

Assessment of Functional Success Predictors in the Treatment of Exudative AMD: A 3-Year Real-World Study

Avaliação de Preditores de Sucesso Funcional no Tratamento da DMI Exsudativa: Um Estudo de Vida Real de 3 Anos

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ABSTRACT

INTRODUCTION: Intravitreal anti-VEGF therapy has been shown to delay progression of neovascular age-related macular degeneration (nAMD) and reduce the incidence of legal blindness. However, a subset of patients exhibits suboptimal responses, with some experiencing significant vision loss. The underlying causes of this variability remain for the most part unclear. Retrospective studies have so far identified potential predictors of visual outcomes. This study aimed to investigate factors associated with functional success in treatment-naïve nAMD patients receiving anti-VEGF therapy over a 3-year period.

METHODS: A retrospective observational study was conducted at a tertiary center in Coimbra (Portugal), including naïve patients who started treatment with anti-VEGF for nAMD between 2017 and 2020 and completed a 3-year follow-up period. Demographics, best corrected visual acuity (BCVA), time until treatment initiation and OCT features were evaluated. Functional success was defined as achieving driving vision (>69 letters) in 3 years. The effects of baseline clinical and OCT markers on functional success were analyzed at last follow-up using mixed-effects models.

RESULTS: One hundred fourteen eyes from 89 patients were included, of which 56.2% were female. Mean age at inclusion was 76.82 (7.23) years. Thirty-nine eyes (34.2%) achieved functional success at last follow-up. Overall, a significant decrease of mean 5.75 (2.15) letters in BCVA was observed during follow-up, from mean 56.98 (95% CI: 52.7, 61.3) at baseline to 51.23 (95% CI: 46.9, 55.6) letters at 3 years ($p=0.009$). A mixed-effects model was used to identify predictors of functional success at 3 years. Higher BCVA at baseline predicted a 1.06 (95% CI: 1.03, 1.09) higher odds of achieving functional success. Similarly, the presence of subretinal fluid at baseline had a 4.20 (95% CI: 1.12, 15.69) higher odds of functional success at 3 years. On the other hand, the presence of type 2 neovascularization was associated with a 0.15 (95% CI: 0.03, 0.90) lower odds of achieving functional success.

CONCLUSION: In this study, BCVA and the presence of subretinal fluid at baseline were significant predictors of functional success. Careful evaluation of clinical and OCT features at baseline may enable better prognostic assessments for patients with neovascular AMD treated with anti-VEGF.

KEYWORDS: Intravitreal Injections; Macular Degeneration/drug therapy; Wet Macular Degeneration/drug therapy; Vascular Endothelial Growth Factor A/antagonists & inhibitors.

RESUMO

INTRODUÇÃO: A terapia intravítrea anti-VEGF demonstrou atrasar a progressão da degeneração macular relacionada à idade neovascular (nAMD) e reduzir a incidência de cegueira legal. Contudo, um subgrupo de doentes apresenta respostas subótimas, resultando em perda significativa de visão. As causas subjacentes desta variabilidade são em grande parte desconhecidas, embora estudos retrospectivos tenham identificado possíveis preditores dos resultados visuais. Este estudo visa investigar fatores associados ao sucesso funcional em doentes naïve com nAMD sob terapêutica anti-VEGF ao longo de um período de 3 anos.

MÉTODOS: Realizou-se um estudo observacional retrospectivo num centro terciário em Coimbra (Portugal), incluindo doentes naïve que iniciaram tratamento com anti-VEGF para nAMD entre 2017 e 2020 e completaram um período de seguimento de 3 anos. Foram avaliadas a melhor acuidade visual corrigida (BCVA), o tempo até ao início do tratamento e as características da OCT. O sucesso funcional foi definido como a obtenção de visão mínima para condução (>69 letras) em 3 anos. Foram utilizados modelos mistos na avaliação de fatores preditivos clínicos e estruturais associados ao sucesso funcional.

RESULTADOS: Foram incluídos 114 olhos de 89 pacientes, dos quais 56,2% eram mulheres. A idade média foi de 76,82 (7,23) anos. Trinta e nove olhos (34,2%) alcançaram sucesso funcional na última visita. Observou-se uma diminuição significativa de 5,75 (2,15) letras na BCVA durante o estudo, de 56,8 (52,7, 61,3) no início para 51,23 (46,9, 55,6) letras ao fim de 3 anos ($p=0,009$). Um modelo de efeitos mistos identificou preditores de sucesso funcional aos 3 anos. Uma BCVA inicial superior esteve associada a uma probabilidade 1,06 (1,03, 1,09) vezes maior de alcançar sucesso funcional. A presença de fluído subretiniano inicial esteve associada a uma probabilidade 4,20 (1,12, 15,69) vezes maior de sucesso funcional, enquanto a neovascularização tipo 2 esteve associada a uma probabilidade 0,15 (0,03, 0,90) vezes menor de sucesso.

CONCLUSÃO: Neste estudo, uma BCVA superior e a presença de fluído subretiniano iniciais foram fatores preditivos significativos de sucesso funcional. Uma avaliação cuidadosa das características clínicas e da OCT pode permitir uma melhor estratificação prognóstica em doentes com nAMD tratados com anti-VEGF.

PALAVRAS-CHAVE: Degenerescência Macular/tratamento farmacológico; Degenerescência Macular Exsudativa/tratamento farmacológico; Fator A de Crescimento do Endotélio Vascular/antagonistas & inibidores; Injeções Intravítreas.

INTRODUCTION

Age-related macular degeneration (AMD) represents a major cause of vision impairment and irreversible blindness in the aging population worldwide, particularly in developed countries.¹ This progressive disease primarily manifests in two forms: dry AMD, and wet or neovascular AMD, which, although less common, leads to the majority of severe vision loss cases.² The pathophysiology of neovascular AMD involves the growth of abnormal blood vessels under the macula, leading to leakage, bleeding, and scarring, ultimately causing rapid and severe vision deterioration.³ The epidemiology of AMD highlights an increasing burden, with prevalence expected to rise as the population ages, emphasizing the need for effective management strategies.⁴

The introduction of anti-vascular endothelial growth factor (anti-VEGF) therapies has revolutionized the treat-

ment landscape for neovascular AMD. These agents target the pathophysiological processes driving neovascularization and have shown significant efficacy in stabilizing and often improving visual acuity in patients.² Clinical trials and real-world studies have validated the efficacy of these treatments, making them the cornerstone of modern therapeutic approaches.^{3,5} Despite these advancements, the response to anti-VEGF treatment can be highly variable among patients.⁶ This variability underscores the necessity for identifying predictive factors that could enhance treatment efficacy and outcomes.⁶

Several predictive factors have been explored in the literature, providing insights into potential determinants of treatment success. Baseline characteristics such as age, lesion size, and initial visual acuity have been associated with the prognosis of visual outcomes.^{5,7} Additionally, optical coherence tomography (OCT) features, including the presence of

intraretinal fluid and retinal pigment epithelium detachment, have been evaluated for their prognostic implications.^{7,8}

Despite the wealth of research, significant knowledge gaps remain in our understanding of the comprehensive array of factors influencing treatment response in real-world settings.^{1,9}

This study aims to address these gaps by conducting a comprehensive assessment of functional success predictors over three years in a real-world cohort of naïve patients with neovascular AMD treated with anti-VEGF therapy.

METHODS

A retrospective, observational, non-interventional study was conducted at a tertiary center, including consecutive treatment-naïve eyes diagnosed with neovascular AMD that underwent a treat-and-extend regimen with intravitreal anti-VEGF injections (ranibizumab and aflibercept) between 2017 and 2020 and completed a 3-year follow-up period. All patients underwent a loading dose of 3 monthly intravitreal injections. Patients were identified using the IRD-PT (Inherited Retinal Dystrophies - Portugal) registry (www.retina.com.pt), a nationwide platform for retinal diseases. Eyes presenting with submacular hemorrhage or vitreomacular interface disorders were excluded.

The study was approved by the local Ethics Committees and complies with the Declaration of Helsinki. Written informed consent was obtained from all study participants.

Demographics (age and sex), initial and final best corrected visual acuity (BCVA), time interval between onset of symptoms and treatment initiation, number of injections, type of macular neovascular membrane (MNV) and initial presence of intraretinal fluid, subretinal fluid or retinal pigment epithelial detachments were evaluated. Functional success was defined as achieving driving vision (>69 letters) in 3 years. The comparison between initial and final BCVA, as well as the effects of baseline clinical and OCT markers on functional success were analyzed at the end of the 3-year follow-up period using mixed-effects models, accounting for inter-eye correlation.

Patient characteristics are presented as mean (SD or 95% confidence interval) for normally distributed continuous variables, median (IQR) for non-normal continuous variables, number (%) for categorical variables and odds ratio (95% confidence interval). The Holm-Bonferroni method was used to account for multiple hypothesis testing. Statistical significance was set at a *p*-value less than 0.05. In this study, statistical analyses were conducted using the R statistical software (version 4.3.1, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

One hundred fourteen eyes from eighty-nine patients were included with a complete 3-year follow-up period. The cohort's baseline characteristics are presented in Table 1. Thirty-nine eyes (34.2%) achieved functional success at last follow-up. Overall, a significant decrease of mean 5.75 (2.15) letters in BCVA was observed during fol-

Table 1. Cohort's baseline characteristics.

Baseline characteristics	
Female sex, n (%)	50 (56.2%)
Age in years, mean (SD)	76.82 (7.23)
Baseline BCVA in ETDRS letters, mean (95% CI)	56.98 (52.7, 61.3)
Interval to treatment in days, median (IQR)	55 (30, 80)
Number of injections, mean (SD)	10.98 (3.84)
MNV type, n (%)	
1	59 (51.8%)
1A	28 (24.6%)
2	15 (13.2%)
3	12 (10.5%)
IRF, n (%)	62 (54.4%)
SRF, n (%)	89 (78.1%)
PED, n (%)	92 (80.7%)

Abbreviations: aneurysmal type 1 neovascularization (1A), best corrected visual acuity (BCVA), confidence interval (CI), Early Treatment of Diabetic Retinopathy Study (ETDRS), interquartile range (IQR), intraretinal fluid (IRF), macular neovascular membrane (MNV), pigment epithelium detachment (PED), standard deviation (SD), subretinal fluid (SRF).

low-up, from 56.98 (95% CI: 52.7, 61.3) at baseline to 51.23 (95% CI: 46.9, 55.6) letters at 3 years (*p*=0.009).

At baseline, 41 (36%) eyes presented with driving vision (>69 letters), 25 (21.9%) with reading vision (60-69 letters), 25 (21.9%) with low vision (36-59 letters) and 23 (20.2%) with legal blindness. At the end of the 3 years, 39 (34.2%) eyes had driving vision, 15 (13.2%) had reading vision, 27 (23.7%) low vision and 33 (28.9%) legal blindness.

Using a generalized linear mixed model (Table 2) that adjusted for correlations between eyes, we identified several predictors of functional success. Specifically, higher baseline BCVA was associated with a 1.06 (95% CI: 1.03, 1.09) higher odds of functional success. Eyes with subretinal fluid at baseline had a 4.20 (95% CI: 1.12, 15.69) higher odds of functional success. Conversely, eyes with type 2 neovascularization at baseline showed a 0.15 (95% CI: 0.03, 0.90) lower odds of achieving functional success.

DISCUSSION

This study confirms and extends previous findings on the role of baseline characteristics in predicting functional success in patients with neovascular AMD treated with anti-VEGF therapy. Consistent with prior studies, we found that higher baseline best corrected visual acuity (BCVA) and the presence of subretinal fluid (SRF) significantly predicted better functional outcomes at 3 years, reinforcing the importance of early treatment initiation before significant vision loss occurs.^{2,6,8}

Our study demonstrated that the presence of SRF at baseline was associated with functional success. This finding aligns with prior research highlighting SRF as a favorable prognostic marker.^{5,8} Some authors noted that eyes with SRF at baseline showed reduced risk of geographic atrophy development and superior visual acuity gains.^{5,7,8} In con-

Table 2. Generalized linear mixed model for predictors of functional success, where female sex and MNV type 1 are reference levels.

	b (SE)	OR (95% CI)	p-value
Intercept	-6.237 (3.091)	0.002 (0.000, 0.837)	0.059
Initial BCVA	0.059 (0.015)	1.061 (1.031, 1.091)	<0.001*
Male sex	-0.155 (0.613)	0.856 (0.258, 2.847)	0.805
Age	0.035 (0.034)	1.036 (0.968, 1.108)	0.393
Interval to treatment	-0.009 (0.006)	0.991 (0.979, 1.003)	0.096
Number of injections	-0.010 (0.076)	0.990 (0.854, 1.148)	0.855
MNV type 1A	-0.972 (0.671)	0.378 (0.101, 1.410)	0.192
MNV type 2	-1.881 (0.908)	0.152 (0.026, 0.903)	0.031*
MNV type 3	-2.076 (1.272)	0.125 (0.010, 1.519)	0.101
IRF	-0.213 (0.597)	0.808 (0.251, 2.605)	0.848
SRF	1.435 (0.673)	4.199 (1.124, 15.694)	0.032*
PED	-0.601 (0.826)	0.548 (0.109, 2.770)	0.475

Abbreviations: aneurysmal type 1 neovascularization (1A), best corrected visual acuity (BCVA), confidence interval (CI), intraretinal fluid (IRF), macular neovascular membrane (MNV), odds ratio (OR), pigment epithelium detachment (PED), standard error (SE), subretinal fluid (SRF).

Asterisk (*) indicate a significant value.

trast, intraretinal fluid (IRF) has been consistently linked to poorer outcomes, underscoring the distinct roles of fluid subtypes in disease progression.^{5,7,8} The protective effect of SRF may reflect its association with less photoreceptor disruption and adaptive tolerance to fluid, enabling sustained visual improvement.^{5,8} These findings reinforce the clinical relevance of fluid localization in guiding personalized treatment strategies.

Interestingly, while some studies report a significant link between type 1 lesions and favorable long-term outcomes, our findings diverge somewhat here.^{5,7} We observed that the presence of type 2 neovascularization was associated with lower odds of achieving functional success. This aligns closely with results from Izquierdo-Serra *et al*, who documented that type 2 neovascular lesions, characterized by growth into the subretinal space and frequent association with subretinal hyperreflective material exudation, resulted in poorer baseline and final visual acuity compared to other lesion types.^{2,6} The implications of these observations are substantial, emphasizing the need for precise baseline assessment of lesion characteristics to tailor treatment plans more effectively and possibly anticipate individual patient responses to anti-VEGF therapy.

Our study also explored factors traditionally believed to influence outcomes, such as age, sex, number of injections, and interval to treatment initiation, but found no significant associations with functional success. This contrasts with other reports suggesting that age, total injection count, and early treatment can influence prognosis.^{4,5} Such differences underscore the variability in treatment responses and highlight the complex interplay of genetic, environmental, and treatment-related factors that can affect patient outcomes.

Moreover, consistent with findings from Baselius *et al*, who reported that driving vision could be maintained in a significant proportion of patients when present at baseline, our study reinforces the clinical relevance of maintaining driving vision as a benchmark for treatment success in real-world settings.⁴

Our study provides a valuable insight into the real-world long-term predictors of functional success as the entire cohort has a complete follow-up period of 3 years. While it is informative, the study is subject to several limitations that merit consideration. As a retrospective, single-center, observational study, it inherently carries the potential for selection bias and unmeasured confounding variables that could influence the outcomes, specifically some structural features such as the development of macular atrophy and subretinal hyperreflective material.

In conclusion, our real-world study highlights the importance of baseline BCVA and the presence of SRF as predictors of functional success in the treatment of nAMD with anti-VEGF therapies. It also prompts further investigation into the complex interplay of neovascular types and other baseline characteristics in shaping patient outcomes, suggesting the potential for more tailored therapeutic approaches based on individual patient profiles.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO

All authors contributed equally and approved the final version to be published.

Todos os autores contribuíram igualmente e aprovaram a versão final a ser publicada.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Rufino Silva: Bayer – C; Roche - C, THEA - C.

Os outros autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

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Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

ETHICAL DISCLOSURES

Conflicts of Interest: Rufino Silva: Bayer – C; Roche - C, THEA - C.

The other authors have no conflicts of interest to declare.

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Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2024).

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