

Effectiveness and safety of ranibizumab in a university hospital

Eficácia e segurança do ranibizumabe em um hospital universitário

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ABSTRACT

Objectives: To evaluate the effectiveness and safety of ranibizumab in the treatment of retinal diseases in a university hospital. **Methods:** Data from patients treated with ranibizumab were collected through participant interviews and medical records. The main measures of effectiveness were variations in visual acuity (VA) and changes in central retinal thickness (CRT). All adverse events that occurred during treatment were recorded for safety assessment. **Results:** A total of 103 patients, representing 154 eyes, were included in the study. The mean variation in VA was a loss of 0.9 letters on the ETDRS scale, and the mean variation in the CRT was a reduction of 12.6 μm . **Conclusions:** Considering the relatively limited changes in VA and CRT measurements, ranibizumab showed a lower degree of effectiveness in the treatment of neovascular diseases of the retinas. Low quantity and the interval between applications may have contributed significantly to the low effectiveness. The vast majority of adverse events reported were related to the medication application procedure.

Key Words: Effectiveness; Safety; Ranibizumab

RESUMO

Objetivos: avaliar a efetividade e segurança do ranibizumabe no tratamento de doenças da retina em um hospital universitário. **Métodos:** os dados dos pacientes tratados com o medicamento ranibizumabe foram coletados através de entrevista com os participantes e informações obtidas em prontuários médicos, as principais medidas de efetividade foram a variação da acuidade visual (AV) e alterações na espessura central da retina (ECR). Todos os eventos adversos ocorridos durante o tratamento foram registrados para avaliação de segurança. **Resultados:** um total de 103 pacientes foi incluído no estudo, representando 154 olhos. A variação média da AV representou uma perda de 0,9 letra ETDRS e a variação média da ECR encontrada foi de redução de 12,6 μm . **Conclusões:** O ranibizumabe apresentou grau de efetividade inferior no tratamento de doenças neovasculares da retina, devido a pouca variação na AV e nas medidas de ECR nos pacientes tratados. A baixa quantidade e o intervalo entre as aplicações podem ser os fatores que contribuíram significativamente para os baixos resultados de efetividade. A ampla maioria dos eventos adversos relatados foram relacionados ao procedimento de aplicação do medicamento.

Palavras-chave: Efetividade; Segurança; Ranibizumabe

Introduction

Some of the most frequent ocular diseases that cause visual loss are associated with pathological neovascularization of the retina and macular edema. Among these diseases, age-related macular degeneration in the neovascular form (AMD), diabetic retinopathy and diabetic macular edema (DME), and retinal vein occlusion (RVO) are of particular epidemiological importance as the main causes of blindness.¹ In these pathologies, vascular endothelial growth factor (VEGF) plays an important role in mediating damage to the retina.²

Over the past two decades, various drugs specifically targeting VEGF have been developed to treat vascular diseases of the retina. Anti-VEGF drugs work by blocking VEGF, leading to regression of abnormal blood vessels and preventing the formation of new vessels.³ These drugs offer clear clinical benefits in the treatment of these diseases.² Treatment initiation within two months of diagnosis is likely to be more beneficial than treatments initiated later.⁴

Ranibizumab was the first drug to demonstrate not only VA stabilization but also improved vision in about 30% of treated patients. The drug is administered intraocularly with an interval of not less than one month, and should be applied until there is no more disease activity. The monitoring and treatment intervals must be determined by the doctor and must be based on the activity of the disease, which can be assessed in terms of visual acuity and/or anatomical parameters.⁵

Treatment with anti-VEGF is currently recommended as the first-line therapy for AMD, DME, and RVO, to the detriment of photocoagulation and intravitreal corticosteroids, and is the therapeutic option that best preserves and even recovers visual acuity in a considerable percentage of cases.⁶

Although the effectiveness of anti-VEGF therapy has been consistently demonstrated in randomized clinical trials (RCTs), gaps and challenges in the real world can represent significant barriers to achieving treatment goals.⁷ The main outcome measures used in effectiveness studies were the difference in visual acuity and central retinal thickness (CRT) measurements before and after treatment.^{8,9} The occurrence

of adverse events was used as a measure of the safety profile.^{10,11}

Thus, the aim of this study was to evaluate the effectiveness and safety of ranibizumab in patients followed up at a public health service.

Methods

This descriptive, observational, and ambispective study involved the follow-up of a cohort of patients undergoing retinal disease treatment with ranibizumab at the Ophthalmology Outpatient Clinic of the Professor Edgard Santos University Hospital in the city of Salvador, Brazil, from October 2018 to February 2020.

Study participants were interviewed to obtain demographic data and evaluate access to treatment, followed by the collection of clinical information from medical records. The outcome measures were visual acuity, measured on the Snellen scale and converted to Early Treatment Diabetic Retinopathy Study (ETDRS) scale values, and CRT measurements, which were obtained using the Spectralis optical coherence tomography (OCT) device (Heidelberg Engineering, MA, USA), measured before and after the last treatment cycle with ranibizumab. The interval between applications and variations in OCT and VA measurements were evaluated. The unit of data collection to measure the effectiveness was the number of eyes treated. All patients who were undergoing treatment during the research period were invited to participate, having signed the Informed Consent Form.

The safety outcomes evaluated were the incidence of ocular and non-ocular adverse reactions and serious adverse events. An adverse event was defined as any undesirable event that occurs in a patient after administration of ranibizumab, regardless of whether or not it was considered to be related to ranibizumab. Thus, all adverse events (ocular inflammation, increased intraocular pressure, presence of infections, damage to the retina and emergence of cataracts); all causes of death; arterial thrombotic events were considered in this research.

The inclusion criteria for participants were treatment for retinal diseases with ranibizumab and

agreement to participate in the study. Patients who received ranibizumab at other institutions, who interrupted or abandoned treatment without medical advice, and those who received other drugs to treat retinal diseases were excluded from this research. The final observation point was interruption of the treatment by the doctor or the observations recorded in the last application of the ranibizumab use cycle until February 2020.

The data were collected in a form prepared by the researchers, and were later compiled into electronic spreadsheets and analyzed comparatively with data obtained from the main clinical trials evaluating the efficacy of ranibizumab. Descriptive statistics were used to characterize the studied population. Data were summarized as mean, median, standard deviation and maximum and minimum values for quantitative variables. Qualitative variables were studied using frequency and percentage values. The study was approved by the Research Ethics Committee of the Hospital Universitário Professor Edgard Santos according to opinion no. 3.677.719.

Results

A total of 115 patients were invited to participate in this study, of which 12 patients refused to participate. Thus, 103 participants and 154 eyes were assessed in this study. Demographic data are shown in Table 1.

The mean initial VA of the treated patients was 43.5 ETDRS letters and the mean final VA was 42.6 ETDRS letters. The OCT exam was performed on 140 of the 154 treated eyes. The average CRT was 380.6 μm , and the final CRT was 368.0 μm . In stratification based on the letters acquired or lost, loss of VA occurred in 37.3% of the cases evaluated (Table 2).

Treated eyes received an average of 7.3 (SD 3.8) applications in each eye during treatment. The average interval between ranibizumab applications was 55.3 (SD 14.6) days, as shown in Table 3.

Conjunctival hemorrhage was the most commonly detected adverse event (76.5%), followed by pain after application (14.7%). Two endophthalmitis events were observed. There was no significant change in intraocular pressure measurements.

Table 01. Demographic data of the participants collected at the Magalhães Neto Ambulatory between October 2018 and February 2020.

Data	Value	Percentage
Participants	103	100%
Number of Eyes Studied	154	100%
Men	54	52%
Women	49	48%
Mean Age	67,9 ($\pm 10,4$)	
<50 years	4	4%
> 50 < 59 years	16	16%
> 60 < 69 years	33	32%
> 70 < 79 years	37	36%
80 and over	13	13%
Family income		
Less than 1 salary	17	16%
Between 1 and 2 wages	59	57%
Between 2 and 3 wages	15	15%
More than 3 wages	12	12%
Skin Color		
White	17	17%
Black	25	24%
Browns	61	59%
Education		
Elementary	57	55%
High school	34	33%
University education	5	5%
Not Studied	7	7%
Marital Status		
Single	26	25%
Married	50	48%
Divorced	6	6%
unmarried	9	9%
Others	12	12%
Origin		
Salvador and Metropolitan Region	29	28%
Inland	74	72%

Table 02. Variation in VA observed in the eyes studied at the Magalhães Neto Ambulatory between October 2018 and February 2020.

VA Variation	Quantity	Percentage
Gain > 15 letters	31	20,1%
Gain < 15 letters	19	12,4%
No Variation	48	31,2%
Loss < 15 letters	21	13,6%
Loss > 15 letters	35	23,7%
Total	154	100,0%

Comparisons of the data obtained from our study with those from the main RCTs are shown in Table 4, while Table 5 presents comparisons with the main effectiveness studies.

In the analysis of the clinical profile, 49 (47.6%) patients had concomitant diabetes and hypertension, 23 (22.3%) had only diabetes and 21 (20.4%) had only arterial hypertension. The general mean age was 67.8 years, with a higher mean age in patients diagnosed with AMD (73.9 years), followed by those with EMD (68.1 years). The distance to consult retinal specialists was greater than 40 km for 59% of the patients studied.

Discussion

This study was conducted in a purely observational manner and provided a comprehensive overview of the treatment of neovascular diseases of the retina in a public health service under real-world conditions. The main expected outcome of treatment with antiangiogenics for retinal diseases is stabilization or improvement of visual acuity. In this study, the difference in the participants' VA at the beginning and at the end of treatment was used as the main outcome measure. The variation in VA represented a loss of 0.9 ETDRS letters overall, indicating that patients treated for neovascular diseases of the reti-

na achieved stability. The mean change observed in the CRT verified in the OCT exam was a reduction of 12.6 μm , indicating stability in the macular edema of the treated eyes. This last point represents a limitation of antiangiogenic therapy, since the presence of macular edema indicates maintenance of disease activity despite the use of ranibizumab. Table 2 shows the changes in VA according to the variation ranges. The results show that 68.5% of treated eyes did not benefit from antiangiogenic therapy.

The treatment regimen with ranibizumab used was pro re nata (PRN). The average interval between applications of 55.1 days was much longer than that recommended by the manufacturer, which is 30 days, and that observed in RCTs and observational studies. According to Table 3, patients with an application interval of up to 39 days gained 7.8 ETDRS letters. However, patients whose application interval was greater than 50 days showed significantly worse results. The interval between ranibizumab applications may explain the low results in the variation of visual acuity observed in this study.

The information described in the RESOLVE, MARINA and CRYSTAL RCTs contrasts with the data obtained in the present study. When the data are compared by pathology, we observed much lower results than those obtained in the RCTs, as shown in Table 4.

Table 03. Relationship between application interval and variation of OCT and AV observed in the eyes studied at the Magalhães Neto Ambulatory between October 2018 and February 2020.

Interval between applications (days)	Number of eyes	Average VA variation	Average OCT variation
30 to 39 days	16	7,8	-77,5
40 to 49 days	48	6,0	-31,0
50 to 59 days	37	-3,5	13,1
60 to 69 days	37	-6,8	-10,7
70 or more	16	-10,1	41,9

Table 04. Comparison between the data obtained and the main RCTs observed in the eyes studied at the Magalhães Neto Outpatient Clinic between October 2018 and February 2020.

Indicator	RESOLVE (EMD)	Present Study (EMD)	MARINA (DMRI)	Present Study (DMRI)	CRYSTAL (OVR)	Present Study (OVR)
Change in VA (letters)	10,3	-0,1	7,2	-9,4	12,1	1,2
Change in OCT	-194,2	-8,7	-123,0	-24,0	NA	-15,4
Number of applications	10,2	6,9	12	7,1	12	6,6
Interval between applications (days)	30	55,5	30	54,3	30	54,3

The number of injections performed in this study was lower than those performed in the main studies, and the interval between applications was higher than the main studies, which may explain the differences in the results obtained by this study. It is worth mentioning that the strict selection and monitoring criteria carried out in phase III studies allow greater control over the variables studied and over the conduct of treatment.^{12,13,14}

The review by Chong, in which the author summarized the results of 20 real-world studies on the use of ranibizumab for AMD, found that the response to treatment with this drug in clinical practice deviates from the results obtained by RCTs. The main factor pointed out for this difference is the lower number of applications of the drug. In Kim's meta-analysis, which also evaluated articles on the effectiveness of treatment for AMD, ranibizumab was shown to be effective in preventing severe vision loss in actual clinical conditions, but the findings suggested that the frequency of injections may be an important factor for obtaining positive results. The POLARIS study evaluated the use of ranibizumab in clinical practice to treat DME. A gain of 4.4 ETDRS letters in the VA was obtained with an average of 4.9 applications in one year. A similar conclusion was presented by Farinha in their study on the treatment of RVO, where the fewer injections than those reported in the RCTs was considered to be an important factor for obtaining the best VA.^{8,9,15,16}

In this study, the number of applications was close to that reported in other effectiveness studies, but the differences in VA and CRT were much lower (Table 5). These results cannot be explained solely by the reduced number of injections. The interval between applications of ranibizumab was much longer than that observed in observational studies, reinforcing the hypothesis that these data may significantly interfere with therapeutic results.

The average distance between the place of residence of the participants and the place of treatment was 301 km, and this distance was greater than 40 km for 61 patients. Boulanger-Scemama evaluated adherence to treatment with ranibizumab for AMD and observed that the rate of noncompliance with treatment was 57%; of this percentage, 51.7% reported the distance between the residence and

treatment site as the main factor. Non-adherence to treatment was quite significant in patients whose travel distance was greater than 40 km.^{17,18} In the present study, treatment adherence was not evaluated; however, the high distances traveled by patients and caregivers for medical assistance and application of ranibizumab may represent a factor for access to treatment and influence the therapeutic findings.

The information collected for the pathologies treated registered that the majority of participants in this study were treated for DME, followed by RVO. This information reflects the epidemiological profile of the Brazilian population, where diabetes and hypertension, the main causes of DME and RVO, are highly prevalent diseases.¹⁹

In the LUMIERE study, patients who underwent the first application within one month after diagnosis showed better VA results than those who waited more than 30 days.²⁰ In this study, the average interval between diagnosis and the first application was 5.9 months. Patients who received their first injection within 60 days of diagnosis had an average final gain of 2.6 ETDRS letters, while patients who received their first injection 60 days after indication had a loss of 1.8 ETDRS letters. The time between the identification of the need for treatment and the first application is crucial to achieve the best response to treatment. The development of a clinical and therapeutic protocol to assist patients with neovascular diseases of the retina that facilitates access to treatment can reduce the time between diagnosis and the initiation of applications, with important effects on the therapeutic response.

Ranibizumab treatment is well tolerated, since endophthalmitis, the most serious adverse event, occurred in only two of 775 applications of the drug, while the most common event was conjunctival hemorrhage. However, these events are related to the procedure of intraocular injections and not to the medication itself. No vascular events or other events that could be directly related to the drug were found.

Conclusion

The information collected in this study demonstrated that ranibizumab was not effective in the treatment of neovascular diseases of the retina, be-

cause of the minimal changes in VA and CRT in the treated patients. The results obtained were much lower than those observed in RCTs and those revealed by observational studies. In addition to the low number of applications of the drug, the interval between applications may be a factor that contributed significantly to the low improvement in VA. The medication proved to be safe in the clinical practice environment, with few adverse events and most of them related to the procedure.

The observational nature of the study design, which included no specific criteria for patient selection, control over the pathologies treated, and treatment conditions, while being subject to factors related to clinical practice may be a limiting factor in this study. On the other hand, observational studies allow a panoramic view of the functioning of a public health service in the treatment of retinal diseases. The information collected can support the implementation of these services, especially with respect to the inclusion of new technologies to treat retinal diseases.

Although the health unit is a referral center for the treatment of retinal diseases, the data obtained refer only to patients treated at this location, making it necessary to conduct studies in other services in order to obtain data that can corroborate or produce more information on the effectiveness of ranibizumab treatment. Furthermore, the information obtained in this study can support the analysis of new technologies in the Brazilian healthcare system, which can assist in the organization and implementation of healthcare services.

References

1. Brand C. Management of retinal vascular diseases: a patient-centric approach. *Eye*. 2012;26(Suppl 1):S1-S16. Available from: <https://www.nature.com/articles/eye201232> doi: 10.1038/eye.2012.32
2. Ip M, Hendrick A. Retinal vein occlusion review. *Asia-Pacific Journal of Ophthalmology*. 2018;7(1):40-45. Available from: <https://www.sciencedirect.com/science/article/pii/S2162098923004395?via%3Dihub> doi: 10.22608/APO.2017442
3. Solomon SD, et al. Anti-vascular endothelial growth factor for neovascular age-related macular degeneration. *Cochrane Database of Systematic Reviews*. 2019;(3):CD005139. Available from: <https://doi.org/10.1002/14651858.CD005139.pub3>
4. Braithwaite T, et al. Anti-vascular endothelial growth factor for macular oedema secondary to central retinal vein occlusion. *Cochrane Database of Systematic Reviews*. 2014;(5). Available from: <https://doi.org/10.1002/14651858.CD007325.pub3>
5. Virgili G, et al. Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis. *Cochrane Database of Systematic Reviews*. 2018;(6). Available from: <https://doi.org/10.1002/14651858.CD007419.pub7>
6. CONITEC. Relatório de Recomendação: Antiangiogênicos (bevacizumabe e ranibizumabe) no tratamento do edema macular diabético [Internet]. Available from: www.conitec.gov.br.
7. Wykoff CC, et al. Optimizing Anti-VEGF Treatment Outcomes for Patients with Neovascular Age-Related Macular Degeneration. *Journal of Managed Care & Specialty Pharmacy*. 2018;24(2-a Suppl):S3-S15. Available from: <https://doi.org/10.18553/jmcp.2018.24.2-a.s3>
8. Chong V. Ranibizumab for the treatment of wet AMD: a summary of real-world studies. *Eye (Lond)*. 2016 Feb;30(2):270-86. Available from: <https://www.nature.com/articles/eye2015217> doi: 10.1038/eye.2015.217
9. Kim LN, et al. Metaanalysis of real-world outcomes of intravitreal ranibizumab for the treatment of neovascular age-related macular degeneration. *Retina (Philadelphia, Pa.)*. 2016;36(8):1418-31. Available from: https://journals.lww.com/retinajournal/abstract/2016/08000/metaanalysis_of_real_world_outcomes_of.2.aspx doi: 10.1097/IAE.0000000000001142
10. Ziemssen F, et al. Intravitreal Ranibizumab Therapy for Diabetic Macular Edema in Routine Practice: Two-Year Real-Life Data from a Non-interventional, Multicenter Study in Germany. *Diabetes Ther*. 2018;9(6):2271-2289. Available from: <https://link.springer.com/article/10.1007/s13300-018-0513-2> doi: 10.1007/s13300-018-0513-2

11. Ohno-Matsui K, et al. Real-world data on ranibizumab for myopic choroidal neovascularization due to pathologic myopia: results from a post-marketing surveillance in Japan. *Eye (Lond)*. 2018;32(12):1871-1878. Available from: <https://www.nature.com/articles/s41433-018-0192-2> doi: 10.1038/s41433-018-0192-2
12. Kaiser PK, et al. Angiographic and optical coherence tomographic results of the MARINA study of ranibizumab in neovascular age-related macular degeneration. *Ophthalmology*. 2007;114(10):1868-1875. Available from: <https://doi.org/10.1016/j.ophtha.2007.04.030>
13. Larsen M, et al. Sustained Benefits from Ranibizumab for Central Retinal Vein Occlusion with Macular Edema: 24-Month Results of the CRYSTAL Study. *Ophthalmology Retina*. 2018;2:134-142. Available from: <https://www.sciencedirect.com/science/article/pii/S2468653017302105> doi: 10.1016/j.oret.2017.05.016
14. Massin P, et al. Safety and Efficacy of Ranibizumab in Diabetic Macular Edema (RESOLVE Study). *Diabetes Care*. 2010;33:2399-2405. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2963502/> doi:10.2337/dc10-0493
15. Stefanickova J, et al. POLARIS study investigators. A noninterventional study to monitor patients with diabetic macular oedema starting treatment with ranibizumab (POLARIS). *Acta Ophthalmol*. 2018 Dec;96(8):e942-e949. Available from: <https://pubmed.ncbi.nlm.nih.gov/29696809/> doi: 10.1111/aos.13771
16. Farinha C, et al. Ranibizumab for the Treatment of Diabetic Macular Oedema in the Real-World Clinical Setting in Portugal: A Multicentre Study. *Ophthalmologica*. 2019;241(1):1-8. Available from: <https://pubmed.ncbi.nlm.nih.gov/29886497/> doi: 10.1159/000489046
17. Droege KM, et al. Adherence to ranibizumab treatment for neovascular age-related macular degeneration in real life. *Graefes Arch Clin Exp Ophthalmol*. 2013 May;251(5):1281-4. Available from: <https://link.springer.com/article/10.1007/s00417-012-2177-3> 10.1007/s00417-012-2177-3
18. Boulanger-Scemama E, et al. Ranibizumab for exudative age-related macular degeneration: A five year study of adherence to follow-up in a real-life setting. *J Fr Ophthalmol*. 2015 Sep;38(7):620-7. Available from: <https://www.sciencedirect.com/science/article/abs/pii/S0181551215001199?via%3Dihub> doi: 10.1016/j.jfo.2014.11.015
19. Freitas LR, Garcia LP. Evolução da prevalência do diabetes e deste associado à hipertensão arterial no Brasil: análise da Pesquisa Nacional por Amostra de Domicílios, 1998, 2003 e 2008. *Epidemiol. Serv. Saúde*. 2012;21(1):07-19. Available from: <http://scielo.iec.gov.br/pdf/ess/v21n1/v21n1a02.pdf>
20. Cohen SY, et al. LUMIERE Study Group. Changes in visual acuity in patients with wet age-related macular degeneration treated with intravitreal ranibizumab in daily clinical practice: the LUMIERE study. *Retina*. 2013 Mar;33(3):474-81. Available from: <https://pubmed.ncbi.nlm.nih.gov/23266880/> doi: 10.1097/IAE.0b013e31827b6324