Intravitreal injection switch to brolucizumab in refractory and chronic neovascular age-related macular degeneration: a real-world study in Brazil

Switch de injeção intravítrea para brolucizumabe em casos crônicos e refratários de degeneração macular relacionada à idade neovascular: um estudo de vida real no Brasil

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ABSTRACT

Objective: To evaluate the therapeutic response to brolucizumab in eyes with chronic neovascular age-related macular degeneration (nAMD) refractory to prior anti-angiogenic treatments.

Methods: This prospective observational study included patients with chronic nAMD who maintained exudative neovascularization after at least three injections of ranibizumab and/or aflibercept without previous episodes of uveitis or vasculitis. Participants received one to three intravitreal injections of brolucizumab. Best-corrected visual acuity (BCVA) was assessed before and 4 weeks after each injection, along with analysis of fluid distribution and measurement of central subfield thickness (CST) using optical coherence tomography.

Results: Nine eyes from seven patients were included. CST reduced in 7 eyes after the first injection (mean reduction of 30.9%). There was significant resolution of subretinal fluid (p = 0.025), and complete fluid reabsorption in all five eyes that received three injections. No significant change in BCVA was observed. Out of 21 injections, 5 (23.8%) resulted in mild adverse events, with no severe cases observed.

Conclusion: Brolucizumab may be an effective therapeutic alternative for refractory nAMD. Although there was no improvement in BCVA, the treatment promoted complete fluid resolution after one to three doses, and no severe adverse effects were observed in this small series.

RESUMO

Objetivo: Avaliar a resposta terapêutica do brolucizumabe em olhos de pacientes com degeneração macular neovascular crônica refratários a outros tratamentos antiangiogênicos.

Métodos: Estudo prospectivo observacional que incluiu pacientes com degeneração macular neovascular crônica que não responderam a, pelo menos, três doses de ranibizumabe e/ou aflibercepte, sem episódios prévios de uveíte ou vasculite. Os participantes receberam entre uma e três injeções intravítreas de brolucizumabe. A acuidade visual foi avaliada antes e 4 semanas após cada injeção, bem como a distribuição de fluidos e a medida da espessura do subcampo central, utilizando tomografia de coerência óptica.

Resultados: Nove olhos de sete pacientes foram incluídos. A espessura do subcampo central reduziu em sete olhos após a primeira injeção (redução média de 30,9%). Houve resolução significativa do fluido sub-retiniano (p = 0,025) e reabsorção completa de fluidos em todos os cinco olhos que receberam três injeções. Não foi observada alteração significativa de acuidade visual. Dentre 21 injeções, 5 (23,8%) resultaram em eventos adversos leves, sem casos graves reportados.

Conclusão: O brolucizumabe pode ser uma alternativa terapêutica eficaz para degeneração macular neovascular refratária. Embora não tenha apresentado melhora significativa na acuidade visual, o tratamento promoveu a reabsorção completa de fluidos retinianos após uma a três doses, sem efeitos adversos graves observados nesta série de casos.

INTRODUCTION

Age-related macular degeneration (AMD) is a chronic, progressive, acquired retinal disease and the main cause of blindness in people older than 65 years.[1,2] Its prevalence is estimated to be approximately 8.7% worldwide, with a projection to reach 288 million people in 2040.[3] The exudative form of AMD is characterized by the formation of macular neovascularization (MNV), and intravitreal application of anti-vascular endothelial growth factor (anti-VEGF) drugs in regular dosing is the gold standard treatment.[4-6]

Responsiveness to anti-VEGF therapy is assessed by clinical and anatomical criteria. Best corrected visual acuity (BCVA), fundoscopy evaluation, and image findings on optical coherence tomography (OCT), such as the presence of intraretinal fluid (IRF), subretinal fluid (SRF), and measurement of the central subfield thickness (CST) are considered when evaluating treatment response after loading dose monthly applications.[7] In cases of sub-optimal or absent response to an anti-VEGF loading dose, practitioners tend to switch to another antiangiogenic drug.[7]

Given the burden of wet AMD worldwide, new strategies of anti-VEGF drugs and treatment regimens are being studied to minimize the necessity of frequent intravitreal applications. In middle and low-income countries, this burden is even greater, especially due to high cost of medications, frequent follow-up appointments, and difficulty in regular accessibility to the healthcare system. The irregular follow-up or restricted availability of intravitreal anti-VEGF injections impairs an adequate treatment regimen.[3] Therefore, it is essential to assess the applicability of these treatments in the context of real-world practice.

Brolucizumab 6mg (Vsiqq®) is a single-chain antibody fragment (26 kDa) that has a higher tissue penetration and longer-lasting effects, given its smaller molecular size compared with other antiangiogenics drugs.[8] The phase 3 clinical trials HAWK and HARRIER demonstrated non-inferiority visual acuity results compared to aflibercept, with greater anatomic outcomes, and the possibility of extending the treatment to 12-week interval regimen after a monthly "loading dose", thereby reducing burden therapy in AMD.[9]

Although Brolucizumab has been used in real-world as a second line therapy in poor or non-responsive cases of neovascular age-related macular degeneration (nAMD), current literature is controversial with regards to its safety profile due to an increased risk of intraocular inflammation and retinal vascular occlusion.[10-13] Nevertheless, Baumal et al.[10] performed a systematic review of real-world studies and reported that the incidence of intraocular inflammation using Brolucizumab varied between zero to 19%, and concluded that the decision to use this drug should be based on a risk-benefit after a thorough patient evaluation suggesting that it should be avoided in patients with history of intraocular inflammation or retinal occlusion.[11]

Therefore, this study aimed to evaluate the therapeutic response to brolucizumab in eyes with chronic nAMD refractory to prior anti-angiogenic treatments.

METHODS

This is a prospective observational study conducted between September 2022 and June 2023 in Recife (PE, Brazil). Selected eyes received between one and three intravitreal injections of brolucizumab, with an average interval of 4 weeks between them. The inclusion criteria were patients older than 50 years with nAMD for at least one year (chronic), and active MNV who were unresponsive to at least three intravitreal injections of other anti-VEGF drugs (aflibercept and/or ranibizumab). Refractoriness was considered when hemorrhage was detected on fundoscopic examination and/or subretinal and IRF was observed on OCT.[7] Participants with media opacities; advanced glaucoma; other retinal pathologies; other causes of intra- or sub-retinal fluid; history of retinal occlusion, posterior uveitis, or other intraocular inflammation previous to the injections; history of myocardial infarction, thrombosis or cerebrovascular accident within the last 6 months were excluded. The study protocol was approved by the Institutional Review Board of the Altino Ventura Foundation (protocol # 5.404.389 and CAAE # 58254022.3.0000.5532) and conducted in accordance with the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants prior to their enrollment.

Sociodemographic data collected included age, sex, and comorbidities. The participants underwent an ophthalmological examination at baseline and 4 weeks after each intravitreal injection. The protocol included documenting any adverse event (AE) or patient complaint, measuring the best-corrected visual acuity (BCVA), and performing biomicroscopy and fundoscopy. All eyes underwent at each visit color fundus photography, spectral domain OCT (SD-OCT), and OCT angiography (OCTA) using the RTVue XR (Optovue, Fremont, CA, USA). OCT analysis included the automated measurement of the CST and the presence of fluid distribution within retinal

layers: IRF, SRF, and sub-retinal pigment epithelium fluid (SRPEF).

The statistical analysis was performed by the Jamovi software (version 2.3.28). Categorical variables were described by their absolute and relative frequencies, while numerical variables were described by their mean, standard deviation (SD), minimum and maximum values. Student's t-test and Friedman's test were used to compare quantitative data before and after injection, while McNemar's test was used for qualitative data.

RESULTS

Nine eyes from seven patients were switched from intravitreal ranibizumab and/or aflibercept to brolucizumab. Six patients (85.7%) were female, and one (14.3%) was male. The mean age was 74.0 years (SD of. 9.2; range: 62-86). Demographic and baseline characteristics are summarized in table 1. All nine eyes received at least one injection of brolucizumab. Seven eyes (77.8%) received two injections, and five of them (55.6%) received three injections. The mean number of injections per eye prior to switching to brolucizumab was 6.2 (SD of 4.5; range: 3-17) injections. The most common comorbidity among patients was systemic arterial hypertension (n = 4; 57.1%).

Table 1. Patients' demographic and medical profile (nine eyes; seven patients)

Variables	
Age (years)	74.0 (9.2; 62-86)
Sex	
Female	6 (85.7)
Male	1 (14.3)
Total number of eyes	Total number of previous injections
5	3
2	9
1	17
1	6
Comorbidities	
Systemic arterial hypertension	4 (57.1)
Diabetes Mellitus	1 (14.3)
Arrhythmia	1 (14.3)
Coronary artery disease	0
Smoking	0

Results expressed as mean (standard deviation; minimum-maximum) or n (%).

The mean BCVA before brolucizumab injection was 1.20 logMAR (SD = 0.54; range: 0.50-2.00) and after was 1.02 logMAR (SD = 0.16; range: 0.90-1.30) (p = 0.497; Table 2). The first brolucizumab injection led to a CST reduction of 30.9%. Mean CST at baseline was 337.1 µm, decreasing to 232.8 µm after the first injection (p = 0.039). Fluid distribution analysis at baseline showed the presence of IRF in 7 eyes (77.8%), SRF in 6 eyes (66.7%), and SRPEF in 2 eyes (22.2%). After the first injection, the number of eyes with IRF, SRF, and SRPEF decreased to 3 (33.3%), 1 (11.1%), and 2 (22.2%), respectively (Figures 1 and 2). Despite the reduction observed in the three parameters analyzed, only SRF showed significant regression (p = 0.025). Complete resolution of IRF, SRF, and SRPEF was observed in all eyes that received 3 applications (n = 5) (Table 2; Figures 1 and 2).

Table 2. Best corrected visual acuity and structural evaluation of the retina of the eyes treated with Brolucizumab per reassessment (n = 9 eyes; n = 7 patients).

Variables		p-value
BCVA, LogMAR		
Pre-injection, n = 9	1.20 (0.54; 0.50-2.00)	0.497
After 1st injection, n = 9	1.00 (0.49; 0.50-1.80)	
After 2nd injection, n = 7	0.96 (0.42; 0.50-1.80)	
After 3rd injection, n = 5	1.02 (0.16; 0.90-1.30)	
CST, µm		
Pre-injection, n = 9	337.1 (124.8; 196-604)	0.069
After 1st injection, n = 9	232.8 (45.2; 158-325)	
After 2nd injection, n = 7	238.7 (47.1; 174-296)	
After 3rd injection, n = 5	239.4 (47.1; 192-276)	
Anatomical fluid distribution		
Intraretinal		
Pre-injection, n = 9	7 (77.8%)	0.102
After 1st injection, n = 9	3 (33.3%)	
After 2nd injection, n = 7	1 (14.3%)	
After 3rd injection, n = 5	0	
Subretinal		
Pre-injection, n = 9	6 (66.8%)	0.025
After 1st injection, n = 9	1 (11.1%)	
After 2nd injection, n = 7	0	
After 3rd injection, n = 5	0	
Sub-RPE		
Pre-injection, n = 9	2 (22.2%)	-
After 1st injection, n = 9	2 (22.2%)	
After 2nd injection, n = 7	1 (14.3%)	
After 3rd injection, n = 5	0	

Results expressed as mean (standard deviation; minimum-maximum) or n (%).
BCVA: best-corrected visual acuity; CST: central subfield thickness; RPE: retinal pigmented epithelium.

A total of 21 injections were administered. Five injections (23.8%) were associated with mild adverse events, including foreign body sensation in three eyes, transient blurred vision in one eye, and vitreous floaters in one eye. No serious adverse events were observed in any treated eye (Table 3).

DISCUSSION

The burden of nAMD treatment affects the elderly population and healthcare systems, particularly in developing countries. These challenges reinforce the importance of cost-effective strategies to optimize treatment regimens.

The present study observed an anatomical improvement in nine eyes that received intravitreal brolucizumab since the first injection. Central subfield thickness is a direct and quantitative measurement of intraretinal edema

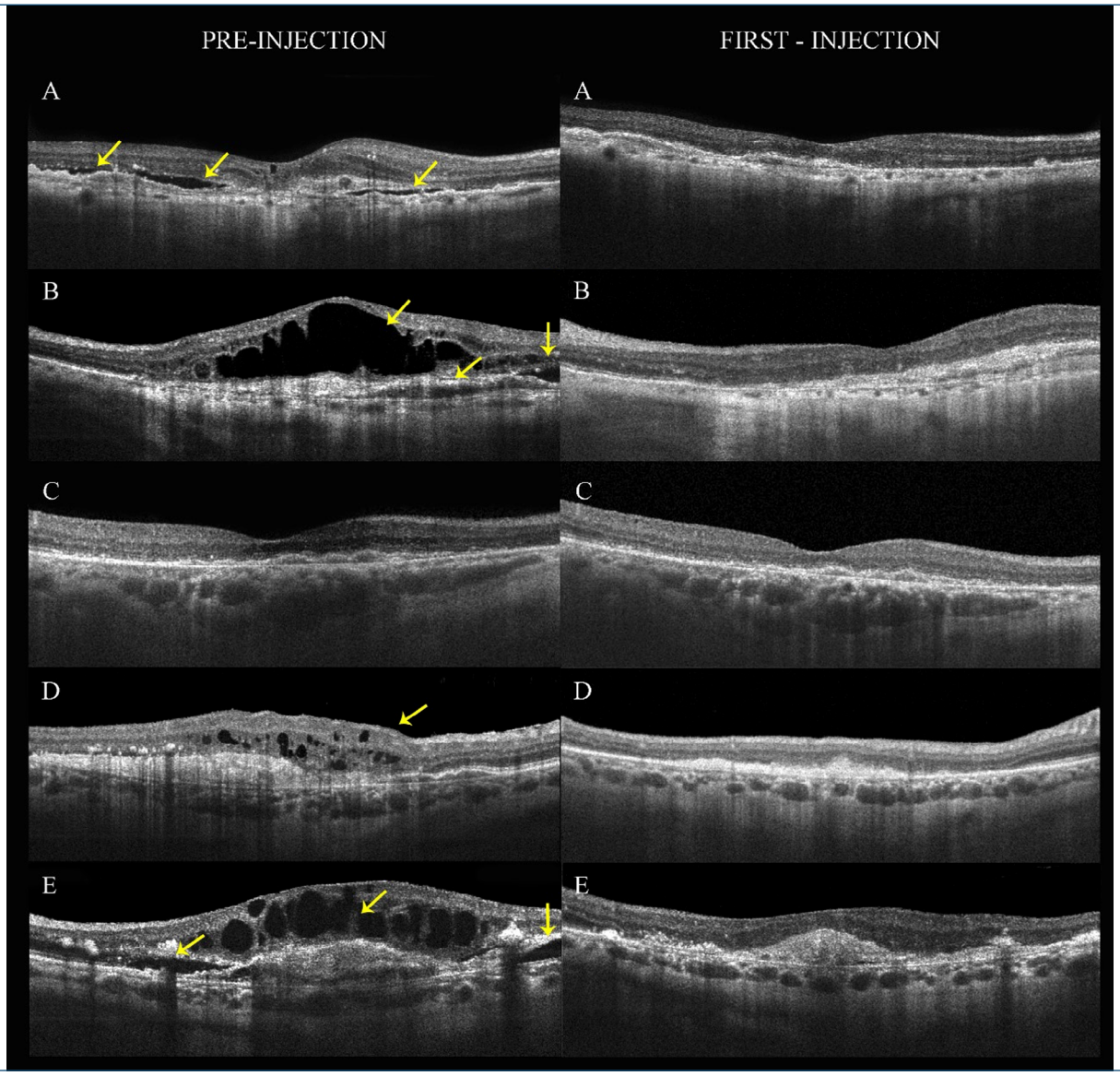

Figure 1. Spectral domain optical coherence tomography of five eyes (A to E) before (left column) and after (right column) the first brolucizumab injection. Yellow arrows point to the presence of fluid distribution within retinal layers before the injection.

Table 3. Mild and severe adverse events identified after brolucizumab intravitreal injections in the sample studied (eyes = 9)

Mild adverse events	n (%)	Severe adverse events	n (%)
Foreign body sensation	3 (14.3)	Retinal detachment	0
Blurred vision	1 (4.8)	Endophthalmitis	0
Vitreous floaters	1 (4.8)	Uveitis	0
Dry eye	0	Retinal vascular occlusion	0
Hyperemia	0	Retinal vasculitis	0

related to MNV exudative activity in the central visual field.[12] In our study, the CST decreased by 30.9%, which is equivalent to a 105 µm reduction. This finding is in accordance with other real-world studies. Similar results were obtained by Ota et al. (n = 48 patients; CST reduction of 66.8 µm; p < 0.001) and Bulirsch et al. (n = 57 patients; CST reduction of 57 µm; p< 0.001).[13,14] The higher CST variation reported in our study may be attributed to a smaller sample size (nine eyes).

Fluid resolution among retinal layers is another marker of suppressing neovascular membrane activity. After the first application of brolucizumab in our study, SRF was absorbed in 83.3% of the eyes (p = 0.025). Dugel et al. compared the SRF reduction using brolucizumab and aflibercept. They showed that IRF and/or SRF resolved in 61% of the eyes using brolucizumab compared to 35% in the aflibercept group.[15] In addition, in our study, complete reabsorption of fluid across all retinal layers was observed in five patients who received a complete loading dose (three) injection. Although statistical correlation could not be proved, these findings suggest meaningful improvement in anatomical markers of MNV activity,

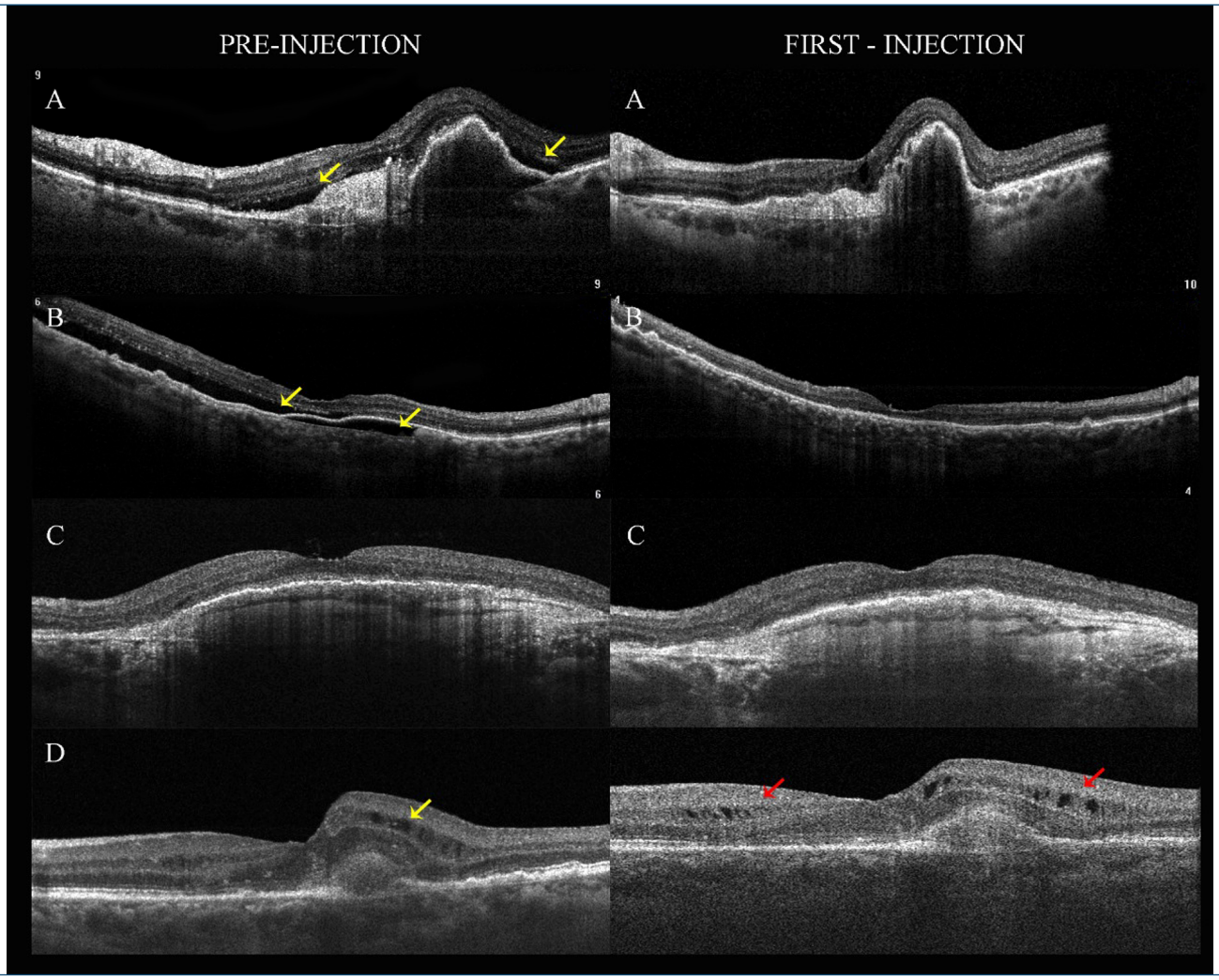

Figure 2. Spectral domain optical coherence tomography of the four additional eyes (A to D) before (left column) and after (right column) the first brolucizumab injection. Arrows point to the presence of fluid distribution within retinal layer pre-injection (yellow arrows) and after the first injection (red arrows).

which is considered a therapeutic response according to Amoaku et al.[7]

Although anatomic improvements were evidenced, there were no changes in visual acuity (p = 0.497). Previous studies with refractory cases of nAMD had similar results, probably because of selection bias: participants with advanced disease, irreversible macular degeneration, or presence of disciform scars.[13,16] Therefore, previous anatomical damage must be considered when interpreting the drug capacity of functional improvement.

In accordance with the pivotal studies by HAWK and HARRIER, the incidence of adverse events was low in this study, and all adverse events were categorized as mild (23.8%). Notably, no severe events were reported. Our findings contrast with the Merlin study, another important pivotal trial, which had to be discontinued due to a high incidence of occlusive vasculitis in participants receiving brolucizumab.[17] Moreover, Wykoff et al., in a systematic review of brolucizumab-related adverse events, analyzed 19 publications (63 cases) that reported retinal vasculitis and/or retinal occlusion.[18] The authors highlighted that the main risk factors of those events are previous intraocular inflammation and/or retinal occlusion. To avoid such complications, patients with the aforementioned profile were not injected with brolucizumab in the institution where this study was conducted. Therefore, this selection criterion, along with a smaller sample size, may explain the lower incidence of severe AEs herein compared to previous studies.[17,19]

The limitations of the current study include a single-center design, selection bias of advanced disease cases (limited visual prognosis), and small sample size. In addition, the treatment discontinuation regimen in some patients before reaching the loading dose, with three

injections limited outcomes. Moreover, an extended follow-up would be necessary to estimate the durability of neovascular suppression that this drug could imply.

CONCLUSION

This study evaluated the response of chronic nAMD cases to brolucizumab after being refractory to other anti-VEGF drugs in a real-world strict Brazilian population. Despite no improvements in visual acuity, our findings suggest that brolucizumab may represent an alternative medication for refractory cases of nAMD, considering its anatomical outcomes that may support a long-lasting therapeutic effect. There were no serious adverse events observed in this sample, likely reflecting the exclusion criteria of previous ocular uveitis or vasculitis. However, it is crucial for safety surveillance that practitioners keep updated and follow manufacturer recommendations regarding the need for drug suspension in case of ocular inflammation, retinal vasculitis, or vascular occlusion.

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AUTHORS' CONTRIBUTION

Gabriel Pinheiro Santos: study design, data acquisition, data analysis and interpretation, manuscript drafting, and critical revision. Raphael Caetano Rosa Abreu: conceptualization, study design, and data acquisition. Matheus Madeiro: data acquisition. Camila V. Ventura: conceptualization, study design, data analysis and interpretation, manuscript drafting, and critical revision. Fabiana Karla Aquino da Costa: conceptualization, study design, and critical revision. All authors approved the final version of the manuscript and are accountable for ensuring its accuracy and integrity.

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