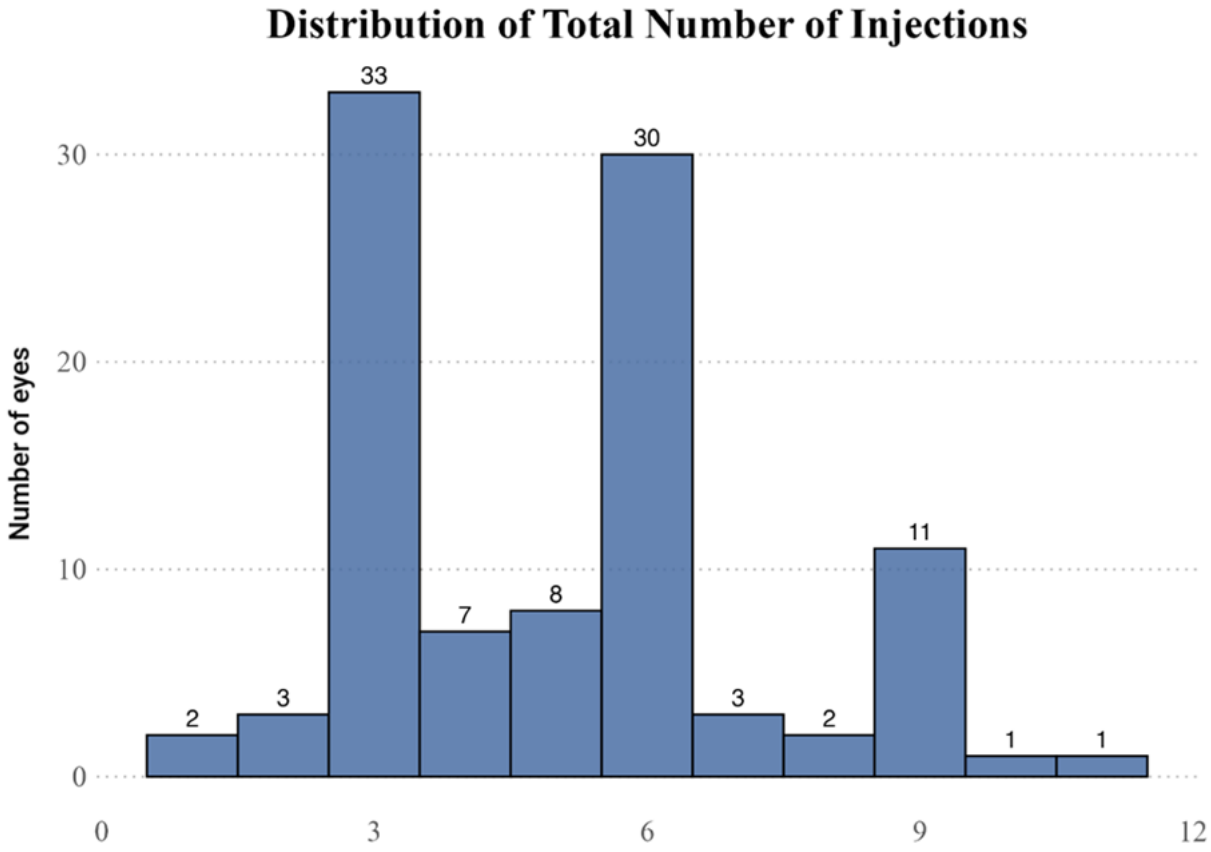
OCT-related anatomical findings	**n (%)**
Subretinal Fluid (SRF)	77 (75,2)
Intraretinal Cystoid Spaces (ICS)	63 (61,4)
Serous Pigment Epithelial Detachment (PED)	9 (8,9)
Retinal Tubulation (RT)	5 (4,9)

Treatment and Follow-up

Across the 12-months follow-up period, the included eyes received a mean of 5.07 ± 2.22, median of 5 (IQR 3 - 6), ranging from one to 11 anti-VEGF injections. Additionally, the mean number of previously received injection (before the period of data assessment defined) was 2.61 ± 4.02, median of 5 (IQR 0 – 4), ranging from zero to 18. **Figure 1** depicts the distribution of injection frequencies, showing that vast majority of eyes receiving three to six injections over the selected period. Notably, two eyes (2.0%) were allocated to the missing data group due to lost to follow-up, which resulted in the final inclusion of 99 eyes in the assessment of visual and anatomical-related outcomes.

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Figure 1. Distribution of Total Number of Injections.



Visual Acuity (VA) Outcomes

With regards to VA-related outcomes, we assessed the changes in the number of letters read on the Snellen chart over the 12-months span time. Following the one year of follow-up, 41 eyes (41.4%) presented an improvement in VA, 32 eyes (32.3%) experienced a decline in VA, and 26 eyes (26.3%) maintained stable VA (**Figure 2**). As noticed in Figure 2, among the 41 individuals who demonstrated remarkable improvement in VA, most of them (46.3%) gained one line, followed by 39.0% who gained two lines. A slightly reduced number of eyes gained three (9.8%), four (2.4%), five (2.4%), or six (2.4%) lines across the study period. On the other hand, among the 32 eyes who presented a worsening in VA, 59.4% lost one line in the Snellen assessment and 12.5% lost two lines. Lastly, loses of three, four, five, and six lines were observed in 15.6%, 6.3%, 3.1%, and 3.1% of eyes, respectively. Interestingly, our data shows that those eyes who presented a median improvement in VA, on average showed a median gain of two lines (ranging from 1 to 6 lines). Conversely, those eyes who presented a worsening of VA, on average lost one line (ranging from 1 to 6 lines). As far as those eyes who were in the group of stable VA (did not present any significant improvement or worsening of VA throughout the evaluated period) is concerned, no median change (zero lines) was observed in our data assessment, indicating a statistically significant association between VA long-term status and change in the number of letters over the course of treatment (p-value < 0.001). Corresponding data is presented in **Table 3**.

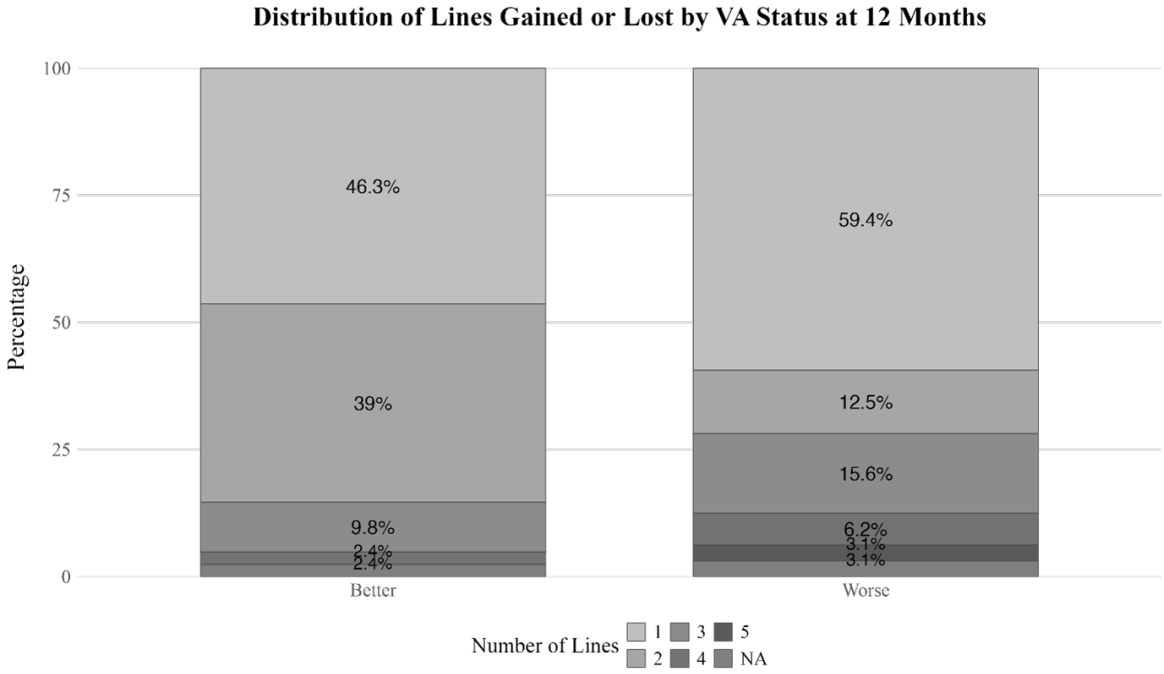
Table 3. Assessment of the number of lines according to the visual acuity status over time

Variables	Status Assessment / Visual Acuity (n=99)			
	Improved n = 41 (41,4%)	**Worsened n = 32 (32,3%)**	**Remained Unchanged n = 26 (26,3%)**	**p-value**
Number of lines after 12-months follow-up	2 (1 – 2) [1 – 6]	1 (1 - 3) [1 – 6]	0 (0 - 0) [0 – 0]	< 0,001

Data represented as median (IQR P25-P75), Range [Minimum – Maximum]; Mann-Whitney test

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Figure 2. Distribution of Lines Gained or Lost by VA Status at 12 Months.



Central Macular Thickness (CMT)

According to our data, CMT measures reduced significantly throughout the study period, with median measurements at baseline of 317 µm and at latest study-time point (12 months of follow-up) 271 µm (p-value < 0.001; Δ = 46 µm). Additionally, the range of CMT also suggested significant decrease, with minimum measurements dropping from 191 µm to 147 µm, besides maximum measurement reducing from 817 µm to 612 µm (as shown in **Figure 3**). On the other hand, we observed that the alteration in CMT features was not significantly modulated by any of the appraised factors, suggesting that baseline characteristics and the number of injections did not independently and solely predict CMT decrease (**Table 4**).

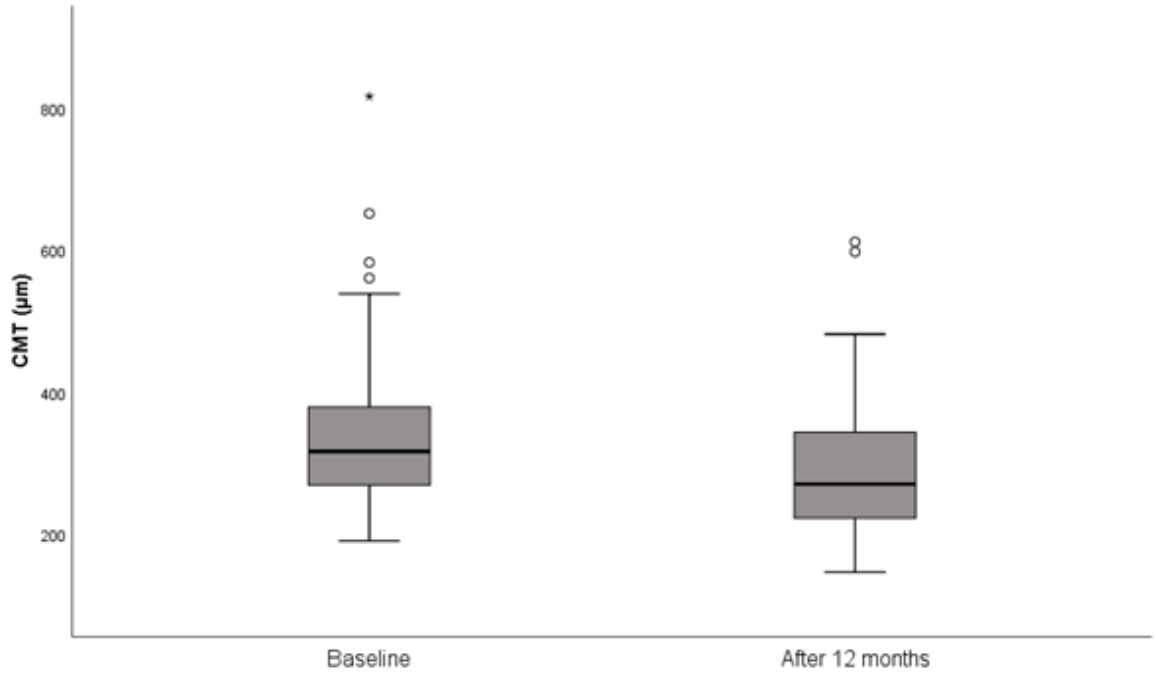
Table 4. Assessment of central macular thickness (CMT) following 12-months pharmacological treatment in accordance with gender, age, comorbidities, the number of visits to ophthalmological care and total number of injections

Variables	Δ CMT (following 12 months of pharmacological intervention)			
	n	Median (IQR P25-P75)	Range Minimum-Maximum	p-value
Age of all eyes (in years; rho)	99	-0,014	-	0,893
Gender of all eyes				
Female	58	-35 (-109; 24)	-470; 279	0,686
Male	41	-30 (-124; 19)	-366; 133	
Diabetes Mellitus				
No	77	-34 (-104; 13)	-470; 133	0,615
Yes	22	-1 (-158; 73)	-356; 279	
Hypertension				
No	29	-21 (-109; 8)	-366; 111	0,783
Yes	70	-37 (-112; 31)	-470; 279	
Active Smoker				
No	87	-37 (-122; 31)	-470; 279	0,252
Yes	11	8 (-21; 13)	-133; 80	
Total number of injections (rho)	99	-0,087	0,499	
Number of visits (rho)	99	-0,083	0,412	

Legend: Teste de Mann-Whitney; rho = Spearman Correlation

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Figure 3. Comparison of Central Macular Thickness (CMT).



Factors Associated with Visual and Anatomical Outcomes

Based on the multiple variables evaluated (i.e., age, gender, comorbidities, number of visits to ophthalmological care, and the total number of injections received), we observed that the number of visits was the only modulator significantly correlated with VA improvement (p = 0.008), as shown in **Table 5**. Included individuals who presented VA enhancement attended a median of ten visits (SD of 2,7), compared to eight visits (SD of 2,5) among those individuals who presented worsening VA patterns. Additionally, those individuals who remained with a stable VA after the pharmacological intervention presented median of 9 (SD of 2,5).

Table 5. Assessment of visual acuity (VA) after one year of treatment according to sex, age, presence of hypertension (HAS), diabetes mellitus (DM), smoking, number of visits and number of injections

Variables	AV Status After 12 months of Pharmacological Intervention			
	Clinical Improvement n = 41	Clinical Deterioration n = 32	Clinically Unchanged n = 26	p-value
Age				
Mean (SD)	75,22 (9,0)	76,41(9,4)	75,69 (10,0)	0,868a
Number of Visits				
Mean (SD)	10 (2,7)	8 (2,5)	9 (2,5)	0,008a
Number of Injections				
Mean (SD)	5 (2,3)	5 (2,0)	5 (2,6)	0,455a
Gender				
Female	25 (61%)	17 (53,1%)	16 (61,5%)	0,747b
Male	16 (39%)	15 (46,9%)	10 (38,5%)	
Diabetes Mellitus				
No	35 (85,4%)	23 (71,9%)	19 (73,1%)	0,310b
Yes	6 (14,6%)	9 (28,1%)	7 (26,9%)	
Hypertension				
No	13 (31,7%)	9 (28,1%)	7 (26,9%)	0,902b
Yes	28 (68,3%)	23 (71,9%)	19 (73,1%)	
Active Smoker				
No	36 (90%)	29 (90,6%)	22 (84,6%)	0,778b
Yes	4 (10%)	3 (9,4%)	4 (15,4%)	

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Association of Baseline OCT-based Anatomical Parameters with VA Outcomes

Initially, we examined the relationship between four OCT-derived anatomical parameters found at baseline and VA-related outcomes at the latest endpoint in our study (12 months), as reported in **Table 6**. Shortly, our findings suggested that ICS were associated with worse visual outcomes (p = 0.016), specifically with 65.6% of enrolled eyes reported experiencing a reduction in VA. However, no association was observed between the presence of SRF (p = 0.892), PED (p = 0.451), or tubulation (p = 0.260) and visual outcomes.

Table 6. Baseline biomarker assessment according to visual acuity status after 1 year of treatment

Biomarker	Status Assessment / Visual Acuity (n = 99)			
	Improved n = 41 (41,4%)	Worsened n = 32 (32,3%)	Remained Unchanged n = 26 (26,3%)	p-value
	n (%)			
Subretinal Fluid (SRF)				
Yes	32 (78%)	24 (75%)	19 (73,1%)	0,892
No	9 (22%)	8 (25%)	7 (26,9%)	
Intraretinal Cystoid Spaces (ICS)				
Yes	19 (46,3%)	21 (65,6%)	21 (80,8%)	0,016
No	22 (53,7%)	11 (34,4%)	5 (19,2%)	
Pigment Epithelial Detachment (PED)				
Yes	3 (7,3%)	2 (6,3%)	4 (15,4%)	0,451
No	38 (92,7%)	30 (93,8%)	22 (84,6%)	
Retinal Tubulation				
Yes	1 (2,4%)	1 (3,1%)	3 (11,5%)	0,260
No	40 (97,6%)	31 (96,9%)	23 (88,5%)	

*Chi-square (x2) with Monte Carlo Simulation

Safety Outcomes

The patient's electronic medical records evaluated did not report any minor or serious adverse event or complication following the intravitreal injection of bevacizumab in our patients.

DISCUSSION

The sample, composed mainly of women with a median advanced age (75 years), reflects the typical profile of patients with age-related macular degeneration. The prevalence of systemic arterial hypertension (SAH) and diabetes mellitus (DM), at 69.7% and 21.3%, respectively, is also consistent with the most prevalent comorbidities in the age group studied. It is important to note that a limiting factor in this study is the lack of information in some medical records, which may have influenced the observed prevalence of comorbidities and smoking. The limited information on smoking is noteworthy, given that the relationship between the exudative form of AMD and smoking is already well established.[31]

Our data suggested the potential influence of OCT-derived anatomical findings on VA improvement. According to our results the presence of ICS at baseline might be negatively correlated with VA improvement among included patients, based on the higher prevalence of ICS among individuals experiencing VA deterioration (p-value = 0.016). On this way, we reinforce findings from previous literature highlighting that ICS indicates a chronic state of retinal pathology and emphasizes the relevance of OCT-based anatomical assessments as a prognostic mechanism. Multiple primary studies have reported similar findings evidencing the negative correlation of ICS with VA improvement and several hypotheses might be listed.[32] First, the chronic degeneration of photoreceptors or the potential disruption of neural signaling in the retina and surrounding structures might directly reflect the presence of ICS among included patients (mostly older patients), which might lead to poorer visual outcomes.[32-34] Additionally, it has been well described that persistent cystoid spaces in the retina may cause mechanical stress, harming the structure, and interfering with retinal function, which combined, hinder the recovery of damaged structured even following the pharmacological treatment.[32-34] Likewise, another potential explanation for the identified findings relies on the fact that ICS typically result from chronically leakage from non-totally functional blood vessels (abnormal vessels), which may cause further events such as intracellular edema.[32-34]. Thus, the persistent fluid backlog within retinal layers potentially correlate

with higher disease burden, decreasing the probability of VA improvement despite the utilization of bevacizumab.

Some authors has reiterated the relevance of RT in cellular reorganization as a response to long-term chronic degeneration. Combined, these factors might contribute to VA improvement in some patients even when RT is present. Additionally, it has described that the development of RT in advanced n-ARMD might suggest an alteration from active degeneration towards a more stable phase (where photoreceptor apoptosis slows down).[35-36] On the other hand, the presence of subretinal fluid, although the most prevalent anatomical finding in this study, did not show a significant association with VA, supporting studies that have already indicated that SRF is not always related to visual prognosis. The FLUID study demonstrated that patients can tolerate a certain amount of SRF without visual impairment. [37,38] In both cases of the relevance of OCT-based anatomical findings previously presented, our findings reinforce the clinical application of OCT-based anatomical results in order to individualize and optimize therapeutical strategies and protocols for n-ARMD patients. [35-36]

Considering the 12 months of follow-up established in our study, we observed that most enrolled patients either improved their VA (n = 41.4%) or maintained their VA stable (n = 26.3%). Several reports published in the body of literature that emphasized that baseline VA outcomes have been demonstrated as a relevant predictor of visual outcomes and provide solid evidence for justifying its utilization in clinical practice.[39–41] It is worthwhile mentioning that eye care and services, including the assessments of VA measures, might be useful not only as a prediction outcome but also support individualized management strategies for patients diagnosed with n-ARMD eligible for anti-VEGF pharmacological therapies. This result reinforces the relevance of initial VA assessments in the hall of procedures utilized in routine ophthalmological care, as this examination is an easy to be performed, cost-effective, based on a non-invasive nature, which, overall, promote early intervention planning and has the potential to identify several eye-related diseases and conditions. We also reiterate another relevant factor that might be applicable to our study findings, particularly related to potential individual variability within our enrolled patients, suggesting that close monitoring and further protocol adaptations of therapeutical regimens are needed and must be anchored on real-time visual performance executed at each follow-up visit – this way the integration of VA metrics into routine care will no solely be used as a prognostic measure but also serve as a critical system in personalizing care.

Our retrospective study showed a significant reduction in CMT, with median CMT reduction from baseline (median of 317 µm) to 271 µm after 12 months of follow up (Δ = 46 µm, $p < 0.001$). Perhaps, for future clinical trials, it might be critical to design studies considering baseline characteristics of eligible patients in terms of anatomical features (e.g., CMT) in order to optimize therapeutical protocols and combination of treatments, instead of utilizing the commonly used "one-size-fits-all" methodology.[45] Interestingly, over the last number of years, the discussion on how to properly integrate CMT findings with functional visual outcomes has gained notoriety in Ophthalmology (i.e., how anatomical improvements or deterioration is related to visual gain or loss).[46-47] Notwithstanding the fact that CMT reduction reflect a positive anatomical response to the delivered treatment, existing evidence have suggested that CMT and VA improvements are not strictly correlated. For instance, studies have found that the presence of ICS in some individuals might interfere in proper visual gains, despite CMT normalization, due to reported chronic retinal disruption.[48-49] Thus, we remarkably flag our findings suggesting that CMT evaluations standalone may be clinically insufficient to predict visual recovery for those patients undergoing anti-VEGF treatment. We strongly advice that alternative testing, including functional tests (i.e., VA measurements, and retinal evaluation) are essential in defining the general eye health among patients with n-ARMD. As far as functional outcomes are concerned, the number of ophthalmological visits was shown as a fundamental factor of VA enhancement, regardless of the number of intravitreal anti-VEGF administrations. Our data show very clearly that those patients who demonstrated enhancement in VA attended a median of 10 medical appointments (p-value = 0.008) in comparison with those patients with worst or stable visual statuses. These results emphasizes that a closer follow-up interval and constant medical relationship might be a relevant factor in guarantying better treatment compliance and better timing for retreatment (or the intravitreal administration of the anti-VEGF drug per se). Therefore, our study, underscores the fact that a successful pharmacological treatment for n-ARMD not only depend on the pharmacological regimen utilized (i.e., PRN or treat and extend protocols), but also on patient's engagement and frequency of monitoring their conditions. We highly emphasize the importance of standardized and structured follow-up schedules, that augment therapeutic outcomes by permitting timely re-intervention.

Our study has several strengths. First, we utilized data from real-world data, including patients from a realistic cohort, collecting center, which is typically not a reality from highly controlled clinical trials in ophthalmology. Additionally, the use of multiple OCT-derived anatomical findings allowed a detailed understanding of anatomical predictors, potentially supporting personalized treatment strategies in the future. Nevertheless, we acknowledge limitations related to our study, including its retrospective design (hindering causal inferences assumptions) and the high variability in our enrolled patients, which may have influenced the results

and models performed. Future studies must be prospective clinical trials, based on proper allocation and randomization of patients, in order to validate our observed findings in real-world populations.

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