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Epidemiological profile of Ranibizumab intravitreal applications

Perfil epidemiológico das aplicações intravítreas de Ranibizumab

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Abstract

The objective of this work is to evaluate the profile of intravitreal applications of Ranibizumab in a population of adults attended at the Benjamin Constant Institute in the year of 2015, taking into account the effect on visual acuity and macular thickness after the treatment. The secondary objective is to present the main indications of this type of treatment in the eye care mentioned above. A retrospective cross-sectional study was performed in individuals over 20 years of age between March and August of 2015 to analyze visual acuity and foveal thickness before and after treatment. The dose of anti-VEGF used was 0.05 ml per application with an interval of four weeks between them. Visual acuity assessment as well as OCT post treatment were performed around 30 days after the last application. Statistical analyses were performed using SPSS software version 21 and the level of statistical significance was of 95% with a value of p <0.05. The study showed that the main condition related to this treatment was non-proliferative diabetic retinopathy associated with macular edema (32.8%). After treatment indicated with Ranibizumab, there was an improvement in the average visual acuity from 0.70 to 0.59 (logMAR) and a regression of the macular thickness, seen in the OCT, from 408.1µm to 337.2µm (p < 0.05). It can be concluded, therefore, that treatment with Ranibizumab in the studied population contributed to a better quality of life of the patients, since most of them presented a statistically significant improvement in the visual acuity after the applications.

Keywords: *Retina; Macular edema; Neovascularization, pathologic; Retinal neovascularization; Observational studies*

Resumo

Objetivo: O objetivo desse trabalho é avaliar o perfil de aplicações intravítreas do Ranibizumab em uma população de adultos atendidos no Instituto Benjamin Constant, no ano de 2015, levando em consideração o efeito sobre a acuidade visual e a espessura macular após tratamento. O objetivo secundário é apresentar as principais indicações desse tipo tratamento no serviço de olhos acima citado. **Métodos:** Foi realizado um estudo retrospectivo seccional, em indivíduos acima de 20 anos entre os meses de março a agosto de 2015, para analisar a acuidade visual e espessura foveal pré e pós tratamento. A dose do anti-VEGF utilizada foi de 0,05ml por aplicação com intervalo de quatro semanas entre elas. A aferição da acuidade visual assim como o OCT pós tratamento foram realizados em torno de trinta dias após a última aplicação. As análises estatísticas foram feitas com uso do software SPSS versão 21 e o nível de significância estatística foi de 95% com um valor de p <0,05. **Resultado:** O estudo mostrou que a principal afecção relacionada a esse tratamento foi a retinopatia diabética não proliferativa associada ao edema macular (32,8%). Após o tratamento indicado com Ranibizumab, houve uma melhora da acuidade visual média de 0,70 para 0,59 (logMAR) e uma regressão da espessura macular, visto no OCT, de 408,1µm para 337,2 µm (valor de p <0,05). **Conclusão:** Pode-se concluir portanto, que o tratamento com Ranibizumab na população estudada contribuiu para uma melhor qualidade de vida dos pacientes, pois a maioria dele apresentou uma melhora estatisticamente significativa na acuidade visual após as aplicações.

Descritores: Retina; Edema macular; Neovascularização patológica; Neovascularização retiniana; Estudo observacional

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Introduction

The use of intra-vitreous antiangiogenic (anti-VEGF) is routine in current ophthalmologic practice, being responsible for the treatment of numerous ocular pathologies. Ranibizumab (LucentisR) inhibits all isoforms of VEGF-A, and because it is a humanized antibody fragment, it readily penetrates the retina.[1]

With increasing life expectancy, age-related macular degeneration (AMD) has been an important cause of decreased visual acuity in individuals older than 50 years. The MARINE and ANCHOR studies showed letter gain, resulting in improved final acuity maintained for up to 12 months in patients with AMD treated with Ranibizumab.[2-4]

Central retinal vein occlusion (CRVO) or central branch retinal vein occlusion (BRVO) are also very common ocular pathologies today. The CRUISE and BRAVO studies showed that the use of Ranibizumab improves not only visual acuity but also macular edema, which can be seen through optical coherence tomography (OCT).[5-7]

Diabetic retinopathy (DR) is still an important cause of irreversible blindness especially in developing countries, and diabetic macular edema is the main cause of reduced visual acuity in these patients. Currently, the most widely used treatment for the management of diabetic macular edema is anti-VEGF. [8]

Ranibizumab's use was approved for all the diseases described above. Studies ensure the sustained improvement of the visual acuity and regression of the retinal alterations. The recommended usage dose of intra-vitreous Ranibizumab ranges from 0.3 to 0.5 mg per application. The interval between them is of 4 weeks.[9]

The objective of the present study is to evaluate the profile of intravitreal applications of Ranibizumab in a population of adults attended at Instituto Benjamin Constant in the year 2015, taking into account the effect on visual acuity and macular thickness after treatment. In addition, the study aims at presenting the main indications of this type of treatment in the eye care service mentioned above.

The present research was previously submitted and approved by the Ethics and Research Committee on Human Beings of Fauldade de Medicina de Valença-RJ.

Methods

Patients with macular edema due to DR or AMD confirmed by fluorescein angiography and macular OCT followed the protocol of a monthly dose of intravitreal injection of 0.05ml (0.5mg) of Ranibizumab for three consecutive months, with an interval of 4 weeks between applications. Patients with neovascularization following proliferative diabetic retinopathy (PDR) or CRVO received only one dose of intravitreal injection of Ranibizumab.

It is important to emphasize that patients with various causes of choroidal neovascularization (angioid streaks, AMD, pathological myopia) who usually had macular edema associated received 3 applications. No patient had application in both eyes the same day. Some patients with DR were treated concomitantly with peripheral photocoagulation.

The variables studied were: Indication of intra-vitreous antiangiogenic use, Age of patients; Improvement of visual acuity after treatment; Regression of macular edema in the OCT - Calculated by means of the difference between the initial and final thickness of the foveal region.

Data was obtained from an institute file separating patients in need of intravitreal injections per week of application. Additional data such as indication of treatment, number of injections recommended, eye affected, gender, age, and pre- and post-treatment visual acuity was taken from the medical records, emphasizing that visual acuity after treatment was assessed approximately 30 days after the last application. The visual acuity was measured with the patient's correction or the super pinhole. In the present study, the central retinal thickness was measured before and after treatment with OCT, facilitating the interpretation of the treatment efficacy by indicating a new need for photocoagulation and/or intravitreal injection. We did not take into account in the study angiographic data before and after treatment with ranibizumab.

Patients with indication of intravitreal injection of ranibizumab without macular edema either by neovascularization or neovascular membrane had their OCTs evaluated. Macular edema was considered as central retinal thickness (foveal thickness) when greater than 250 µm as measured by Spectralis OCT.

The visual acuity was measured through the Snellen table, and later converted into Logmar according to the table of notations used to represent the visual acuity.

The visual functions were classified according to Avila et al. Mild or non-deficient visual impairment was rated as normal vision, and moderate to severe visual impairment was rated as low vision. Avila et al. rank up to 20/70 as normal vision according to the Snellen table, so all values up to 20/60 (0.5 on the logMAR scale) were considered as normal. Moderate to severe visual impairment encompassed visual acuity values worse than 20/70 and better than 20/400, i.e., 20/80 to 20/320 (logMAR 0.6 to 1.2). And blindness was them defined as worse than or equal to 20/400 (<1.3 on the logMAR scale).

For the purpose of statistical analysis, all patients with AV less than 1.3 were rated with VA equal to 1.4 on the logMAR scale. For the descriptive analysis, a frequency measure of simple prevalence type was used, besides the use of measures of central tendency and dispersion (average, standard deviation, median and quartiles). For the comparative analysis, we used the Student-t test for numerical variables, with a significance level of 95% ($p < 0.05$). Statistical analyzes were performed using the software SPSS version 21.

Results

We evaluated a population of 180 people, with 90 being male patients and 90 female patients. The average age of the study population was 65.38 years (SD 10.82). Several retinal pathologies were documented in this study as indications for intravitreal therapy, the main one being NPDR associated to macular edema, followed by PDR with macular edema, comprising 32.8% and 17.8% respectively (Table 1).

Initially, we analyzed 241 eyes regarding visual acuity and 220 eyes regarding OCT, emphasizing that there were patients in the study with only one eye evaluated and others with both eyes. Finally, we finished with 195 eyes evaluated before and after treatment in relation to VA, and 171 eyes evaluated at the initial and final moments of the OCT. The final numbers in relation to the initial

ones presented a reduction due to the losses during the work, such as death and lack of information in the medical record (Table 2).

The average visual acuity before treatment was 0.70, and 0.59 after treatment, in logMAR, with an average improvement of 0.1. On the OCT, the average central retinal thickness before treatment was 408.1 microns, decreasing to 337.2 microns with an average improvement of 70.87 microns, both with a value of $p < 0.05$ (Table 3).

Of the patients analyzed before treatment, most of them were ranked as subnormal according to the visual function and comprising 41% of cases, followed by patients with normal vision in 40% of cases, and 19% blind.

Comparing patients after treatment, 95.77% of patients with normal vision maintained visual acuity, 33.33% of patients with normal vision had improvement for normal vision, and among the blind 25 % changed category going to low vision, although most of them remained blind (Table 4).

Regarding the central retinal thickness, 83% of patients analyzed had macular edema before treatment, and 38 patients (17%) had central retinal thickness of less than 250μm.

Regarding the increase in central retinal thickness, 27.59% of the 145 patients with macular edema evolved with normalization of the central retinal thickness, and the majority of these patients remained with foveal thickness greater than 250 μm, despite the treatment and the statistically significant improvement of the macular thickness. (Table 5)

Table 1
Main diseases with indication of intravitreal therapy in the study population

Indication	N	%
NPDR with ME	59	32.8
PDR with ME	32	17.8
PDR without ME	20	11.1
CRVO/BRVO with ME	20	11.1
AMD with SRNVM and ME	17	9.4
AMD with ME and without SRNVM	7	3.9
Cystoid macular edema after facetomya	5	2.8
Neovascular Glaucoma by PDR	5	2.8
Angioid streaks with SRNVM and ME	5	2.8
Degenerative Myopia with SRNVM and ME	2	1.1
Polypoid vasculopathy with SRNVM and ME	2	1.1
Pseudoviteliform dystrophy with ME	1	0.6
ME with lamellar hole to be clarified	1	0.6
Vitreous hemorrhage to be clarified	1	0.6
Vitelliform maculopathy with ME	1	0.6
Retinal angiomatous proliferation with ME	1	0.6
Chronic Central Serous with ME	1	0.6
Total	**180**	**100**

Table 2
Descriptive evaluation of visual acuity in logMAR and central retinal thickness in microns before and after treatment with Ranibizumab

	Initial Visual Acuity	Post-treatment Visual Acuity	Difference of Visual Acuity (A-P)	Initial Foveal Thickness	Post-treatment foveal Thickness	Difference of Foveal Thickness (A-P)
Valid N	241	195	195	220	174	171
Average	0.672	0.595	0,070	403.56	336.52	70.87
Median	0.800	0.600	0.000	351.50	295.50	41.00
Standard Deviation	0.445	0.478	0,358	178.42	146.97	153.77
Minimum	0.000	0.000	-1.100	153.00	148.00	-362.00
Maximum	1.400	1.400	1.200	954.00	917.0	776.00
Percentile 25	0.200	0.000	0.000	262.25	233.25	0.00
Percentile 50	0.800	0.600	0.000	351.50	295.50	41.00
Percentile 75	1.000	1.000	0.100	522.75	408.00	115.00

Table 3
Pair evaluation of visual acuity in logMAR and central retinal thickness in microns of patients evaluated before and after treatment

Pair Evaluation		N	Average	Standard Deviation	Pair Average	Pair Standard Deviation	95%CI of pairs	P-value
Visual Acuity	***Initial***	195	0.707	0.4463	0.111	0.376	0.058 – 0.164	0.00
	Post-treatment		0.595	0.4784				
Foveal Thickness	***Initial***	171	408.1	175.98	70.87	153.77	47.66 – 94.08	0.00
	Post-treatment		337.23	148.13				

Table 4
Distribution of patients according to their visual function before and after treatment

	Initial Visual Acuity Classification Normal	Initial Visual Acuity Classification Subnormal	Initial Visual Acuity Classification Blindness
Classification of Visual Acuity after Treatment Normal	68 (95.77%)	28 (33.33%)	3 (7.50%)
Classification of Visual Acuity after Treatment Subnormal	1 (1.41%)	44 (52.38%)	10 (25%)
Classification of Visual Acuity after Treatment Blindness	2 (2.82%)	12 (14.29%)	27 (67.50%)
Total	71 (100%)	84 (100%)	40 (100%)

Table 5
Distribution of patients according to the central macular thickness before and after treatment

	Classification of Initial Foveal Thickness Normal	Classification of Initial Foveal Thickness Edema
Classification of Foveal Thickness after Treatment Normal	17 (65.38%)	40 (27.59%)
Classification of Foveal Thickness after Treatment Edema	9 (34.62%)	105 (72.41%)
Total	26 (100%)	145 (100%)

Discussion

Finger et al identified an age group of patients compatible with the one found in our study, in which the majority of patients evaluated was between 65 and 80 years old. [10] Regarding gender, there are wide variations in the studies, in Wang at al work, and most of the patients were male, but according to The Catt Research Group, the majority of patients with AMD were female. [11-12]

The majority of patients had visual acuity stabilization or improvement after use of Ranibizumab. Studies show similar results to that found in the present study, suggesting that the improvement in the VA may be sustained up to the first 4 months of follow-up. [10]

The central retinal thickness also showed regression after treatment with Ranibizumab, presenting in most cases regression of macular edema, maintaining the value of $p < 0.05$. Almeida et. al. studied the regression of macular edema after treatment with Ranibizumab in patients with AMD, showing the improvement of macular edema in mm3.[13] In a study in patients with AMD, Wang et al. showed an average retinal thickness in microns ranging from 492.44 before treatment to 476.31 after treatment. [11]

Our work showed positive results, even if losses occurred, which could have been minimized if there was better documentation of visual acuity and OCT in the medical records after the applications, thus contributing to the increase in the sample number. Another limitation of the study was the reduced follow-up time. Despite the limitations, the results shown are compatible with those found in the literature. The study showed improvement of visual acuity and regression of macular edema through OCT, both with statistical significance.

Our study was carried out in a federal institution in a developing country representing results compatible with "real life", and difficulties related to financial support and family structure should be considered. Studies like ours are important to ratify the importance of intravitreal therapy in the present days since this treatment prevents the disease to evolve with greater severity.

Conclusion

The present study is relevant since we do not find scientific documentation with the evaluation of this demand in the ophthalmological service. It confirms the importance of intravitreous therapy in the present day, because besides being an increasingly accessible and safe treatment, it allows a sustained improvement of the visual acuity and regression of the central retinal thickness, contributing for the maintenance of the usual retinal anatomy and consequently less damage to the cells of the retina, leading to a more effective and lasting control of the retinal pathology and thus helping improve the quality of life of the patients.

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