Evaluation of short-term prognostic factors of ranibizumab in patients with dabetic macular edema

Avaliação de fatores prognósticos a curto prazo com o uso de ranibizumabe em pacientes com edema macular diabético

Tereza Cristina Moreira Kanadani[1], Bruna Stefane Silva Cotta[2], Anna Carollina Cardoso Rezende de Souza[2], Ana Paula de Oliveira Costa[2], Denise Matos Takahashi[2]

Abstract

Purpose: *Study the prognostic factors for short-term visual improvement in pacients treated with ranibizumab (IVR) for diabetic macular edema (DME).* ***Methods:*** *cross-sectional descriptive study in which 41 eletronic medical records of patients who attended in a private medical clinic in Belo Horizonte - Minas Gerais in a period of August / 2016 to May / 2017. It was verified general data and previous history of patients who received consecutive monthly IVR for DME, analyzing sex, age and presence of previous treatment as possible prognostic factors determining the changes in visual acuity measured by the Snellen table after the monthly procedure.* ***Results:*** *In the total sample, 51.2% were female subjects. The mean age was 64.20 ± 7.54 years. Age, previous treatment and gender were not correlated with better visual acuity in any time.* ***Conclusion:*** *The major strategy of DME treatment nowadays is intravitreal injections, which have proved to be an effetive way of visual acuity improvement. However, many patients do not exhibit the expected outcome or are refractory to treatment. Aiming to predict the treatment efficacy in short term - also to provide the patient a reasonable expectation about the outcome - based on prognostic factors, new clinical studies are necessary since there are so few that approach this subject - such an important treatment of a very prevalent disease.*

Keywords: *Macular edema; Diabetic retinopathy; Ranibizumab; Visual acuity; Angiogenesis inhibitor*

Resumo

Objetivo: Investigar fatores prognósticos a curto prazo em pacientes portadores de edema macular diabético (EMD) tratados com injeções intravítreas (IV) de ranibizumabe (RZB). **Métodos:** Estudo descritivo transversal, retrospectivo, analisou-se 41 prontuários de uma clínica privada na cidade de Belo Horizonte - Minas Gerais, do período de agosto de 2016 a maio de 2017. Verificou-se dados gerais e história pregressa de pacientes que receberam IV mensais consecutivas para EMD, investigando-se sexo, idade e presença de tratamento prévio como possíveis fatores prognósticos determinantes nas mudanças na acuidade visual após o procedimento mensal. **Resultados:** No total da amostra, 51,2% eram indivíduos do sexo feminino. A média de idade foi de 64,20 ± 7,54 anos. Não houve associação estatisticamente significativa entre idade, gênero ou realização de tratamento prévio e melhora na acuidade visual. **Conclusão:** A principal estratégia de tratamento para o EMD estabelecida atualmente é através das injeções IV que apresentam eficácia comprovada na melhora da acuidade visual. Entretanto, aproximadamente metade dos pacientes não exibem resposta completa ou são refratários a essa abordagem terapêutica. Nesse sentido, o reconhecimento de fatores prognósticos pode ajudar os oftalmologistas a tomar decisões mais individualizadas, decidindo quais pacientes com EMD responderá às terapias anti-VEGF. Tendo em vista que não há estudos para averiguar os efeitos a curto prazo após injeções IV, no contexto apenas dessa melhora visual, esse trabalho se propôs a avaliar os possíveis fatores prognósticos, que se refletem em uma melhor resposta ao tratamento anti-VEGF, a partir da análise da melhor acuidade visual corrigida, em um contexto real da prática oftalmológica.

Descritores: Edema macular; Retinopatia diabética; Ranibizumabe; Acuidade visual, Inibidores da angiogênese

[1] Faculdade de Ciências Médicas de Minas Gerais, Belo Horizonte, MG, Brazil.
[2] Academic Course in Medicine, Faculdade de Medicina Ciências Médicas de Minas Gerais, Belo Horizonte (MG), Brazil.

The authors declare no conflicts of interests.

Received for publication 07/02/2018 - Accepted for publication 22/03/2018.

Introduction

Diabetic retinopathy (DR) is one of the leading causes of loss of sight, particularly through diabetic macular edema (DME). It is estimated that, after 15 years of disease progression, 80% of patients with type 2 diabetes mellitus (DM) and 97% of type 1 DM have some degree of retinopathy.[1,2] In Brazil, it is estimated that half of the DM patients are affected by DR.[3] With its progressive development, diabetic retinopathy leads to blindness in a large percentage of cases.[4,5] Rigorous glycemic control and blood pressure as well as periodic eye examination are the main factors to prevent the occurrence of DME. Regarding the treatment currently available, we can emphasize laser photocoagulation. However, clinical studies have shown that intravitreal antiangiogens also have efficacy in the treatment of patients with DME.[6]

In DME, the decomposition of the internal hematoretinal barrier causes extravasation of proteins, lipids and fluids in the retina exceeding the kinetics of clearance, causing macular edema and visual damage. Although laser treatment has been a established strategy of care for DME, as the loss of sight decreases compared to untreated patients, the beneficial effect is limited. However, many recent randomized studies have provided evidence that intravitreal (IV) injections can significantly improve the visual acuity of patients with DME, which dramatically changed the strategy to treat this pathology in several ophthalmic centers[7], bringing further improvement since ranibizumab was approved as the first anti-VEGF agent.[8]

Currently, the efficacy of ranibizumab for DME is unquestionable since many studies have indicated a clear validity with its use, including the DRCR.net I, RIDE and RISE, READ 2, RESOLVE, RESTORE and REVEAL protocols.[9-11] Despite the anti-VEGFs are effective in most DME patients, approximately 40% to 50% of patients do not have complete response or are refractory to this therapeutic approach. To date, there are no reliable methods to determine which patients with DME are potentially responsive or non-responsive to anti-VEGF therapy.[12]

The ability to determine which patients with DME will react to intravitreal therapies would help identify patients who need alternative treatment strategies. In this sense, determining the prognosis of patients more accurately can lead to the development of more individualized therapies for patients with DME.[6] It is in this context that the present study delimits its objective when investigating the relation between prognostic factors such as age, gender, age group and previous treatment, and a better response to anti-VEGF treatment based on the analysis of the best corrected visual acuity (BCVA) in a real context of ophthalmological practice.

Methods

A cross-sectional, retrospective study was carried out based on the study of 41 electronic medical records of patients attended in a private clinic in the city of Belo Horizonte - Minas Gerais from August 2016 to May 2017.

According to clinical data and protocols where the treatment was feasible, IV injections were given in a sterile way (0.5 mg/0.05 mL) using a 30 gauge needle. Prior to injection, paracentesis of the anterior chamber was performed using a 27 gauge needle to prevent increased intraocular pressure. Topical antibiotics were prescribed prophylactically for one week after IV injection.

The research was carried out in accordance with resolution 196/96 of Conselho Nacional de Saúde regarding the guidelines and regulatory norms of research involving human beings and approved by the Research Ethics Committee (CEP) for Medical Sciences - MG under the protocol number CAAE 79321917.9.0000.5134.

Due to the specificity of the research (data of medical records), it was not possible to obtain the Informed Consent Form of each patient, but a Term of Commitment was made in the Use of Data.

The analysis of medical records was based on the variables of gender, age group, baseline disease, best visual acuity without correction, date of injection, previous clinical and surgical treatments, especially with anti-VEGF agents. The visual acuity was assessed according to the Snellen table for all patients.

The inclusion criteria were the medical records of adult DME patients aged 45 years or older who used ranibizumab. Those medical records that did not have a confirmed diagnosis or had age-related macular detachment (ARME) and/or other unspecified pathologies, totaling the exclusion of 24 medical records (Figure 1) were excluded.

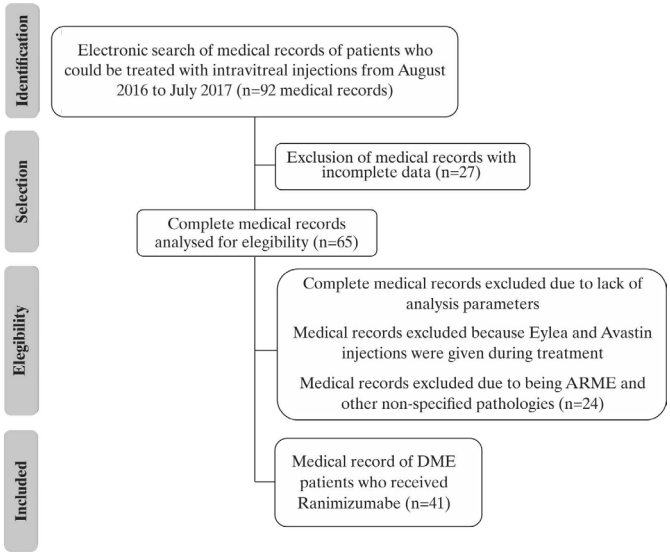

Figure 1: Selection of medical records analysed in the study

Statistical analysis

The categorical variables were presented as counts and percentages, and the numerical ones as average ± standard deviation. The numerical variables were tested for the normality of Shapiro-Wilk. The chi-square test of independence or Fisher's exact test was used to evaluate the association between categorical variables. The analysis was developed in the free program R version 3.3.2, and the significance level adopted was 5%.

Results

The sample comprised 41 MDE patients who had only one ranibizumabe injection, and 51.2% of them were females. The average age was 64.20 ± 7.54 years, and 39% of patients

Table 1
Characterization of patients of the sample

Variable	n=41
Gender	
F	21 (51.2)
M	20 (48.8)
Age†	64.20 ± 7.54
45 to 60 years	16 (39)
61 to 70 years	14 (34.1)
Older than 70 years	11 (26.8)
Applications	
Right eye	33 (80.5)
Left eye	39 (95.1)
Both eyes	31 (75.6)
Previous treatment	4 (9.8)

†Data presented as n (%) and average ± SD

were between 45 and 60 years old. The percentage of patients receiving applications in the right eye was 80.5%; in the left eye it was 95.1%; and in both eyes, 75.6%. Only 9.8% of the patients underwent previous treatment (Table 1).

All appointments had a 30-day interval between them. There was an increase in percentages of improvement in the second and fourth visits in the right eye (57.1% and 60%, respectively), and also among male patients and those aged 61-70 years (Table 2). Regarding the left eye (Table 3), there was a general increase in the percentages of improvement from the second to the fourth appointment among the male patients and among those who had undergone previous treatment. There was no relation between improvement in the visual acuity and gender, nor between VA and age. There was also no statistical correlation between the best VA and previous treatment in none of the eyes.

Table 2
Improvement in the visual acuity according to the general characteristics of the individuals in the right eye

Variable	2nd appointment (n=21) n(%)	3rd appointment (n=20) n(%)	4th appointment (n=15) n(%)
Total	12 (57.1)	10 (50)	9 (60)
Gender			
F	7 (63.6)	8 (66.7)	4 (44.4)
M	5 (50)	2 (25)	5 (83.3)
P-value	0.670F	0,170F	0.287F
Age			
45 to 60 years	4 (66.7)	4 (57.1)	4 (66.7)
61 to 70 years	4 (50)	4 (57.1)	4 (57.1)
Older than 70 years	4 (57.1)	2 (33.3)	1 (50)
P-value	-	-	-
Previous Treatment	-	-	1 (100)
P- value	-	-	-

The improvements were evaluated in relation to the immediately previous appointments. The p-values refer to the following tests: Fisher's Fexate and Oqui-square of independence

Table 3
Improvement in the visual acuity according to the general characteristics of the individuals in the left eye

Variable	2nd appointment (n=26) n(%)	3rd appointment (n=18) n(%)	4th appointment (n=12) n(%)
Total	15 (57.7)	8 (44.4)	7 (58.3)
Gender			
F	7 (50)	5 (55.6)	3 (37.5)
M	8 (66.7)	2 (25)	5 (83.3)
P-value	0.452F	0,63F	-
Age			
45 to 60 years	8 (61.5)	4 (50)	2 (50)
61 to 70 years	5 (62.5)	2 (33.3)	3 (60)
Older than 70 years	2 (40)	2 (50)	2 (66.7)
P-value	-	-	-
Previous Treatment	3(75)	-	1 (100)
P- value	0,614F	-	-

The improvements were evaluated in relation to the immediately previous appointments. The p-values refer to the Oqui-square test of independence and Fisher's Fexate.

Discussion

Although the literature shows good results with the use of ranibizumab for the treatment of DME, not all patients follow this premise. In the clinical practice there are those who give a poor response to this drug. Thus, it is important for the patients to know what to expect regarding the result of the treatment based on the initial condition ant taking into consideration certain variables inherent to each individual. Unfortunately, few studies have attempted to evaluate the prognostic factors involved in visual improvement and anatomical changes after IV for DME, and those who did so evaluated factors associated only to the long-term results of one or two years.[13]

In practice, it makes patients anxious, as they get concerned with not only long-term results, but also they wonder what to expect in the short haul, the weeks after the intervention. The study carried out by Minami et al.[7] showed a significant correlation in the VA change between one day and one month after the application of RZB IV. Thus, it is possible to predict the improvement in the VA one month afterwards by measuring the difference one day after the application. This conduct would then allow patients to know what to expect from the treatment during the first month. Many times, they get frustrated and less available to go on with the treatment because they do not see a clear visual or anatomic improvement. Thus, said factors which may interfere on the result of the treatment were the focus of the present study.

The statistical analysis of the present study showed that there was no association between age and visual acuity improvement, and said result is consistent with the study of Channa et al [14], a long-term study evaluating results after 24 months, which in addition to not showing a relation between age and change in the VA, also stated that patients with worse visual outcome had worse baseline VA.

However, the result found here is different from other data found in the literature. Lai et al. have shown that patients with less advanced age and worse baseline corrected visual acuity (BCVA) tend to have a more significant improvement of visual acuity after three monthly IV injections for MDE.[13] Minami et al. [7] reported that patients with worse baseline VA tend to have a greater increase in visual outcome, although there was no statistically significant relation (p = 0.06) between baseline VA and improvement after one month. The "DRCR.net", RISE and RIDE studies also showed superior improvement in younger patients with poorer BCVA, although such studies have carried out a long-term evaluation. The discrepant improvement observed in these patients can be explained by the "ceiling effect", since those patients with worse BCVA have a greater potential for improvement of visual acuity.[9,10,11] Besides, in comparison with older patients, the macula of younger patients can tolerate better the fluid without losing visual potential. Younger patients treated with ranibizumab showed a good visual gain, as well as a greater visual acuity benefit in the study of MDE treatment carried out by Rede de Pesquisa Clínica de Retinopatia Diabética (DRCR.net).[15]

Although men presented significant improvement in the right and left eyes when analyzing the data and each appointment in isolation, there was no statistical significance regarding gender as a determining factor for improvement of visual acuity. In the study of Channa et al.[14], there was a higher percentage of women (p = 0.03, in univariate analysis) in the group with the worst visual outcome (59%) when compared to the group with the best outcome (35%). Lai et al. Demonstrated that, when compared to women, men were more likely to have a final BCVA of 20/40 or better.[13] In a similar analysis of patients in the DRCR.net study, women were more predisposed than men to have a worse visual outcome in the univariate analysis, but this was not significant in the multivariate analysis. If future studies indeed confirm the existence of a gender-related difference in the visual outcome for patients with DME treated with anti-VEGF, we will be facing a major issue, since this discrepancy might suggest a hormonal interaction - which would open new study strands in relation to the molecular mechanisms involved in DME.[15,16]

There was also no association between visual acuity improvement and previous treatments (p = 0.614).

The fact that all eyes were treated by a single physician is both an advantage and a limitation. On one hand, it provides homogenous practice standards for follow-up and treatment indications, but on the other hand, it is a potential source of bias. Follow-up management was based on the subjective evaluation of the attending physician, but also on the patients' availability under real conditions. A more active treatment regimen would probably have produced a better visual result.

A critical look on the study helps us conclude that because it is a retrospective analysis using medical records, the search for other prognostic factors related to the general state and other data of the patients is compromised. In addition, probably the observation of a larger sample would give us a better view regarding the factors studied. In addition, it was not possible to exclude influences from the course of the natural disease prior to IV injection on the final results.

Conclusion

Ao tratar o EMD, a natureza sistêmica do diabetes deve When treating DME the ophthalmologist must always keep in mind the systemic nature of diabetes. A multidisciplinary assessment among physicians of different specialties is needed to maximize treatment outcomes. In conclusion, inhibition of VEGF plays a key role in the treatment of diabetic maculopathy. Intravitreal ranibizumab in various treatment regimens is proven to be safe and effective in the treatment of DME. Serious ocular complications are rare, although there are still considerations regarding systemic cardiovascular safety in specific groups of patients. Inhibition of VEGF should also play a significant role in the treatment of diabetic retinopathy in patients with and without DME. Intravitreal ranibizumab revolutionized the treatment of diabetic maculopathy in recent years, and has proven its effectiveness in multiple clinical trials and in daily clinical practice.

In this study, it was not possible to definitively conclude whether the short-term effects of an IV injection are correlated to the prognostic factors analyzed, such as age, gender and previous treatment. Thus, the issue raised by other authors15 of possible hormonal interactions different between men and women involving the evolution of the disease with IV applications could not be elucidated. Randomized trials are therefore needed to assess whether the short- or long-term effects of an IV injection can be predicted based on age, gender, and other patient characteristics.

References

1. Klein R, Klein BE, Moss SE, Davis MD, Demets DL. The Wisconsin epidemiologic study of diabetic retinopathy. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. Arch Ophthalmol. 1984;102(4):520-6.
2. Silva VB, Temporini ER, Moreira FD, Kara-Jose N. Tratamento da retinopatia diabética: percepções de pacientes em Rio Claro (SP) - Brasil. Arq Bras Oftalmol. 2005;68(3):363-8.
3. Brasil. Ministério da Saúde. Estatísticas [Internet]. [citado 2017 Ago 20]. Disponível em: <http://www.portalweb01.saude.gov.br/saude/aplicacoes/noticias/noticias_detalhe.cfm?Co_seq_noticia HYPERLINK>.
4. Hirata CA, Fang T, Casella AM, Elieser M, Abujamra S. Prevalência de retinopatia em uma população de diabéticos. Arq Bras Oftalmol. 1986;49(1):31-3.
5. Fickweiler W, Schauwvlieghe AM, Schlingemann RO, Maria Hooymans JM, Los LI, Verbraak FD; BRDME Research Group. Predictive Value of Optical Coherence Tomographic Features in The Bevacizumab and Ranibizumab Inpatients with Diabetic Macular Edema (Brdme) Study. Retina. 2017 Apr 11. doi:10.1097/IAE.0000000000001626.
6. Brasil. Ministério da Saúde. Secretaria de Ciência, Tecnologia e Insumos Estratégicos Departamento de Gestão e Incorporação de Tecnologias em Saúde. Antiangiogênicos (bevacizumbe e ranibizumabe) no tratamento do edema macular diabético. Brasília (DF): Ministério da Saúde, 2015. (Relatório de Recomendação da Comissão Nacional de Incorporação de Tecnologias no SUS – CONITEC. n. 119).
7. Minami Y, Nagaoka T, Ishibazawa A, Yoshida A. Short-term effects of intravitreal ranibizumab therapy on diabetic macular edema. BMC Ophthalmol. 2017; 36(9):1726-32.
8. Dervenis N, Mikropoulou Am, Tranos P, Dervenis P. Ranibizumab in the treatment of diabetic macular edema: a review of the current status, Unmet Needs, and Emerging Challenges. Adv Therapy. 2017;34(6):1270-82.

9. ETDRS Research Group. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report Number 2. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1987;94(7):761-74.
10. Mitchell P, Bandello F, Schmidt-Erfurth U, Lang GE, Massin P, Schlingemann RO, Sutter F, Simader C, Burian G, Gerstner O, Weichselberger A; RESTORE study group. The RESTORE study: ranibizumab monotherapy or combined with laser versus laser monotherapy for diabetic macular edema. Ophthalmology. 2011;118(4):615-25.
11. Nguyen QD, Brown DM, Marcus DM, Boyer DS, Patel S, Feiner L, Gibson A, Sy J, Rundle AC, Hopkins JJ, Rubio RG, Ehrlich JS; RISE and RIDE Research Group. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. Ophthalmology. 2012;119(4):789-801.
12. Couto JA, Oliveira LA. As principais causas de cegueira e baixa visão em escola para deficientes visuais. Rev Bras Oftalmol. 2016; 75(1):26-9.
13. Lai I-A, Hsu W-C, Yang C-M, Hsieh Y-T. Prognostic factors of short-term outcomes of intravitreal ranibizumab in diabetic macular edema. Int J Ophthalmol. 2017;10(5):765-71.
14. Channa R, Sophie R, Khwaja AA, DV Do, G Hafiz,1 QD Nguyen, PA Campochiaro, * and The READ-2 Study Group†. Factors affecting visual outcomes in patients with diabetic macular edema treated with ranibizumab. Eye (Lond). 2014;28(3):269-78.
15. Bressler SB, Qin H, Beck RW, Chalam KV, Kim JE, Melia M, Wells JA 3rd. Diabetic Retinopathy clinical research network factors associated with changes in visual acuity and central subfield thickness at 1 year after treatment for diabetic macular edema with ranibizumab. Arch Ophthalmol. 2012;130(9):1153-61.
16. Wilkinson CP, Ferris FL 3rd, Klein RE, Lee PP, Agardh CD, Davis M, Dills D,Kampik A, Pararajasegaram R, Verdaguer JT; Global Diabetic Retinopathy Project Group. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology. 2003;110(9):1677-82. Review.

Corresponding author:
Faculdade Ciências Médicas de Minas Gerais
Tereza Cristina Moreira Kanadani
Alameda Ezequiel Dias, 275, Centro, Belo Horizonte - MG, Brazil
E-Mail: moreirakanadani@hotmail.com