Case Report

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Ophthalmology Research

Retinal Vasculitis Secondary to Brolucizumab

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ABSTRACT

Clinical Case: *An 85-year-old woman with neovascular AMD (OD) was treated with brolucizumab. After the second injection, she presented severe visual loss (BCVA (OD) of 0.3 to 0.01), intense vitritis, and vasculitis with retinal artery occlusion. Treatment with systemic and topical corticosteroids and laser panphotocoagulation was initiated, achieving stability of the condition.*

Discussion: Brolucizumab-induced retinal vasculitis is a rare but severe complication, likely immune-mediated. Early detection is crucial to prevent irreversible damage. This case highlights the need for strict monitoring and immediate management of inflammatory signs, emphasizing the importance of pharmacovigilance in advanced anti-VEGF treatments.

Keywords

Retinal vasculitis, Brolucizumab, neovascular AMD.

Introduction

Neovascular age-related macular degeneration (AMD) represents one of the leading causes of blindness in older adults worldwide. Treatment with anti-VEGF agents has revolutionized the approach to this disease, allowing effective control of neovascularization and retinal exudation. In this context, brolucizumab emerged as a third-generation option with the promise of spacing intravitreal injections and, consequently, reducing the treatment burden for patients. Its initial approval was supported by the results of clinical trials (HAWK and HARRIER) that demonstrated comparable efficacy to other anti-VEGF agents, with a potentially more flexible administration schedule [1,2].

However, after its introduction into clinical practice, cases of intraocular inflammation beyond classic uveitis began to be reported, manifesting as retinal vasculitis and vascular occlusions. Although rare, this phenomenon can have serious consequences, including permanent vision loss. Findings suggested an immuno-mediated or type III hypersensitivity component to the drug, leading to increased vigilance measures and the establishment of specific management guidelines to detect and treat these inflammatory episodes early [3].

We present the first case of retinal vasculitis associated with brolucizumab in our center with the aim of reviewing the nature of retinal vasculitis, its proposed pathophysiology, clinical characteristics, and therapeutic approach.

Clinical Case

We present the case of an 85-year-old female patient with a history of chronic hypertension and dyslipidemia, who visited our emergency department one year ago due to decreased visual acuity and metamorphopsia in her right eye (OD) with a one-month evolution. Her medical history only included cataract surgery in both eyes (OU) over 10 years ago.

On examination, she presented a best corrected visual acuity (BCVA) of 0.3 in OD and 0.9 in the left eye (OS). Anterior segment examination showed proper pseudophakia OU without other relevant findings. Fundus examination revealed macular drusen OU and a subfoveal subretinal hemorrhage in OD. Macular optical coherence tomography (OCT) showed the presence of a type 1 neovascular membrane (MNV) with subretinal fluid (Figure 1). With a diagnosis of neovascular AMD, intravitreal brolucizumab (Beovu®, Novartis, Basel) treatment was initiated, achieving neovascular inactivity with just one dose. The patient did not attend subsequent follow-ups and was lost to follow-up

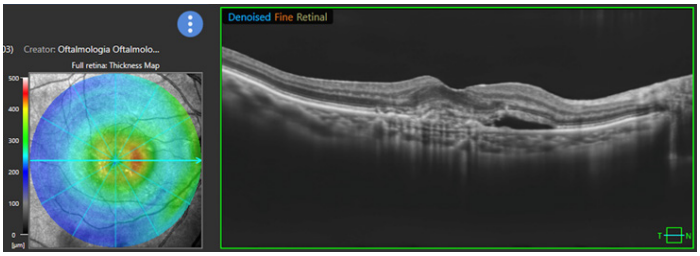

Figura 1: Imagen de OCT estructural en visita basal. Se evidencia presencia de MNV tipo 1 con líquido subretiniano. Tomado con Nidek RS-3000 Advance.

Six months after the initial brolucizumab dose, the patient returned via emergency services reporting new vision loss in OD. A new macular OCT showed recurrence of the previous MNV and an increased amount of subretinal fluid (Figure 2). A new brolucizumab injection was decided. Fifteen days after this second intravitreal injection, she reported profound visual loss, with BCVA decreasing from 0.3 to 0.01 in OD. Anterior segment examination revealed central corneal "mutton-fat" endothelial precipitates, Tyndall +, vitritis +++, and fundus examination showed arterial occlusion zones in both superior and inferior branches, with perivascular hemorrhages in arteries and veins OD (Figure 3). Treatment with oral prednisone 60 mg/day, prednisolone eye drops every 4 hours, and a cycloplegic drop every 8 hours was started. Over the following four weeks, the corticosteroid dose was progressively reduced until discontinuation. By the fourth week, the patient achieved BCVA improvement up to 0.4 OD, and due to the extensive retinal ischemia secondary to vasculitis, fluorescein angiography was avoided, proceeding instead with retinal panphotocoagulation (PFC), achieving stabilization of the condition (Figure 4).

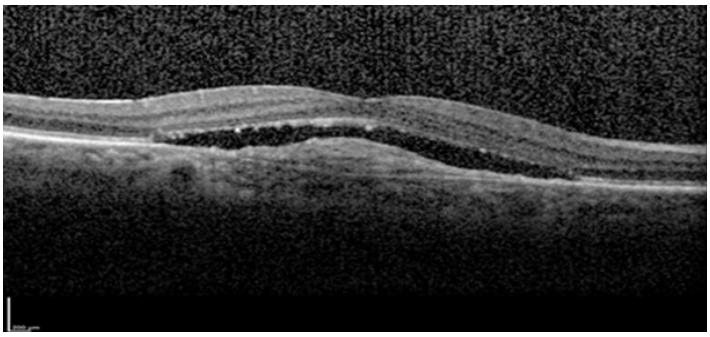

Figure 2: Imagen de OCT estructural al momento del debut del cuadro inflamatorio. Se mantiene MNV tipo 1 con aumento del fluido subretiniano. Tomado con Heidelberg Spectralis.

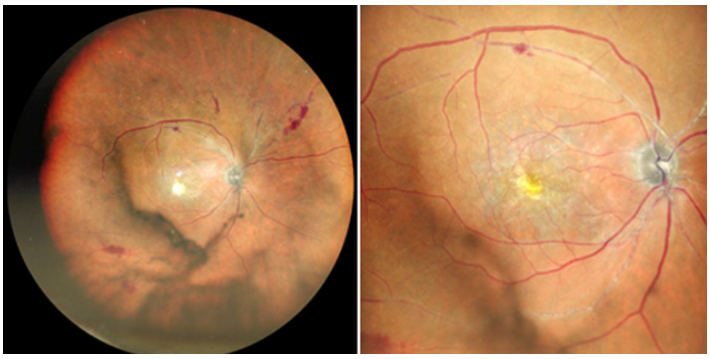

Figura 3: Retinografía cSLO ultra campo amplio (izquierda) y convencional (derecha) al momento del debut del cuadro inflamatorio. Se evidencia sombras secundarias a la vitritis, oclusión de vasos arteriales temporales y nasales y hemorragias perivenosas. Tomado con Nidek Mirante.

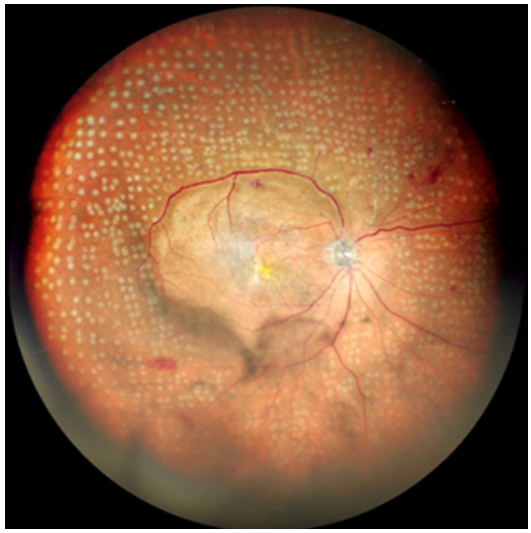

Figure 4: Retinografía cSLO ultra campo amplio posterior a tratamiento con fotocoagulación láser retiniana a las cuatro semanas de iniciado el cuadro. Tomado con Nidek Mirante.

Discussion

This case highlights one of the most serious and feared complications of brolucizumab in neovascular AMD treatment: retinal vasculitis with vascular occlusion. Although infrequent, this adverse event has been reported since the drug's introduction in clinical practice and has generated great concern due to its potential to cause irreversible vision loss [4].

Brolucizumab was approved based on phase III clinical studies HAWK and HARRIER, which compared its efficacy and safety with aflibercept 2 mg in patients with neovascular AMD. In both trials, brolucizumab demonstrated efficacy comparable to aflibercept in terms of visual acuity improvement and retinal fluid reduction, additionally allowing a more flexible treatment regimen with the possibility of injections

every 12 weeks in a significant proportion of patients [5].

In the HAWK study, which included 1,082 patients, and in the HARRIER study, with 743 patients, about 50% of patients treated with brolucizumab could maintain a 12-week dosing interval without disease activity, representing an advantage over aflibercept. However, despite these benefits, higher rates of intraocular inflammation (IOI) were observed in the brolucizumab group (4.6% in HAWK and 3.6% in HARRIER) compared to aflibercept (0.6% in HAWK and 1% in HARRIER) [6]. At the time of approval, the nature and potential severity of these adverse reactions were not fully understood.

After commercialization and more widespread use in clinical practice, severe IOI cases were reported, including uveitis, occlusive retinal vasculitis, and irreversible vision loss, leading to a reassessment of the drug's safety profile [4].

The exact mechanisms of brolucizumab-induced ocular inflammation are not yet fully elucidated, but an immune-mediated origin has been postulated. Anti-brolucizumab antibodies have been identified in patients who developed retinal vasculitis, suggesting a hypersensitivity response mediated by immune complexes [7]. Complement activation and cell-mediated inflammation may contribute to the inflammatory cascade culminating in retinal vascular damage. Additionally, the small molecular size of brolucizumab (26 kDa) allows greater tissue penetration, which could facilitate antigenic epitope exposure to the immune system, promoting an exaggerated inflammatory response in some individuals [8]. This immune response could progress in stages, initially manifesting as uveitis and, if untreated, progressing to vasculitis with vascular obstruction.

Witkin et al. also described significant intraocular inflammation cases without retinal vasculitis, suggesting different inflammatory mechanisms [9]. These observations add to findings by Sharma et al., who proposed that the inflammation observed in brolucizumab-treated patients could be mediated by an exacerbated immune response, possibly due to immune complex formation and complement activation [7].

The KINGFISHER study by Singh et al. evaluated brolucizumab's safety in diabetic macular edema patients, finding that although effective in retinal fluid reduction, it presented a higher rate of inflammatory adverse events compared to other anti-VEGF treatments [10].

Our patient's case exemplifies this severe adverse phenomenon. Initially, she was treated with brolucizumab for a type 1 neovascular membrane associated with AMD. After a first injection, the disease remained inactive, but with subretinal fluid recurrence, a second administration was decided. Days after this dose, she experienced severe and rapid visual acuity loss, accompanied by marked ocular inflammatory signs. Examination revealed "mutton-fat" keratic precipitates, severe vitritis, and multiple arterial occlusion areas, consistent with inflammatory retinal vasculitis. This presentation aligns with retinal vasculitis cases associated with brolucizumab described in the literature [11,12]. The observed branch artery occlusion suggests severe vascular compromise, with structural damage potentially affecting visual recovery.

Given the increasing number of serious complication reports, safety alerts and recommendations have been issued regarding strict monitoring of patients treated with Beovu®, with special attention to early IOI signs and thrombotic events [13]. Management should be immediate, with systemic and topical corticosteroids to mitigate inflammation and prevent irreversible retinal damage. In our patient, oral prednisone at 60 mg/day, topical corticosteroids, and cycloplegics were administered to reduce inflammation and prevent further complications. Various studies have suggested that visual prognosis in these cases depends on how quickly immunosuppressive treatment is initiated [14]. However, when vascular occlusion is extensive, recovery may be limited.

In 2022, management guidelines for brolucizumab by the Spanish Society of Ophthalmology were published [15]. They include patient profile selection and risk-benefit stratification. They emphasize the importance of pre-treatment examination to rule out IOI signs and subsequent examinations after each dose to monitor IOI and vasculitis, especially during the first year of treatment. Corticosteroids are established as first-line treatment, with dose and route depending on the severity of the condition, associated with PFC laser and vitrectomy as needed.

The treatment protocol has also been modified. Phase III studies (HAWK and HARRIER) used a loading dose of three injections separated by four-week intervals. Currently, the loading dose has been reduced to only two injections separated by six weeks and subsequent review, implying lower initial molar administration of the drug [16].

Currently, the informed consent form of the Spanish Society of Retina and Vitreous (SERV) for Beovu® in AMD includes "severe risks" such as intraocular inflammation and vasculitis. It is important to mention these risks to the patient and the higher probability of occurrence compared to other current anti-angiogenic drugs to enable a fully informed decision [17].

Conclusion

Retinal vasculitis is a serious complication of brolucizumab treatment. Although the incidence is low, ophthalmologists must be vigilant for inflammatory signs in patients treated with this drug. Early identification of intraocular inflammation is crucial since management should be immediate and intensive with systemic and topical corticosteroids.

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