

Retrospective study to assess the impact of ranibizumab 0.5mg in the visual acuity of patients with macular diseases in a real life context

Estudo retrospectivo para avaliar o impacto de ranibizumab 0,5mg na acuidade visual de pacientes com doenças maculares num contexto de vida real

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ABSTRACT

Objective: The primary objective of the study is to evaluate, in a population in the state of Bahia, Brazil, the impact of ranibizumab in best-corrected visual acuity of patients with macular disease and macular edema. **Methods:** This study did a retrospective and observational assessment visual acuity of the group of patients followed at the Professor Edgard Santos University Hospital and Oftalmodiagnose Eye Hospital in 2011 and 2012 in a real life context. **Results:** The impact on sample patients post-treatment demonstrated favorable outcome with an increase in visual acuity of 32%, which means improvement of more than one line in the snellem chart. **Conclusion:** Improvement in visual acuity of this group was observed from baseline to the end of follow up in a real-life context.

Keywords: Macular degeneration/therapy; Retinal neovascularization; Visual acuity; Monoclonal antibodies/therapeutic use

RESUMO

Objetivo: O objetivo principal do estudo é avaliar, em uma população no estado da Bahia, o impacto do ranibizumab na acuidade visual melhor corrigida de pacientes com doença macular e edema macular. **Métodos:** Para isso, fizemos uma avaliação retrospectiva e observacional da acuidade visual do grupo de pacientes seguidos no Hospital Universitário Professor Edgard Santos e Oftalmodiagnose Hospital de Olhos em 2011 e 2012 em um contexto de vida real. **Resultados:** O estudo demonstrou desfecho favorável com aumento da acuidade visual de 32%, o que significa melhora de mais de uma linha no quadro snellem. **Conclusão:** A melhora da acuidade visual desse grupo foi observada desde o início até o final do seguimento em um contexto da vida real.

Descritores: Degenaração macular/terapia; Neovascularização retiniana; Acuidade visual; Anticorpos monoclonais/uso terapêutico

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INTRODUCTION

The macula contains at its center the fovea, the region of the greatest concentration of cones in the human eye, and it is responsible for central and high-resolution vision. The loss or dysfunction of this region, which may occur due to the formation of neovascularization and / or edema, is a major cause of visual loss in the world and leads to a severe loss of a patient's quality of life. Among the maculopathies, we highlight age-related macular degeneration (AMD), diabetic macular edema (DME) and retinal venous occlusions (RVOs). It is estimated that the wet form of AMD, which is more severe and rapidly progressive, afflicts 2.5 million people in the world.^(1,2) Diabetic macular edema affects approximately 7% of diabetic patients, with a 39% associated vision loss.^(3,4) In turn, venous occlusions affect 16 million people in the world, with 520 new cases per million people.⁽⁵⁾ The use of anti-vascular endothelial growth factors (anti-VEGFs) have proven efficacious for the treatment of different macular diseases in several clinical studies. The first controlled trials that demonstrated the efficacy and safety of ranibizumab for the treatment of patients with wet age-related macular degeneration (AMD) were MARINA⁽⁶⁾ and ANCHOR⁽⁷⁾ in 2006. This utilization of anti-VEGF agents changed the natural history of AMD. In Denmark,⁽⁸⁾ there was a 50% reduction in cases of blindness associated with AMD after the approval of ranibizumab. In Israel, this decrease was 51%,⁽⁹⁾ and in Scotland, 59%.⁽¹⁰⁾ These data show the importance of introducing this agent in the treatment of AMD. The anti-VEGF agents also have proven their importance in the treatment of retinal vascular occlusions through controlled studies such as BRAVO and CRUISE.⁽¹¹⁻¹⁴⁾ In diabetic patients, anti-VEGF agents were also important, especially in the control of diabetic macular edema, which is a major cause of decreased vision in this group. Studies such as RISE and RIDE have proven this importance.⁽¹⁵⁾ In clinical practice, we observed the use of these agents in heterogeneous populations and uncontrolled schemes. Some research confirmed the effectiveness of anti-VEGF in a flexible schedule of use, where there is no fixed number of injections.⁽¹⁶⁾ The CATT study showed that treatment according to the patient's need is as effective as a monthly fixed regimen.⁽¹⁷⁾

Despite this information, the epidemiological data on maculopathies and gains that anti-VEGFs have brought to this population are scarce in Brazil.

OBJECTIVES

The objective of the study is to evaluate, in a population in the state of Bahia, the impact of ranibizumab in the best-corrected visual acuity of patients with macular disease and macular edema.

Thus, the aim of this study is to make a retrospective and observational assessment of the impact of ranibizumab use in the visual acuity of the group of patients followed at the Professor Edgard Santos University Hospital and Oftalmodiagnose - Eye Hospital in a real-life context.

The study also aims to :

1. Evaluate the prevalence of the major causes of visual impairment by macular disease in these patients.
2. Describe the demographic characteristics of these patients (age and sex).
3. Determine average injections in patients treated in this context.

METHODS

Study design

This is an observational (noninterventional), retrospective study.

Population

Between the years 2011 and 2012, the Professor Edgard Santos University Hospital was the referral center for the treatment of macular disease in the state of Bahia.

This is a pre- and post-observational (noninterventional), retrospective study, which included patients treated at the Professor Edgard Santos University Hospital, between April 2011 and April 2012, coming from the retina clinic of the Professor Edgard Santos University Hospital and Oftalmodiagnose - Eye Hospital. Pertinent data were retrospectively collected. Age, sex, diagnosis, initial and final visual acuity, and number of injections were evaluated.

In this center, some patients received treatment on a pro re nata regimen (PRN), and some were given the drug in the loading dose, according to the main protocols described for each indication, but the final decisions about treatment were made by the patient's physician. Then, the patients were supposed to be followed monthly with testing of visual acuity, slit lamp and fundus examination.

The accuracy was measured by the Snellen chart, assessing the visual acuity before and after treatment in the population in a real-life context. The measurement was performed, with the same Snellen chart and in the same examination room, by different physicians but in a standardized way.

Fluorescein angiography and optical coherence tomography - OCT were utilized according to the evolution of each patient and the investigator's experience. In cases where macular thickening was seen on OCT or on fundus examination, or active leakage was noted on fluorescein angiography, the indication for injection was made based on the experience of the investigator.

Inclusion criteria

- Patients diagnosed with macular diseases between April 2011 and April 2012, according to the OCT, fluorescein angiography and / or eye exam, received one or more ranibizumab injections with documented follow-up to the end of their treatment.
- Naive patients and those previously treated up to three months before the follow-up period were included.

Exclusion criteria

- Patients with less than one year of follow-up.
- Patients treated with bevacizumab less than 3 months before the study initiation or during the monitoring period.
- Patients treated with intravitreal steroids or photodynamic therapy at any time.
- Assessments
- All data, including demographics, were collected retrospectively from patients' medical records.

Statistical analysis

The mathematical formula used in this study to obtain the final sample was based on the method for determining the sample size of finite populations. The minimum sample calculated was 147 patients. The categorical variables were expressed by absolute and relative frequencies, and the continuous variables were expressed

by central tendency and dispersion measures (median, mean, and standard deviation). Two-tailed tests were performed, and p values of less than 0.05 were considered statistically significant. The equality of the data was verified by the Kolmogorov-Smirnov test. The Wilcoxon signed-rank test for paired samples was used to compare the visual acuity of the same patients at two different time points before and after treatment with ranibizumab. The software Microsoft Excel® and SPSS 20.0 were used for statistical analyses.

RESULTS

A total of 238 patients were screened, and 147 of them were enrolled. The other patients were excluded because they did not have sufficient information in their medical records or did not receive ranibizumab during that period.

The demographic characteristics of the patients, the prevalence of the major causes of visual impairment by macular disease and the average number of injections per patient are shown in table 1.

Table 1

Demographic and clinical characteristics of patients		
Demographic Characteristics		
Sex, 147		
Male	62	42%
Female	85	58%
Age, (years)*		
Average (Standard deviation)	68 (14)	
Median	69	
Age group *140 (%)		
19 to 59 years	28	20%
> 59 years	112	80%
Age group *n (%)		
	19 to 59 years	> 59 years
Male	12 (21%)	45 (79%)
Female	16 (20%)	67 (80%)
Causes n (%)		
AMD	55	37%
DM	45	30%
RVO	22	15%
Others	25	17%
Injections		
Mean (SD) of injections per patient		3.51(2.33)
Median injections per patient		3.00

* Variable with 140 valid patients

* AMD: age-related macular degeneration, DM: diabetes mellitus, RVO: retinal vein occlusion, SD: standard deviation.

Change in visual acuity

The Wilcoxon signed-rank test demonstrated that there was a statistically significant difference in patients' visual acuity (VA) before and after treatment with ranibizumab ($p=0.004$).

The impact on sample patients' posttreatment demonstrated a favorable outcome with an increase in visual acuity of 32% (Figure 1), which corresponds to an improvement of more than one line in the Snellen chart. The graph was plotted on a logarithmic scale, which is useful when the data cover a wide range of values, making the scale easier to view and analyze.

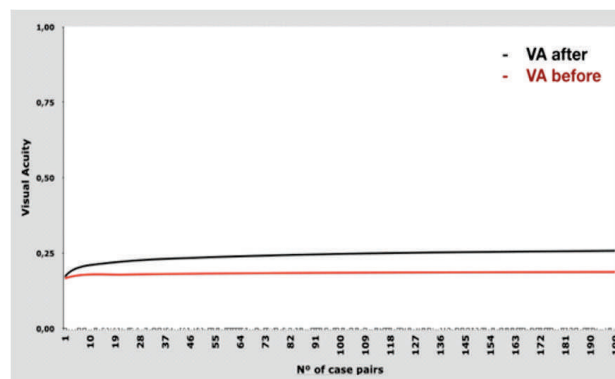


Figure 1: Comparison of visual acuity before and after treatment with ranibizumab

Table 2
Response to treatment by age group

Response	18 to 59 years (%)	> 59 years (%)
Improvement	49	34
Decline	17	21
Unchanged	34	45

DISCUSSION

Patients from Professor Edgard Santos University Hospital and Oftalmodiagnose Eye Hospital who were diagnosed with macular disease and treated with ranibizumab according to standard practice were retrospectively monitored to determine the impact of ranibizumab use in visual acuity, in a real-life context.

In this retrospective study visual acuity improved from baseline initially. Because it is an uncontrolled group, this study has a limitation of the variable follow-up period for each patient. The follow-up period considered was from the beginning of treatment until the patient's last documented visit. The average number of injections that each patient received during his or her entire treatment was lower than what most patients receive in just one year in other countries, in a real-life context.^(12,15,18,19) Consistent with clinical trials, clinical practice studies suggest that maintaining visual gains is related to a greater number of injections.^(20,21) Despite this fact, improvement in visual acuity was observed from baseline to the end of follow-up. This initial change in visual acuity in a real-life context has been previously demonstrated in other observational studies around the world.^(18,19) Some other studies in a real-life context have shown stabilization but no improvement in vision over time.⁽²²⁾ In other groups, improvement was achieved but was not maintained after a longer follow-up period.⁽²³⁾ At the follow-up of the HORIZON study, when patients stopped receiving fixed doses of medication and entered a variable regimen, similar to the real-life context, there was a decrease in visual acuity, which did not recover even if a more rigorous treatment regimen was instituted.⁽²⁴⁾ The number of injections received by each patient was variable, but we should consider this as a typical aspect of the real-life context of the study. The use of an anti-VEGF and the visual results in the real-life regime were evaluated in several countries. The strength of our study is the evaluation of these data in Brazil, where a real-life

context represents not only the immense ethnic diversity of the group but also the difficulty of access to high-cost treatments in developing countries.

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