Effectiveness of treatment of exudative age-related macular degeneration with anti-vascular endothelial growth factor drugs

Efetividade do tratamento da doença macular relacionada à idade exsudativa com drogas antifactor de crescimento endotelial vascular

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ABSTRACT

Objective: To characterize the effectiveness of anti-vascular endothelial growth factor drugs in exudative age-related macular degeneration.

Methods: Retrospective longitudinal study of 54 patients with age-related macular degeneration receiving bevacizumab or aflibercept. Demographic data, visual acuity, and central retinal thickness measurements were collected. Improvement/stability of visual acuity and reduction in retinal thickness configured satisfactory responses.

Results: Among the 60 eyes studied, there was no difference (p = 0.262) in satisfactory response when using bevacizumab (48.5%) or aflibercept (63.0%). Snellen's visual acuity, letter gain, and retinal thickness showed improvement or maintenance in 55.0%, 32.8%, and 78.3% of cases, respectively. The percentage of improvement/maintenance was higher in eyes with an initial visual acuity of < Snellen 20/400 (70.0% versus 40.0%; p = 0.002).

Conclusion: A higher percentage of improvement/stabilization of visual acuity and macular thickness was observed in patients with age-related macular degeneration, with better response in patients with visual acuity worse than Snellen 20/400.

RESUMO

Objetivo: Caracterizar a efetividade de medicamentos antifactor de crescimento endotelial vascular na degeneração macular relacionada à idade exsudativa.

Métodos: Estudo longitudinal retrospectivo em 54 pacientes com degeneração macular relacionada à idade que usaram bevacizumab ou aflibercept. Foram coletados dados demográficos, da acuidade visual e da espessura central da retina. Melhora/estabilidade da acuidade visual e redução da espessura configuraram respostas satisfatórias.

Resultados: Entre 60 olhos estudados, não houve diferença (p = 0,262) de acordo com o uso de bevacizumab (48,5%) ou aflibercept (63,0%). Acuidade visual segundo Snellen, ganho de letras e espessura retiniana demonstraram melhora ou estabilidade em 55,0%, 32,8% e 78,3% dos casos, respectivamente. Entre os olhos com acuidade visual inicial < 20/400, o percentual de melhora/estabilidade foi superior (70,0% *versus* 40,0%; p = 0,002).

Conclusão: Em pacientes com degeneração macular relacionada à idade, foi percebida uma maior proporção de melhora ou estabilização da acuidade visual e espessura macular, com melhor resposta entre os pacientes com visão pior que 20/400.

INTRODUCTION

Age-related macular degeneration (AMD) is a degenerative and progressive disease that affects the central area of the retina (macula) and often leads to impaired central vision. The exudative subtype results in the formation of a neovascular membrane (NRVM), which is responsible for approximately 90% of the cases of blindness, defined as visual acuity (VA) of 20/200 or less.[1,2] In Brazil, the prevalence is estimated at 2.2% in people aged 70 to 79 years and up to 10.3% in people over 80 years old.[3]

Although the pathophysiology of AMD is not yet fully understood, it is thought to be associated with oxidative stress, changes in choroidal blood flow, degeneration of Bruch's membrane and chronic inflammation leading to a loss of local homeostasis.[1] The imbalance between pro-inflammatory and angiogenic factors leads to the formation of drusen, changes in the retinal pigment epithelium (RPE), and the development of neovascular membranes. The most important mediator in the pathophysiology of this disease is the vascular endothelial growth factor A (VEGF-A). The extravasation of plasma contents into different layers of the retina leads to neuronal damage and the formation of a subretinal scar.[1,2]

There is currently only a treatment for exudative AMD that potentially improves vision. It is based on the administration of drugs into the vitreous cavity that block the activity of VEGF-A and thus inhibit vascular permeability and angiogenesis.[1,2]

A systematic review of 5,496 participants from 12 clinical trials randomized to anti-VEGF drugs or control therapy showed the occurrence of morphological changes in the process of choroidal neovascularization, including a decrease in central retinal thickness measured by optical coherence tomography (OCT).[4] Among the randomized clinical trials (RCTs) included, the ABC trial study found a gain in VA of 15 or more letters in 21 (32%) patients treated with anti-VEGF drugs, compared to only 2 (3.0%) individuals in the control group.[4] In addition, the proportion of patients who lost less than 15 letters of VA was significantly higher with anti-VEGF therapy than with standard therapy (91% and 67%, respectively). The average VA increased by seven letters with an average of seven anti-VEGF injections, while the VA in the control group decreased by about 9.4 letters.[5]

Although data obtained in RCTs remain the gold standard in demonstrating efficacy, the conditions under which anti-VEGF is used in the real world (effectiveness) generally differ from the situations encountered in clinical trials and may lead to different results. In fact, of the 308 intravitreal injections administered to patients with AMD in a study conducted by Costa et al., only 25% of individuals showed documented improvement in VA.[6] In 36% of cases, the analysis was inconclusive as VA data was sparse in the medical records, and 39% showed worsening or maintenance of VA.[6]

A multicenter cohort investigated the long-term results of anti-VEGF therapy in participants in large RCTs.[7-9] Approximately 7.0 years after the injections were administered, the number of letters increased or remained stable in 43% of the eyes, while 34% showed a deterioration of 15 letters or more (mean reduction of 8.6 letters; $p < 0.005$). In 98% of the eyes, autofluorescence imaging revealed macular atrophy with an average area of 9.4 mm, which correlated with poorer visual outcomes ($p < 0.001$).[10]

In Brazil, the treatment of AMD with aflibercept has been approved in the Unified Health System (SUS, Sistema Único de Saúde) since 2018.[11] Therefore, given the historical and known regional inequality in our country, it is important to know real world data about what has happened with this treatment in different referral services in Brazil.[11]

Therefore, this study aims to characterize the use of anti-VEGF drugs and evaluate treatment outcomes in patients treated in a reference service for AMD treatment in northeastern Brazil. This situation represents the conditions of daily clinical practice in a real population, that is, in real conditions of access to services and health care in a public teaching hospital that provides services to the SUS.

METHODS

Study design, population, and location

A retrospective cohort study was conducted, which was reviewed and approved by the Ethics Committee for Research of the Escola Bahiana de Medicina e Saúde Pública under protocol number 5.612.114/2022. The exposure was the use of anti-VEGF drugs, in this case treatment with bevacizumab or aflibercept, the latter being the treatment of choice of the Brazilian Ministry of Health.[12] The outcomes studied were therapeutic effectiveness data measured by VA and macular thickness on OCT.

The target population of the study consisted of patients diagnosed with exudative AMD, according to the consensus of the Brazilian Ministry of Health.[13] We included those who were treated with the antiangiogenic drug bevacizumab or aflibercept between October 2014 and August 2021 at the Humberto Castro Lima Hospital (HHCL), a reference ophthalmology institution in Bahia, in northeastern Brazil. Those who had used bevacizumab

or aflibercept at other institutions, who had interrupted or discontinued treatment without medical advice, and patients who had used drugs for the treatment of retinal diseases other than bevacizumab or aflibercept, who had not completed the initial three-dose regimen, or whose data were incomplete were excluded. In addition, participants classified with grade 4 and 5 visual impairment according to the First Consensus of the Brazilian Society of Visual Impairment[14] were excluded.

Routine care and procedures for the use of anti-vascular endothelial growth factor

Patients attending the HHCL Retina Clinic are assessed by their medical records and VA testing with correction, slit lamp biomicroscopy, tonometry, and retinal mapping. If they are diagnosed with exudative AMD, they undergo OCT of the macula using the Cirrus HD-OCT 4000 device with spectral domain technology and are referred for intravitreal injection of anti-angiogenic drugs.

The anti-angiogenic injection is performed in the operating rooms of the HHCL by an ophthalmologist specialized in the retina. After the injection, the patient is observed for 60 minutes and, if there are no adverse reactions, the patient is discharged from the hospital. If the patient has any adverse effects, they will continue to be observed by the anesthesia team until they can be safely discharged. The patient will be instructed to take antibiotic eye drops containing moxifloxacin every 6 hours for 7 days and to return for a re-examination the day after the procedure.[15]

During this first postoperative examination, a medical history and a biomicroscopic examination of the eye are performed. The patient is given comprehensive instructions, and an appointment is scheduled for the second application of the medication, one month after the first one. The patient is advised to come back sooner if there are complications in the eye. Two further applications are carried out with an interval of 30 days. Thirty days after the last application, a VA test and an OCT of the macula are performed. After these tests, the retinologist assesses the therapeutic response and whether a new cycle of injections is required.

In HHCL, the *Pro Re Nata* (PRN) method is used, in which the patient receives an initial load of three-month applications, followed by regular monitoring and the resumption of a new cycle of three applications if disease activity is detected. There is also the treat and understand (TE) method, in which monthly applications are carried out until the disease has stabilized. Then, the application intervals are extended, reducing the need for monthly visits. This approach is not used for HHCL.

Data collection and operationalization procedures

For data collection, we used clinical information from the medical records of participants who had undergone treatment for AMD according to the above-mentioned inclusion and exclusion criteria. All requested data were recorded in an electronic worksheet.

The demographic data collected were age (in years), gender (male/female) and place of residence. Data were collected on patients' medical records, such as the presence of comorbidities, previous ophthalmologic treatments, use of ophthalmologic medications, and information on access to treatment, such as waiting time for antiangiogenic injection and whether it was obtained through the justice system.

The variables gender, place of residence, affected eye, type of medication used and presence of comorbidities were classified as categorical variables. The variables classified as quantitative were age, number of applications of the anti-VEGF drug, retinal thickness, and VA. The following variables were used to perform the effectiveness analysis and measure the results: VA measured by the ophthalmologist during the consultation based on the Snellen scale and LogMar, letter gain, and central retinal thickness measured by OCT. The measurement of VA on the Snellen scale was converted to letters according to the formula proposed by Gregori et al. of the Early Treatment Diabetic Retinopathy Study (ETDRS).[16] This form of measurement was used because the data obtained are easier to analyze compared to the measurement of fractions on the Snellen scale.

In the service studied, VA under 20/400 is measured using the counting fingers (CF) and hand movement (HM) method. Counting fingers was graded in meters, measured as the distance between the examiner and the patient, including the following categories: CF near face (20/2000), CF at 5 m (20/800), CF at 4 m (20/600), CF at 3 m (20/800), CF at 2 m (20/1000), CF at 1 m (20/1200).

The classification proposed by the Consensus of the Brazilian Society for Low Vision was used.[14] Participants with VA between 20/70 and 20/1200 were classified into three categories according to the degree of visual impairment (Figure 1), including mild visual impairment (≥ 20/70), moderate visual impairment (< 20/63 and ≥ 20/200), severe visual impairment (< 20/200 and ≥ 20/400), and blindness, category 3 (< 20/400 and ≥ 20/1200).

Visual acuity Categories	Less than	Equal to or greater than
Mild disability or no visual impairment 0		6/18 3/10 (0.3) 20/70
Moderate visual impairment 1	6/19 3.2/10 (0.3) 20/63	6/60 1/10 (0.1) 20/200
Severe visual impairment 2	6/30 1/10 (0.1) 20/200	3/60 1/20 (0.05) 20/400
Blindness 3	3/60 1/20 (0.05) 20/400	1/60 1/50 (0.02) 5/300 (20/1200)
Blindness 4	1/60 1/50 (0.02) 5/300 (20/1200)	Light perception
Blindness 5	Light perception	
9	Undetermined or unspecified	

Source: Translated from Haddad et al.[14]

Figure 1. Classification of degrees of visual impairment.

The OCT measurements of VA and macular thickness taken before treatment and at the last visit as part of the series of appointments were used to analyze efficacy. The number of injections and duration of use were compared between the two types of anti-VEGF drugs analyzed. A gain in letters, an increase in VA on the Snellen, LogMar scales, and a reduction in central retinal thickness were considered to be improvement in VA. The information obtained was described for each eye examined. Thus, if a patient had both eyes treated, the analysis was performed independently for each eye.

Data analysis

Data were expressed as mean (standard deviation [SD]) or median (25^{th} – 75^{th}), maximum and minimum values for quantitative variables, where applicable. Categorical variables were analyzed using simple and relative frequency. Comparisons of proportions and means between two variables were performed using the chi-square test or Fisher's exact test, where applicable, and the t-test or Mann- Whitney nonparametric test, where applicable.

Visual acuity, letter gain, and retinal thickness before and after application were compared using the paired t-test or the non-parametric Wilcoxon test, where indicated. Effectiveness results were presented based on the change in VA, letter gain, and retinal thickness compared to the start of treatment and the proportion of patients with improvement, worsening, or no change in these variables between the first and last injection of bevacizumab or aflibercept. Satisfactory response was defined as the occurrence of a stable lesion (maintenance of VA) or an improvement in VA.

In addition, effectiveness was analyzed according to the degree of visual impairment at the start of treatment. To compare the groups with more impaired vision (categories 2 and 3) and the groups with less impaired vision (categories 0 and 1), the classifications "worse vision" and "better vision" were assigned respectively.

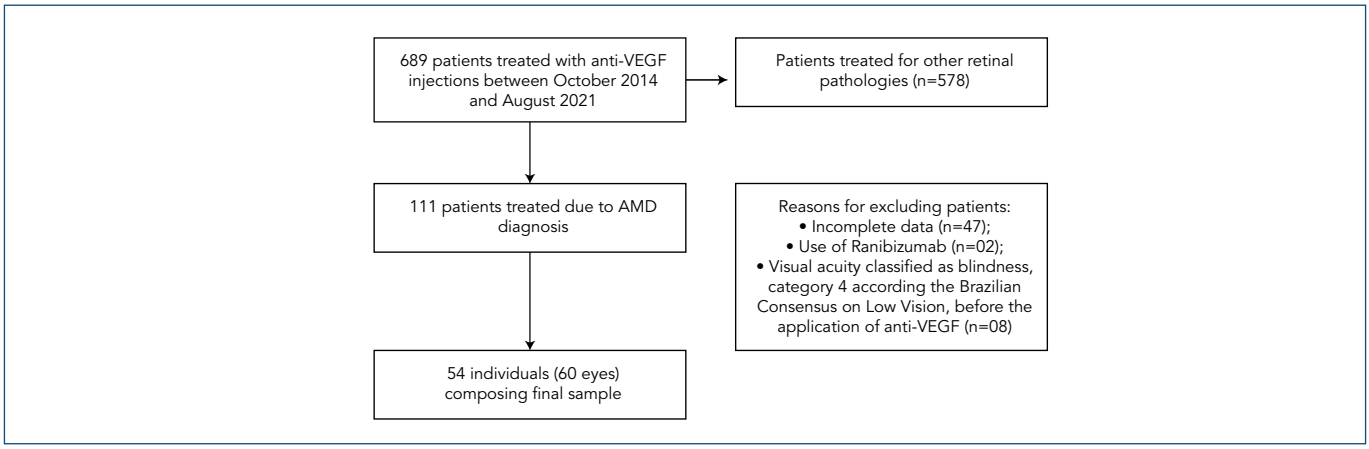
Considering the inclusion of anti-angiogenics in the SUS recommended by CONITEC,[11] the period evaluated in years was divided between before the guideline on anti-VGE treatment in the SUS, Protocolo Clínico e Diretrizes Terapêuticas (PCDT) (2014 to 2018) and after the PCDT (from 2019). The data was analyzed using the statistical software Stata®, version 17.0. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Characterization of the sample studied

A total of 689 patients treated with anti-VEGF injections between October 2014 and August 2021 were identified. Of them, 111 had a diagnosis of AMD (Figure 2). According to the eligibility criteria of the study, those whose data were incomplete (47), who had used ranibizumab (2) and whose VA was classified as category 4 blindness of the Brazilian Low Vision Consensus[14] before anti-VEGF application (8) were excluded. The 54 individuals (60 eyes) that formed the final sample had a mean (SD) age at first anti-VEGF injection of 74.7 (9.4) years, ranging from 44.5 to 93.2 years, and were predominantly female (63.1%; 34/60). All were from Salvador, the state capital, and retirees predominated. Table 1 describes the other clinical characteristics.

Of the 54 patients, 60 eyes were examined, the right eye (RE) in 30 (50.0%) cases. The first intraocular injection was performed at a mean (SD) age of 74.7 (9.4) years, with a median (25^{th}-75^{th}) of 75.7 (68.9 - 81.1) years. The median (25^{th}-75^{th}) time between requesting the drug (prescription) and the first intraocular injection was 123.0 (78.0 - 214.0) days, with a range of 3 to 489 days and a



VEGF: vascular endothelial growth factor; AMD: age-related macular degeneration.

Figure 2. Study sample selection stages.

Table 1. Sociodemographic, medical history and clinical characteristics of the 54 patients with age-related macular degeneration who underwent anti-vascular endothelial growth factor intervention between October 2014 and August 2021

Features	
Sex	
Male	20 (35.9)
Female	34 (64.1)
Age (at first anti-VEFG injection), years old	
Under 60	3 (5.6)
60-70	15 (27.8)
70-80	20 (37.0)
Over 80	16 (29.6)
Economic activity	
Retired	22 (40.7)
Housewife	1 (1.9)
Work activity	4 (7.4)
Not informed	27 (50.0)
Hypertension present	30 (55.6)
DM present	15 (27.8)
Previous pan-retinal photocoagulation	4 (7.4)
Associated ophthalmic changes	
Glaucoma	8 (14.8)
Cataract	20 (40.8)
Use of FACO during treatment	5 (9.3)
Use of eye drops	9 (16.7)
Ocular hypotensive	7 (77.7)
Lubricant	1 (11.1)
Dimethylpolysiloxane	1 (11.1)

Results expressed as n (%).
VEGF: vascular endothelial growth; DM: diabetes mellitus; FACO: phacoemulsification for cataracts.

mean (SD) of 153.0 (121.9) days. There was no difference between the mean (SD) time elapsed between requesting the drug (prescription) and performing the first intraocular injection between the years 2014/2018 and after 2018, when the first PCDT was published (p = 0.276) and there was no correlation between the year of the first anti-VEGF injection and the time elapsed between request and performance (r = -0.054; p = 0.687). Judicialization on the guarantee of the right to use anti-VEFG drugs was not necessary for any of the individuals treated.

The most used drug was bevacizumab, in 55.0% (33/60) of treated eyes, followed by aflibercept, in 45.0% (27/60). After 2018, bevacizumab was the most used anti-VEGF agent (87.5%), while between 2014 and 2018, aflibercept was predominant, with 23 (82.1%) eyes (p<0.001).

On average, ± (SD, 6.4 [4.3]) injections were administered, with a median (25^{th}- 75^{th}) of 5.5 (3.0-8.0) injections, ranging from 3.0 to 22.0 applications. There was no difference (p = 0.109) between the mean ± SD number of injections administered depending on whether bevacizumab (5.6 [3.8] injections) or aflibercept (7.3 [4.7] injections) was used.

Evaluation of the effectiveness of anti-vascular endothelial growth factor drugs using the visual acuity according to Snellen

Visual acuity, measured with the Snellen chart, was characterized before the first application of anti-VEGF, as described in table 2.

Of the 60 eyes examined, 19 eyes (31.6%) showed deterioration, 27 eyes (45.0%) showed stability, and 14 eyes (23.3.0%) showed improvement. Considering the last two results as satisfactory, a total of 68.3% of the eyes with available data showed adequate progress. There was no significant difference between the mean ± SD number of anti-VEGF injections administered between the groups with and without therapeutic response (5.8 [3.7] versus 7.0 [4.8]; p = 0.315), nor in the time elapsed in days between the first and last injection in the groups with and without response (274.3 [317.1] versus 434.8 [514.6]; p = 0.262).

There was a trend towards a better response with worsening VA classification (p_{trend} = 0.062), as described in table 3.

Table 2. Distribution of pre-application visual acuity, according to the Snellen chart, stratified by type of anti-vascular endothelial growth factor (bevacizumab or aflibercept) in 60 eyes with age-related macular degeneration undergoing anti-vascular endothelial growth factor application between October 2014 and August 2021

Visual acuity*	All	Aflibercept	Bevacizumab
Mild disability or no visual impairment (0)	9 (15.0)		
20/30	3 (5.0)	-	3 (100.0)
20/60	1 (1.7)		1 (100.0)
20/70	5 (8.3)	2 (40.0)	3 (60.0)
Moderate visual impairment (1)	21 (35.0)		
20/80	1 (1.7)	-	1 (100.0)
20/100	4 (6.7)	1 (25.0)	3 (75.0)
20/200	16 (26.7)	7 (43.8)	9 (56.2)
Severe visual impairment (2)	3 (5.0)		
20/400	3 (5.0)	-	3 (100.0)
Blindness (3)	27 (45.0)		
20/600	2 (3.3)	1 (50.0)	1 (50.0)
20/800	2 (3.3)	1 (50.0)	1 (50.0)
20/1000	8 (13.3)	4 (50.0)	4 (50.0)
20/1200	15 (25.1)	11 (73.3)	4 (26.7)

Results expressed as n (%).
* Classification according to I Brazilian Consensus on Low Vision.[14]

Of the 27 eyes classified as category 3 blindness, 19 of them (19/27; 70.4%) showed a satisfactory response, either because their VA stabilized (15/27; 55.6%) or improved (8/27; 29.6%). The percentage of improvement/stability was higher in the eyes classified as "worse vision" at baseline than in the eyes with better vision (70.0% versus 40.0%; p = 0.002). Of the 30 eyes with worse vision, 11 had VA greater than 20/400 after treatment (11/30; 36.7%), with 29.6% (8/27) of the eyes categorized as blindness, category 3, having VA of 20/400 or greater and seven of these eyes having VA ≥ 20/200 (Table 3).

There was no difference (p = 0.262) between the percentage of satisfactory response depending on the use of bevacizumab (16/33; 48.5%) or aflibercept (17/27; 63.0%).

Evaluation of the effectiveness of anti-vascular endothelial growth factor drugs according to retinal thickness

Regarding retinal thickness measured by OCT, there was a large loss of data for anti-VEGF assessment prior to therapy, as data were only available for 23 eyes (38.3%). Of these, 18 (78.3%) showed a reduction in thickness, on average ± SD of 142.4 (119.9) μm, representing a therapeutic improvement based on this indicator.

There was consistency in the results in terms of reduction in retinal thickness measured with OCT, regardless of deterioration or improvement/stabilization in 56.5% (13/23) when considering VA measured with the Snellen chart.

All but one eye examined using bevacizumab (91.7%) showed an improvement in retinal thickness, while 63.6% (7/11) of eyes using aflibercept showed an improvement in this parameter (p = 0.155). The presence of "worse vision" at baseline was not associated with a better response in terms of retinal thickness reduction (90.0% versus 69.2%; p = 0.339).

Evaluation of the effectiveness of anti-vascular endothelial growth factor drugs according to letter gain

A letter gain was observed in 20 eyes (87.0%), ranging from 1 to 21 letters. Twelve eyes that received aflibercept injections (44.4%; 12/27) and 8 eyes that received bevacizumab (24.2%; 8/33) showed letter gain (p = 0.302). On average [SD], letter gain was higher in aflibercept-treated eyes (8.2 [5.5] versus 4.2 [4.7]; p = 0.046) than in bevacizumab-treated eyes. No greater mean letter gain was

Table 3. Characterization of the response, measured by the Snellen scale, to treatment with anti-vascular endothelial growth factor in 60 eyes, according to initial visual acuity category, between October 2014 and August 2021

Initial visual acuity*	N(%)	Final visual acuity*				
		Light DV (0)	DV Mod (1)	Severe DV (2)	Blindness (3)	Blindness (4)
Mild disability or no visual impairment (0)	9 (15.0)	3 (33.3)	2 (22.2)	1 (11.1)	3 (33.3)	0
20/30	3 (5.0)	2 (66.7)	-	1 (33.3)	-	-
20/60	1 (1.7)	-	1 (100.0)	-	-	-
20/70	5 (8.3)	1 (20.0)	1 (20.0)	-	3 (60.0)	-
Moderate visual impairment (1)	21 (35.0)	5 (23.8)	8 (38.1)	1 (4.8)	6 (28.6)	1 (4.8)
20/80	1 (1.7)	-	1 (100.0)	-	-	-
20/100	4 (6.7)	1 (25.0)	1 (25.0)	-	2 (50.0)	-
20/200	16 (26.7)	4 (25.0)	6 (27.5)	1 (6.25)	4 (25.0)	1 (6.25)
Severe visual impairment (2)	3 (5.0)	1 (33.3)	-	1 (33.3)	1 (33.3)	-
20/400	3 (5.0)	1 (33.3)	-	1 (33.3)	1 (33.3)	-
Blindness (3)	27 (45.0)	2 (7.4)	5 (18.5)	1 (3.7)	15 (55.6)	4 (14.8)
20/600	2 (3.3)	-	-	-	2 (100.0)	-
20/800	2 (3.3)	-	1 (50.0)	-	-	1 (50.0)
20/1000	8 (13.3)	1 (12.5)	1 (12.5)	-	5 (62.5)	1 (12.5)
20/1200	15 (25.0)	1 (6.7)	3 (20.0)	1 (6.67)	8 (52.3)	2 (13.3)

Results expressed as n (%).
* Classification according to I Brazilian Consensus on Low Vision.[14]

observed in those who had poorer vision at baseline (7.5 [6.7] versus 5.6 [4.3]; p = 0.678).

DISCUSSION

This study presents data on the real-world use of anti-VEGF drugs for the treatment of exudative AMD by the SUS in a reference service in Bahia, northeastern Brazil. Sixty eyes of 54 patients treated with bevacizumab or aflibercept were studied. They were predominantly women, people over 60 years of age, and with visual impairment (blindness) up to grade 3. The results analyzed, i.e. VA by Snellen, letter gain, and retinal thickness, showed improvement or stability in 55%, 32.8%, and 78.3% of cases, respectively.

The profile of the individuals comprising the final study sample corresponded to the distribution expected for the disease,[3] except for the higher proportion of eyes with grade 3 visual impairment, as eyes with VA of less than 20/400 are not officially indicated for the use of anti-VEGF by the Brazilian Ministry of Health.[11]

The percentage of therapeutic response varied depending on the outcome assessed. The higher percentage for VA improvement/stability relative to letter gain occurs because, in the study, many eyes with an initial VA of less than 20/400 were observed to have visual improvement that did not affect letter gain.

It should be noted that visual impairment is associated with impaired performance and difficulties in everyday tasks related to vision, affecting the visual, functional, psychological, social, and economic domains. The resulting problems can lead to limitations in performing tasks that require vision in education, work, and leisure, which reduces the quality of life of people with low vision.[17] In Brazil, Roque et al. demonstrated a significant impact on the quality of life of people with AMD, as they found that most scores on The National Eye Institute - Visual Function Questionnaire-25(NEI-VFQ-25) subscale were significantly lower in the AMD group compared to the control group.[18] In this study, the authors also observed in 48 patients with exudative disease treated with anti-VEGF drugs that the mean NEI-VFQ-25 scores improved significantly from baseline to 4-month follow-up in almost all subscales, indicating an impact on the quality of life of these individuals.[18] This improvement in quality of life was accompanied by an improvement in macular thickness on OCT, characterized by a significant mean reduction of 36.74 µm (p = 0.012) from the start of treatment to 4 months afterwards (first cycle of anti-VEGF injections).[18]

Although quality of life was not measured in the present study, as it was a retrospective cohort based on data from medical records, and no gain in letters was observed in individuals with category 3 blindness, the change in VA from, for example, 20/1200 to 20/600 that occurred in some of the eyes studied may improve daily activities and justifies the greater response in VA relative to the gain in letters.

In addition, 78.3% of the eyes showed an improvement in retinal thickness, with a mean ± SD thickness reduction of 142.4 (119.9) µm, the highest response rate among the efficacy endpoints studied. In addition, approximately 44.5% of patients who showed improvement in retinal thickness on OCT had no improvement in VA, which may be explained by retinal atrophy or anatomical changes in the outer layers of the retina.[12,13] This result should be analyzed with caution given the large loss of complete OCT data, which may have led to selection bias.

Although our study did not find a statistically significant difference between the percentage of satisfactory response between aflibercept and ranibizumab, these percentages were more favorable for the use of aflibercept (63.0% versus 48.5%, p = 0.262). Few studies with a comparative analysis approach between the effectiveness of aflibercept and bevacizumab in the treatment of AMD were identified in the literature. Recently, Kanadani et al. studied 131 patients with the exudative form of nAMD. After random selection for the use of bevacizumab, ranibizumab, or aflibercept, they found no statistically significant difference between pre- and post-treatment in the measurement of best-corrected VA by the drug used.[19] This result seems to support the Brazilian PCDT, which recommends the use of the three anti-VEGF for the treatment of nDMA.[20]

It is noteworthy that the average gain in VA observed in our clinical practice was lower than the average gain reported in RCTs, 45 which, however, did not differ from other effectiveness studies. Carrasco et al. conducted a meta-analysis to evaluate the effectiveness and cost-effectiveness of the use of aflibercept in the treatment of AMD.[21] This study found a mean gain of 5.3 letters according to the ETDRS letters, compared with the mean gain of 6.4 letters (median 5.0 letters) found in our study, with the mean number of injections being the same in both studies (7.1 and 7.3, respectively).[21] Moreover, the AQUILA study, conducted in 4 Latin American countries, reported a one-year improvement in mean ± SD letter gain of 5.2 (18.3) in those who had not been treated and 3.1 (15.3) letters in those who had previously been treated with intravitreal aflibercept, which is not different from the improvement observed in the present study.[22]

Real-world effectiveness studies are important to provide data on the effect observed when drugs are used in less controlled settings such as RCTs.[23] Kim et al. conducted real-world studies comparing the outcomes of TE and PRN regimens.[24] Patients treated with TE received more injections than patients treated with PRN and reported better outcomes at 52 weeks.[19,23] The TE regimen with ranibizumab was associated with better outcomes and a lower number of injections. This suggests that the poorer outcomes in real-world studies may be due to the lower number of injections compared to RCTs.[23]

The results of this study could be underestimated because we observed a long waiting time to receive an intravitreal injection in the patients studied. This period without treatment could have been a determining factor for the final VA, since the neovascularization of this pathology progressively damages the photoreceptor layer of the retina. This point emphasizes the need to improve access, which is not only possible by incorporating the drug into the SUS. Studies should be conducted in Brazil to explore a better approach to maximize the effectiveness of anti-VEGF drugs.

The current protocol recommended by the Ministry of Health for the treatment of exudative AMD (PCDT) does not recommend treatment with intravitreal injections of antiangiogenic drugs if VA is below 20/400.[20] Nevertheless, in the present study, we found a better response to the medication in eyes of VA category 3.[14] In addition to a significantly higher percentage of improvement/stability compared to eyes with better baseline vision (70.0% versus 40.0%), a tendency towards better response with worsening of VA classification was observed. These data are consistent with recent studies,[25,26] such as that of Ying et al., who examined predictors of VA five years after starting treatment with ranibizumab or aflibercept.[25] Patients with poorer initial VA had poorer absolute VA values, but a greater proportional gain in VA with treatment.[24] In the cohort conducted by Lovestam et al.[26] comparing the response to aflibercept in patients with different visual acuities, the gain in letters was more pronounced in patients with a baseline VA of ≤ 35 letters (gain of 13.2 ± 18.3-41.0) than in patients with a baseline VA of 36-69 letters (gain of 5.7 ± 14.1-62.7) and ≥ 70 letters (loss of 2.4 ± 11.3-72.3 letters).[26]

The participants in this study with a VA of less than 20/60 are treated in the clinic for the visually impaired at HHCL and receive orientation about mobility as well as on how to use optical aids for distance and near vision. Patients with low vision who gain letters have an increase in functionality depending on the amount of vision gained, but a negligible increase in letters has no impact on their everyday life. This is one possible reason why PCDT contraindicates a costly treatment for a practical benefit that is still uncertain. This calls for new studies with this focus, especially with larger sample sizes, multicenter studies, and longer follow-up periods.

As a limitation of this study, we would like to emphasize the small number of eyes examined, especially for the retinal thickness result, which is due to insufficient data. This low number of patients can be explained by the fact that the study was conducted almost entirely before the Brazilian Government Ordinance Nº 18 of May 7, 2021, which provides aflibercept and ranibizumab for the treatment of AMD in patients over 60 years of age, as well as before the Municipal Ordinance Nº 389 of September 13, 2022, which provides additional financial incentives for ophthalmologic treatments in Salvador. Nevertheless, the population included in the study reflects the reality of access to anti-VEGFs on the SUS health system in Bahia, since the ophthalmology outpatient clinic of the HHCL is a reference unit for the treatment of retinal diseases. The data therefore reflects the real effectiveness of these drugs.

Thus, prospective, multicenter Brazilian studies will be of great importance to obtain data to support the efficacy of bevacizumab and aflibercept and provide further information, including defining the real effectiveness of anti-VEGF treatment for eyes with pre-treatment VA less than 20/400.

CONCLUSION

A higher percentage of improvement/stabilization of visual acuity and macular thickness was observed in patients with age-related macular degeneration. This improvement did not differ from that observed in other effectiveness studies worldwide. However, the effectiveness observed is lower than the results obtained in RCTs. In addition, a better response was observed in patients with visual acuity worse than Snellen 20/400, but this condition is not included in the recommendations for the use of anti-VEGF in Brazil. Since it is possible to improve the life of people with severe visual impairment with anti-VEGF drugs, multicenter studies should be conducted in the Brazilian population with AMD to verify in which conditions the results are better.

AUTHOR'S CONTRIBUTION

Melo RCSL: Project administration, Conceptualization, Writing-Original Draft, Methodology, Investigation,

Visualization; Souza CCS: Conceptualization, Resources, Forma analysis, Writing-Review and Editing; Amorim E; Ledo IC: Investigation, Data collection, Writing-Review; Oliveira DC: Conceptualization, Resources, Investigation, Supervision, Writing-Review; Boa-Sorte N: Conceptualization, Methodology Curation, Data, Formal analysis, Supervision, Writing-Review and Editing.

All authors have approved the final version of the manuscript and are responsible for all aspects of the manuscript, including ensuring its accuracy and integrity.

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