Early Outcomes of Brolucizumab Switch in Wet Age-Related Macular Degeneration: A Tertiary Portuguese Hospital Experience

Efeitos Precoces do *Switch* para Brolucizumab na Degenerescência Macular Ligada à Idade: Experiência de um Hospital Terciário Português

Marta Correia [1], Margarida Baptista [1], Miguel Cordeiro [1], Maria Picoto [1], Fernanda Vaz [1]

[1] Hospital de Egas Moniz, Centro Hospitalar de Lisboa Ocidental, Lisboa, Portugal

Recebido/Received: 2022-10-15 | **Aceite/Accepted:** 2023-08-01 | **Published online/Publicado online:** 2023-11-03 | **Publicado/Published:** 2023-12-29

DOI: https://doi.org/10.48560/rspo.28282

ABSTRACT

INTRODUCTION: Age-related macular degeneration (AMD) is the leading cause of blindness in the developed world. The use of anti-vascular endothelial growth factor (VEGF) revolutionized the treatment of neovascular AMD (nAMD) despite being a known burden to both patients and healthcare systems. Brolucizumab is a newer anti-VEGF agent, whose noninferiority to aflibercept in visual outcomes in treatment-naïve eyes with nAMD was demonstrated in two clinical trials. A secondary favorable outcome was the extended dosing intervals in more than half of eyes treated with this agent. Although it exhibited a safety profile comparable to aflibercept, the rate of intraocular inflammatory events was superior. Few studies report the outcomes of non-naïve patients after switching to brolucizumab. Our aim is to evaluate the functional and anatomic outcomes, and safety of brolucizumab in nAMD patients previously treated with other anti-VEGF agents with poor response in our center.

METHODS: Retrospective and observational study in patients with nAMD receiving intravitreal treatment with anti-VEGF that showed no response or persistent presence of significant intra- and/or subretinal fluid despite injections intervals of 6 weeks or less. Those patients switched to therapy with brolucizumab between January to August of 2022. Functional (best corrected visual acuity [BCVA], intraocular pressure [IOP]) and anatomical (central subfield thickness [CST], presence of intra- and/or subretinal fluid and presence of pigment epithelial detachment) outcomes were measured and analyzed both at baseline and at a posterior visit 8-to-12 weeks after the first injection. Any sign of adverse effect was reported. For statistical analysis SPSS v.28 was used. Results were deemed significant if $p < 0.05$, in the parametric, non-parametric and categorical tests used.

RESULTS: Thirteen eyes of 12 patients, with a mean age of 77.4 ± 11.6 years and 41.7% of females, switched to brolucizumab during the mentioned period, receiving a mean of 1.77 ± 0.8 injections. Patients were previously followed for a mean of 43.1 ± 25.6 months and received a median of 23 ± 31 other anti-VEGF injections. After the switch, it was observed a significant change in the treatment interval ($p = 0.008$). A significant mean change in BCVA of -0.17 ± 0.19 logMAR (95% CI: -0.278; -0.053, $p = 0.007$), as well as in CST of -43.38 ± 57.70 μm (95% CI: -78.25; -8.52; $p = 0.019$) was

found. A significant reduction was observed regarding subretinal fluid (p= 0.031), but no change was observed in the presence of intraretinal fluid or pigment epithelial detachment. There were no reported adverse effects.

CONCLUSION: Our results align with previous clinical trials and reports of real-world settings of naïve and non-naïve treatment patients treated with brolucizumab. The improvement in functional and anatomical outcomes in addition to extending treatment interval demonstrates that this agent is a promising treatment against nAMD and reduces the burden of repeated intravitreal injections. Despite no reports of intraocular inflammation in this cohort, careful patient selection, a vigilant follow-up and suitable patient education for warning signs is vital.

KEYWORDS: Brolucizumab; Macular Degeneration/drug therapy; Wet Macular Degeneration/drug therapy.

RESUMO

INTRODUÇÃO: A degenerescência macular ligada à idade (DMI) é a principal causa de cegueira nos países desenvolvidos. O uso de agentes *anti-vascular endothelial growth factor* (VEGF) revolucionou o tratamento da DMI exsudativa, apesar dos importantes encargos para os doentes e sistemas de saúde. O brolucizumab, um novo anti-VEGF, teve em dois ensaios clínicos comprovada a sua eficácia funcional e anatómica. Apesar de um perfil de segurança comparável ao aflibercept, a taxa de inflamação intraocular foi consideravelmente superior. Poucos estudos reportam os resultados do brolucizumab em doentes previamente tratados com outros agentes anti-VEGF e com fraca resposta a esta terapêutica. Neste estudo pretendemos avaliar os resultados clínicos, anatómicos e de segurança do uso de brolucizumab nestes doentes.

MÉTODOS: Estudo observacional e retrospectivo em doentes a receber tratamento com injeções intravítreas de anti-VEGF por DMI neovascular, sem resposta ao tratamento ou com presença persistente de fluído intra- e/ou subretiniano apesar de intervalos entre injeções de 6 semanas ou inferior. Estes doentes fizeram o switch para brolucizumab entre Janeiro e Agosto de 2022. A avaliação e comparação incluía dados funcionais (melhor acuidade visual corrigida [MAVC], pressão intraocular [PIO]) e estruturais (espessura foveal central [EFC], presença de fluído intra- e/ou subretiniano e/ou descolamento do epitélio pigmentar) basais e após 8 a 12 semanas da primeira injeção de brolucizumab. Foi reportada a presença de qualquer efeito adverso. A análise estatística foi realizada utilizando a versão 28 do SPSS. Valores de $p < 0,05$ foram considerados significativos.

RESULTADOS: Treze olhos de 12 doentes, com idade média de 77,4 ± 11,6 anos e 41,7% do sexo feminino, realizaram o switch para brolucizumab no período mencionado, recebendo uma média de 1,77 ± 0,8 injeções. Previamente, tinham sido seguidos por uma média de 43,1 ± 25,6 meses e tratados com uma mediana de 23 ± 31 injeções de outros anti-VEGF. Após a alteração para brolucizumab foi observada uma mudança significativa no intervalo de tratamento (p = 0,008). Observou-se uma melhoria significativa na MAVC de -0,17 ± 0,19 logMAR (95% IC: -0,278; -0,053; p = 0,007), assim como uma redução na EFC de -43,38 ± 57,70 μm (95% IC: -78,25; -8,52; p = 0,019). A redução de fluído subretiniano também demonstrou ser significativa (p = 0,031), mas não se registaram alterações no fluído intrarretiniano ou descolamento do epitélio pigmentar. Não se registaram efeitos adversos.

CONCLUSÃO: Os nossos resultados do uso de brolucizumab equiparam-se à literatura tanto em doentes previamente tratados como não. A melhoria nos resultados funcionais e estruturais, assim como a extensão do intervalo entre injeções demonstra que esta molécula é uma arma promissora no tratamento da DMI neovascular, permitindo reduzir o encargo de injeções intravítreas repetidas. Apesar de no nosso grupo não terem sido registados casos de inflamação intraocular é vital uma adequada seleção de doentes, o seu seguimento cuidadoso e educar os doentes para os seus principais sinais de alarme.

PALAVRAS-CHAVE: Brolucizumab; Degenerescência Macular/tratamento farmacológico; Degenerescência Macular Exsudativa/tratamento farmacológico.

INTRODUCTION

Age-related macular degeneration (AMD) is a leading cause of severe visual impairment in the developed world, accounting for 8.7% of all blindness across the world.[1] As older age is the main risk factor for the development of disease and its more severe types, the prevalence of AMD is bound to increase accompanying the exponential population ageing.[1]

Despite no cure for AMD has been found, progression of non-exudative forms of the disease can be slowed with changes in lifestyle and intake of multi-vitaminic supplements, as demonstrated by the Age-Related Eye Disease Study (AREDS) group.[2] The advent of anti-vascular endothelial growth factor (VEGF) therapy revolutionized the management and outcomes in patients with neovascular AMD.[3–5] However the personal, medical and economic burden of monthly intravitreal injections is well known, and not a viable solution in many places around the world, as many patients receive treatment less frequently in a real-world setting than preconized in clinical trials.[6] Therefore, newer molecules and/or delivery systems are being developed and under clinical trials to enhance efficacy and to reduce medical and treatment appointments, and the complications associated with them.

Brolucizumab is a humanized single-chain antibody fragment that inhibits all isoforms of anti-VEGF-A.[6] First approved by US Food and Drug Administration in October 2019 for the treatment of nAMD, the European Medicine Agency approval soon followed in February 2020.[7]

Two clinical trials – HAWK and HARRIER – demonstrated noninferiority of brolucizumab regarding visual results in treatment-naïve eyes with nAMD compared to aflibercept.[8,9] Additionally, secondary outcomes favored brolucizumab, namely a decrease in central subfield thickness (CST) on the optical coherence tomography (OCT) scans and extended dosing intervals in more than half of eyes treated with 6 mg of brolucizumab. This is believed to be consequence of the smaller molecular size (26 kDA), allowing brolucizumab to achieve molar concentrations 10 times superior to aflibercept and 20 times superior to ranibizumab at a dose of 6 mg.[6,7]

Regarding the safety profile of intravitreal brolucizumab, it demonstrated a safety profile similar to aflibercept in the initial reports of HAWK and HARRIER trials.[8,9] However, it showed already a higher rate of inflammatory events in eyes treated with higher brolucizumab doses when compared to aflibercept (4.4% *vs* 0.8% respectively). An independent review committee underwent a post-hoc analysis of these intraocular inflammation (IOI) events and confirmed the incidence of IOI 4.6%, mostly with concomitant retinal vasculitis, and 2.1% of the total cases associated also with vascular occlusion.[10,11]

Few studies report the outcomes of non-naïve patients after switching to brolucizumab. Thus, the aim of the authors is to evaluate the clinical and anatomic responses to brolucizumab as well as its safety in nAMD patients previously treated with other anti-VEGF agents that showed no response or insufficient response after intravitreal treatment, in a tertiary Portuguese hospital.

METHODS

The authors conducted a retrospective study in patients with nAMD whose intravitreal therapy switched to 6 mg brolucizumab between January and August of 2022 in Hospital de Egas Moniz, Centro Hospitalar de Lisboa Ocidental. The study adhered to the tenets of the Declaration of Helsinki.

All patients were identified using electronical medical records or intravitreal injections electronical planning. Inclusion criteria were: nAMD listed as the primary indication for treatment, previous intravitreal injections of aflibercept, ranibizumab and/or bevacizumab and persistent presence of functionally significant intraretinal fluid (IRF) or subretinal fluid (SRF) despite treatment intervals of 6 weeks or less.

The patients were previously under a treat-and-extend (T&E) regimen starting with a loading dose of three injections each 4-weeks of aflibercept, ranibizumab or bevacizumab, with an increment of 2-week according to structural response in OCT. Upon switching, a T&E regimen was used, starting at 6-week interval of brolucizumab injections.

Demographic data and information concerning the previous and brolucizumab treatments and the adverse effects were retrieved by consulting also medical records. The last appointment before the first injection of brolucizumab was regarded as the baseline visit. At each visit best-corrected visual acuity (BCVA) on a Snellen decimal scale, intraocular pressure in mmHg (IOP) and complete ophthalmic examination was performed, including dilated fundoscopy. Any signs of IOI or other adverse effects were reported when present.

Spectral-domain OCT scans were performed using Heidelberg Spectralis®, Heidelberg Engineering, Heidelberg, Germany. Automated identification with manual adjustments of internal limiting membrane and Bruch's membrane was performed to allow the determination of CST (μm), defined as the average retinal thickness between ILM and BM within 1 mm of the fovea. Additionally, the presence of IRF, SRF and/or pigment epithelial detachment, and the type and localization of macular neovascularization (MNV) was also thoroughly recorded.

For statistical analysis SPSS was used (IBM SPSS Statistics® V.28). The description of categorical variables was based on absolute frequencies and percentages. Quantitative variables were summarized by mean±standard deviation (SD) and median±interquartile range (IQR) for parametric and non-parametric variables, respectively. The BCVA results were converted to the logarithm of the minimum angle of resolution (logMAR) scale for statistical analysis.

Functional and anatomical outcomes were determined at baseline visit and 8 to 12 weeks after the first brolucizumab injection. The outcomes are the differences between each parameter between the two visits. The comparison of these outcomes was performed using t-test with 95% confidence interval (CI) for parametric variables and the Wilcoxon

signed-rank test for non-parametric variables. The comparison of the paired categorical variables was performed using McNemar test. *P*-values inferior to 0.05 were considered statistically significant.

RESULTS

STUDY COHORT

Between January 2022 and August 2022, 13 eyes of 12 patients were switched to brolucizumab in our center, according to the above-mentioned inclusion criteria.

Table 1 summarizes the demographic and disease characteristics of this study cohort.

Five patients (41.7%) were female and the mean (±SD) age was 77.4 (± 11.6) years.

No patient had history of prior episodes of intraocular inflammation.

Table 1. Patient demographic and previous history characteristics.

Characteristic	
Per patient	**n=12**
Age (years), mean±SD	77.4 ± 11.6
Gender, n (%)	
Female	5 (41.7)
Male	7 (58.3)
Per eye	**n=13**
Laterality, n (%)	
Right eye	5 (38.5)
Left eye	8 (61.5)
Number of previous anti-VEGF injections, median±IQR	23 ± 31
Duration of previous follow-up with nAMD (months), mean±SD	43.1 ± 25.6
Prior anti-VEGF agents used, n (%)	
Aflibercept	10 (76.9)
Ranibizumab	2 (15.4)
Bevacizumab	1 (7.7)
Previous injection interval (weeks), median±IQR	4 ± 1
Number of brolucizumab injections, mean±SD	1.77 ± 0.8
Current injection interval (weeks), median±IQR	7 ± 2
Type of MNV, n (%)	
Type 1	10 (76.9%)
Type 2	3 (23.1%)
Type 3	0 (0%)
Localization of MNV, n (%)	
Subfoveal	8 (61.5)
Juxtafoveal	4 (30.8)
Extrafoveal	1 (7.7)

MNV, macular neovascularization; VEGF, vascular endotelial growth factor

PIOR NAMD CHARACTERISTICS

In 61.5% (n=8) of affected eyes, MNV was reported to be subfoveal, followed by juxtafoveal location (n= 4, 30.8%). Most MNV were classified as type 1 (n=10, 76.9%).

All patients were previously treated with other anti-angiogenic drugs. Those patients previously received a median (IQR) of 23 (±31), over a mean (±SD) period of 43.1 (± 25.6) months.

The majority (n= 10, 76.9%) were injected with aflibercept, followed by ranibuzumab (n=2, 15.4%) and lastly by bevacizumab (n=1, 7.7%).

The median (±IQR) interval between treatments before introduction of brolucizumab was 4 ± 1 weeks.

SWITCH TO BROLUCIZUMAB

A total of 23 brolucizumab injections with a mean (±SD) of 1.77 ± 0.8 injections per eye were performed between January and August 2022. The current median (±IQR) week interval in the patients receiving brolucizumab was 7 ± 2 weeks.

Wilcoxon signed rank teste identified a significant difference in injection interval before and after the switching to brolucizumab (n=13 Z= -2.671, $p = 0.008$).

No adverse effects were reported during this period, with special focus to absence of IOI and retinal vasculitis. No patient needed to discontinue brolucizumab regarding all causes.

CLINICAL OUTCOMES

Mean (±SD) BCVA was 0.73 (±0.56) logMAR (equivalent to 48 ETDRS letters) prior to the first brolucizumab intravitreal injection. In the follow-up visit, which occurred 8 to 12 weeks after the first injection, mean (±SD) BCVA was 0.57 (±0.52) logMAR (equivalent 57 ETDRS letters). A statistically significant mean (±SD) change of -0.17 (± 0.19) [95% CI: -0.278; -0.053] was found ($p = 0.007$).

A non-significant change in mean (±SD) IOP of 0.77 ± 3.41 [95% CI: -1.297; 2.836] was detected in the follow-up visit ($p = 0.433$).

See Table 2 for functional and anatomical values at baseline and the follow-up visits. Table 3 reports the quantitative change in measurable outcomes.

Table 2. Clinical and anatomical characteristics at baseline and at follow-up visit.

Characteristic	Baseline	Follow-up visit
BCVA (logMAR), mean ± SD	0.73 ± 0.56	0.57 ± 0.52
IOP (mmHg), mean ± SD	12.85 ± 2.70	13.62 ± 3.64
CST (µm), mean ± SD	335.62 ± 81.70	292.33 ± 78.83
Presence of IRF, n (%)	4 (30.8%)	3 (23.1%)
Presence of SRF, n (%)	10 (76.9%)	4 (30.8%)
Presence of pigment epithelial detachment, n (%)	2 (15.4%)	2 (15.4%)

BCVA, best corrected visual acuity; CST, central subfield thickness; IOP, intraocular pressure; IRF, intraretinal fluid; SRF, subretinal fluid

Table 3. Functional and anatomical outcomes after switching to brolucizumab.

Outcome	Mean±SD	95% CI	p value
Change in BCVA (logMAR)	-0.17 ± 0.19	-0.28 – -0.05	0.007
Change in IOP (mmHg)	0.77 ± 3.42	-1.30 – 2.84	0.433
Change in CST (μm)	-43.38 ± 57.70	-78.25 – -8.52	0.019

BCVA, best corrected visual acuity; CST, central subfield thickness; IOP, intraocular pressure; IRF, intraretinal fluid; SRF, subretinal fluid

ANATOMICAL OUTCOMES

Regarding anatomical quantitative parameters the mean CFT regressed from 335.62 ± 81.70 μm to 292.33 ± 78.83 μm, which represents a significant mean change of -43.38 ± 57.70 μm (95% CI: -78.25; -8.52; $p = 0.019$).

At baseline 10 eyes (76.9%) presented with SRF, 4 eyes (30.8%) with IRF and 4 eyes (30.8%) with pigment epithelial detachment. All patients presented with at least one of these characteristics at baseline.

At follow-up visit, only 40% of the eyes with SRF maintained its presence and a McNemar test showed that the two proportions were statistically different ($p = 0.031$, 2-sided).

Changes in the presence of IRF were not significant, as 3 eyes (23.1%) maintained its presence. No changes in the presence of epithelial pigment detachment were observed.

DISCUSSION AND CONCLUSION

The search for an efficacious chronic therapy for nAMD, showing sustained both favorable functional and anatomical results, is still an unmet goal.

Our findings revealed both good anatomical and functional outcomes after switching intravitreal therapeutic to brolucizumab in eyes previously treated with other anti-VEGF agents that showed no response or maintained recalcitrant levels of retinal fluid. Our data showed significant reduction in CST and regression of SRF that goes in conformity with previous reports regarding the benefit in anatomical parameters in these type of patients in a real-world setting.[7,12,13]

However, the significant increase in visual acuity showed in the present report does not come in conformity with those previously mentioned reports, that showed no significant change in functional outcomes. The exception is the report by Bilgic *et al*, wherein the authors hypothesize that the gain in visual acuity comes from the fact that the patients have a lower BCVA at baseline than those of the HAWK and HARRIER trials and therefore have more potential to regain vision.[14] Our patients presented with an intermediate level of baseline BCVA (48 ETDRS letters), between HAWK (60.6 letters) and HARRIER (61.2 letters) and the former report (40 letters in the switch group) which may be an explanation for our registered improvement in BCVA.[8,14]

Regression of SRF detected by OCT in 60% of patients with prior fluid in the follow-up visit aligns with previous results, supporting the stronger vascular leakage inhibition of brolucizumab due to its molecular properties – a smaller molecular size, allowing for a higher molar dosing in ocular tissues.[9] The increased drying effect of brolucizumab, sustained at 8-to-12-week period of our observation, could also contribute to the described visual gain.

Also regarding the higher molar dosing is the extension in injection interval observed in our cohort. However, patients started brolucizumab at 6-week intervals and the follow-up period for these patients of only 8-to-12 weeks is insufficient to support this claim in the future. Future reports of our results for follow-up times similar to the clinical trials are desirable.

In our cohort, the patients were followed for nAMD and treated with anti-VEGF agents for a mean period of 43.1 ± 25.6 months, roughly equivalent to 3.5 years. This long history of nAMD contributes for irreversible morphological changes that can also limit the functional and anatomical gains with brolucizumab injections, when compared with naïve injections patients or patients with an early nAMD diagnose, although our results do not support this affirmation.

Another major difference found in our cohort when compared to HAWK and HARRIER trials is the absence of occurrence of IOI and retinal vasculitis adverse. Since the first report of those clinical trials, a 4.6% rate of intraocular inflammation was described, that can range from anterior uveitis to more severe cases of retinal vasculitis with or without arteriolar occlusion.[8,9] Since then, those results were confirmed in a post-hoc analysis, that also revealed that the majority of IOI and retinal vasculitis events occurred in the first 6 months after the initiation of brolucizumab, with a mean 3.9 ± 2.21 injections until the first IOI-related adverse effect.[10] Again, our analysis encompassed only the first 3 months after switching to brolucizumab with a mean of 1.77 ± 0.8 injections. Consequently, the patients are still at risk of developing intraocular adverse effects, as the pathophysiology of this process is still not well understood. Regarding the possibility of precocious IOI adverse effects, patients were taught to recognize alert symptoms and instructed to seek immediate ophthalmology care. Additionally, ongoing vigilance is of the outmost importance, and follow-up visits should not be masked by the positive functional and anatomical nAMD results.

Various limitations should be considered for this study. First, the observational and retrospective nature of our study, as the results are dependent of prior medical reports and different medical registration techniques. Secondly, the small cohort of 12 patients, which does not allow for more statistically robust results. Likewise, is the already mentioned short review period following the switch to brolucizumab. Truer functional and anatomical results and results regarding the incidence of adverse effects should be made

clearer in future reports as the follow-up time increases. Another important limitation is the use of only BCVA as a functional outcome. It is known that reading acuity is a better marker of disease progression in patients with macular disease and low vision, as both reading comprehension and speed are compromised, and quality of life is severely reduced as the disease advances.[15,16] However, the lack of standardized reading tests and the absence of adaptation to clinical practice difficult the retrieving of this data in retrospective studies.

In conclusion, in our small cohort we found benefits with the switch to brolucizumab, as it led to improved visual acuity, reduction in CST, regression of SRF and longer treatment intervals, in a subset of patients already more treatment demanding. Despite no reports of IOI in this cohort, careful patient selection, a vigilant follow-up and suitable patient education for warning signs is vital. Despite the listed limitations, it is our opinion that these results are a truthful depiction of real-world use of brolucizumab, an anti-VEGF agent showing to be promising weapon to battle nAMD and reducing the burden of repeated intravitreal injections.

PRIZES AND PREVIOUS PRESENTATIONS / PRÉMIOS E APRESENTAÇÕES PRÉVIAS

Accepted to Poster in the 65th Portuguese Ophthalmology Congress, December 2022.

Aceite para Poster no 65º Congresso Português de Oftalmologia, Dezembro de 2022.

CONTRIBUTORSHIP STATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

All authors contributed to the study design and data acquisition and interpretation.

All authors participated in the writing and critical revision of the manuscript and approved its final version.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.

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

ETHICAL DISCLOSURES

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

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 with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).

Provenance and Peer Review: Not commissioned; externally peer reviewed.

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Corresponding Author/
Autor Correspondente:

Marta Correia
Rua da Junqueira, 126,
1349-019 Lisboa, Portugal
marta.s.correia.95@gmail.com

ORCID: 0000-0002-6322-8825