OCCLUSIVE RETINAL VASCULITIS FOLLOWING INTRAVITREAL BROLUCIZUMAB FOR WET AGE-RELATED MACULAR DEGENERATION

Okluzyjne zapalenie naczyń siatkówki po doszklistkowym podaniu brolucizumabu w terapii wysiękowego zwyrodnienia plamki związanego z wiekiem

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Abstract

Brolucizumab is a humanized single-chain fragment of a monoclonal antibody that blocks vascular endothelial growth factors. The aim of this paper is to present a case of occlusive retinal vasculitis with intraocular inflammation following intravitreal administration of brolucizumab in a patient with wet age-related macular degeneration. An 84-year-old woman complained of decreased visual acuity in the right eye and floaters in the visual field. These symptoms occurred 54 days after the first intravitreal injection of 6 mg brolucizumab. Snellen visual acuity decreased from the pre-injection level of 0.6 to 0.05. An intraocular inflammatory reaction was detected. Ophthalmoscopy of the right eye revealed oedema of the optic nerve disc, pale foci of ischemia in the form of "cotton wool spots", retinal haemorrhages, and perivascular sheathing of retinal arteries with their multifocal complete or partial occlusion. Based on the clinical picture and diagnostic tests, the patient was diagnosed with occlusive retinal vasculitis with intraocular inflammation as a complication of intravitreal brolucizumab. Treatment included local and systemic steroid therapy. Right eye visual acuity improved reaching 0.4. A secondary sectoral reduction in the thickness of the nerve fibre layer of the right eye was found, with visual field defect. Conclusions. Early diagnosis and initiation of appropriate treatment as soon as possible can prevent severe vision loss in most cases of rare vascular inflammatory complication after intravitreal brolucizumab. However, ischemia associated with vasculitis may cause permanent changes in the morphology of retinal nerve fibres and lead to visual field deficits.

Streszczenie

Brolucizumab jest humanizowanym jednołańcuchowym fragmentem przeciwciała monoklonalnego, blokującym czynnik wzrostu śródbłonka naczyń. W pracy przedstawiono przypadek okluzyjnego zapalenia naczyń siatkówki z zapaleniem wewnątrzgałkowym, które wystąpiło po doszklistkowym podaniu brolucizumabu u pacjentki z wysiękowym zwyrodnieniem plamki związanym z wiekiem. 84-letnia kobieta zgłosiła się z powodu osłabienia ostrości wzroku w prawym oku oraz mętów w polu widzenia. Objawy te pojawiły się 54 dni po pierwszej iniekcji doszklistkowej 6 mg brolucizumabu. Ostrość wzroku pogorszyła się z przediniekcyjnej wartości 0,6 według tablicy Snellena do 0,05. Stwierdzono obecność wewnątrzgałkowego odczynu zapalnego. W badaniu oftalmoskopowym prawego oka uwidoczniono obrzęk tarczy nerwu wzrokowego, blade ogniska niedokrwienia (tzw. kłębki waty), drobne krwotoki siatkówkowe, pochewki zapalne przy naczyniach tętniczych siatkówki z ich wieloogniskową okluzją – całkowitą lub częściową. Na podstawie obrazu klinicznego i wyników badań diagnostycznych rozpoznano okluzyjne zapalenie naczyń siatkówki z towarzyszącym zapaleniem wewnątrzgałkowym jako powikłanie po podaniu brolucizumabu. W leczeniu zastosowano steroidoterapię miejscową i ogólną. Odnotowano poprawę ostrości wzroku w prawym oku do 0,4 wg Snellena. Zaobserwowano wtórne sektorowe zmniejszenie grubości warstwy włókien nerwowych tego oka, z ubytkiem w polu widzenia. Wnioski: U pacjentów z rzadkim naczyniowym powikłaniem zapalnym po doszklistkowym podaniu brolucizumabu, wczesne rozpoznanie i jak najszybsze wdrożenie odpowiedniego leczenia w większości przypadków może zapobiec ciężkiej utracie widzenia. Jednak niedokrwienie towarzyszące zapaleniu naczyń może trwale zmienić morfologię włókien nerwowych siatkówki i ograniczyć pole widzenia.

Keywords: wet age-related macular degeneration; intraocular inflammation; brolucizumab; occlusive vasculitis

Słowa kluczowe: wysiękowe zwyrodnienie plamki związane z wiekiem; zapalenie wewnątrzgałkowe; brolucizumab; okluzyjne zapalenie naczyń

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Introduction

Brolucizumab is an intravitreal vascular endothelial growth factor (VEGF) blocker. It was approved by the U.S. Food and Drug Administration (FDA) for the treatment of wet age-related macular degeneration (wAMD) in 2019. The European Medicines Agency (EMA) followed with its approval in 2020. Brolucizumab is a humanised single-chain Fv (scFv) antibody fragment produced by recombinant DNA technology in *Escherichia coli*. It is the smallest molecule among the currently available anti-VEGF drugs. Its molecular weight is 26 kDa and is significantly smaller compared to aflibercept (114 kDa) and ranibizumab (48 kDa) [1–3].

Brolucizumab is administered intravitreally at a dose of 6 mg. It delivers a 12-fold higher molar dose as compared to 2 mg aflibercept and 22-fold higher molar dose as compared to 0.5 mg ranibizumab [1]. The drug has a strong inhibitory effect and high affinity for all VEGF-A isoforms. Inhibition of the VEGF pathway has been shown to slow the progression of neovascular lesions, suppress endothelial cell proliferation, and reduce vascular permeability.

The molecular structure of brolucizumab contributes to significantly improved morphological outcomes of wAMD therapy, including reduced central retinal thickness and decreased fluid accumulation (intraretinal, subretinal, and beneath the retinal pigment epithelium), which are indicators of disease activity [2–4]. In clinical practice, brolucizumab is used to treat wAMD in both treatment-naïve patients and those who have become unresponsive to other anti-VEGF agents [5].

Despite the unquestionably good outcomes of intravitreal wAMD therapy, both inflammatory and non-inflammatory adverse events (AEs) associated with anti-VEGF treatments, including brolucizumab, have been reported. Intraocular inflammation (IOI), either sterile or infectious, is the most serious complication. Retinal vasculitis is a newly identified AE of brolucizumab [6, 7].

In this paper, we present a clinical case of occlusive retinal vasculitis (ORV) with intraocular inflammation (IOI) following intravitreal administration of brolucizumab in a patient diagnosed with wAMD.

Case report

An 84-year-old woman reported to the Department of Ophthalmology of the Military Institute of Medicine – National Research Institute due to blurred vision with accompanying decreased visual acuity (VA) in the right eye and floaters in the field of vision. Although these symptoms occurred 54 days after the first intravitreal injection of 6 mg brolucizumab into the right eye for wAMD, the patient presented four days after symptom onset. The woman had previously been treated under a drug programme and had been receiving an intravitreal anti-VEGF drug, aflibercept, in her right eye. Despite repeated injections, the neovascular membrane activity persisted with the presence of fluid collections. Therefore, a decision was made to switch to brolucizumab. Her left eye did not show any significant abnormalities. The woman received chronic treatment for systemic diseases such as hypertension, type 2 diabetes mellitus and gout.

Ophthalmological examination showed reduced right VA from the pre-injection Snellen acuity of 0.6 to 0.05. Visual function in the left eye was normal. The intraocular pressure (IOP) was normal in both eyes. Slit-lamp examination of the anterior segment of the right eye revealed minimal deep injection (redness), fine corneal endothelial deposits, and grade +1 inflammatory cells in the anterior chamber (AC), without hypopyon. The posterior segment of the right eye showed grade +1 inflammation in the vitreous chamber. In addition to degenerative macular changes, ophthalmoscopy and true colour ultra-widefield fundus imaging of the right eye found a pale optic disc with blurred oedematous borders, pale peripapillary cotton wool ischemic spots, peripheral retinal and vascular haemorrhages, as well as perivascular sheathing along the retinal arteries, with their complete (greyish inflammatory material inside the vessels) or partial multifocal occlusion, with interruption of the blood column in the vessel (Fig. 1A). The anterior and posterior segments of the left eye were normal.

Fluorescein angiography (FA) (Fig. 2A) showed delayed filling of the retinal vascular bed with retrograde flow of the dye into the right ocular vessels, extensive peripapillary and peripheral nonperfusion zones in the posterior pole (temporal quadrants), partially preserved perfusion in the macula lutea, complete or partial arterial occlusion with segmentally disrupted dye flow, dye leakage through the vessel walls in the late phases of the examination in a few retinal arteries, and dye leakage on the optic disc.

Spectral domain optical coherence tomography (SD-OCT) of the right macula revealed elevation of the retinal pigment epithelium without intraretinal or subretinal fluid. Increased reflectivity of the inner retinal layers was observed in the perifoveal zone with blurring of the retinal lamellar structure, suggesting ischemia (Fig. 3B).

Due to the symptoms of right IOI, laboratory workup was done, including erythrocyte sedimentation rate

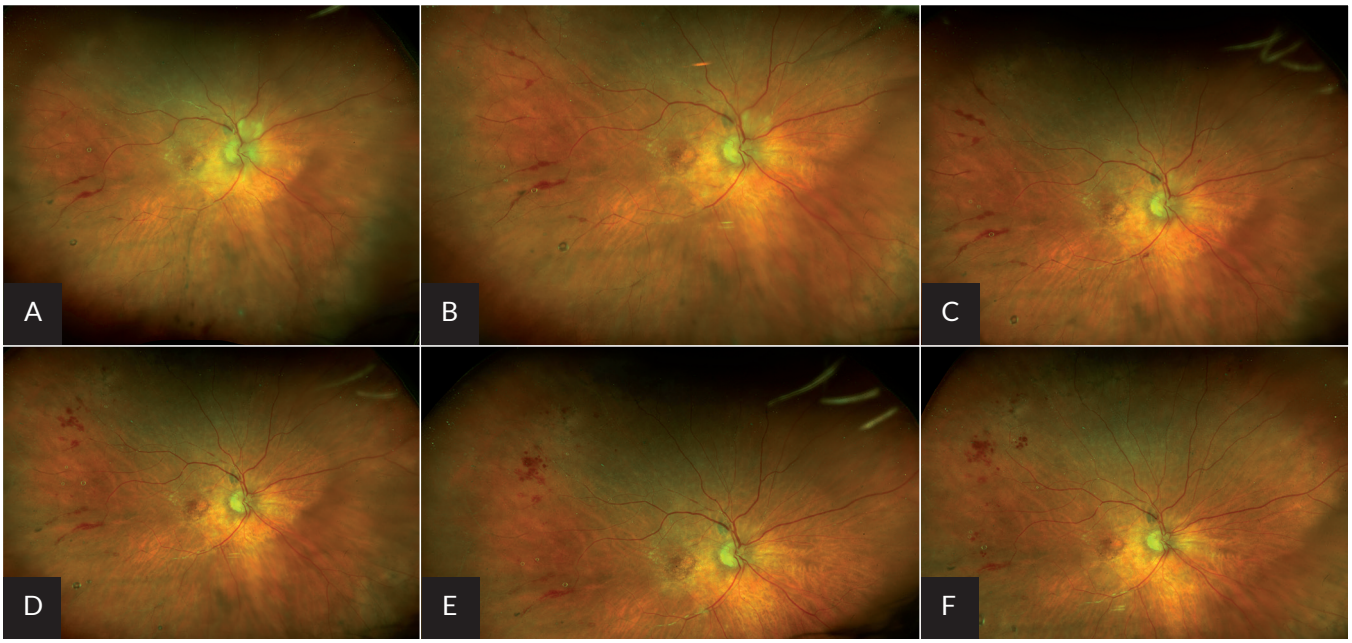

Figure 1. Colour images of the fundus of the right eye. **A.** On admission. **B.** One week after treatment onset. **C.** At 2 weeks. **D.** At 6 weeks. **E.** At 8 weeks. **F.** At 10 weeks

(ESR), C-reactive protein and peripheral blood count with differential. No abnormalities were found, which allowed, among other things, to exclude giant cell arteritis.

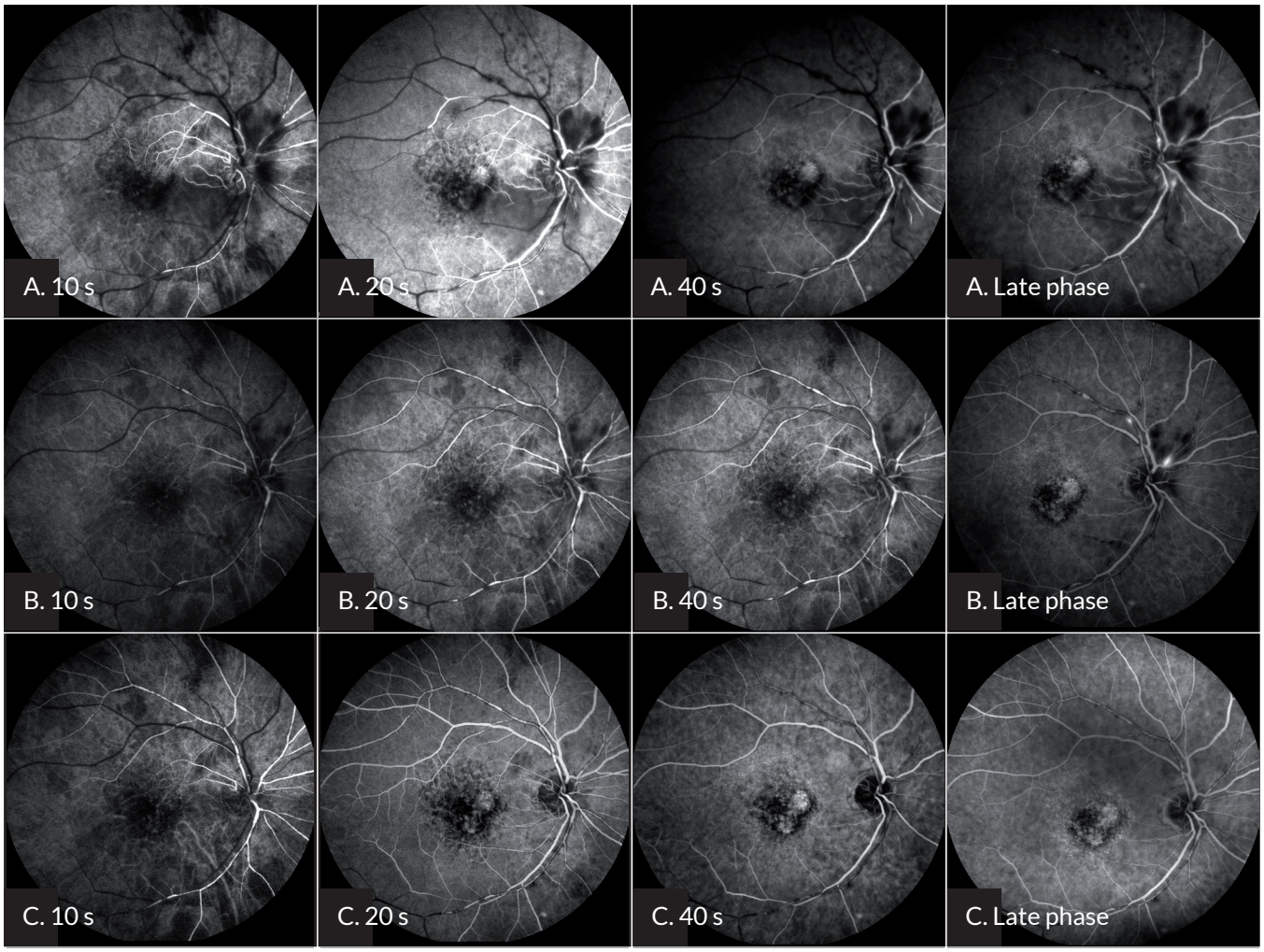

Figure 2. Fluorescein angiography (FA) of the right eye. **A.** On admission and ORV diagnosis. **B.** One week after treatment onset. **C.** One month after treatment onset

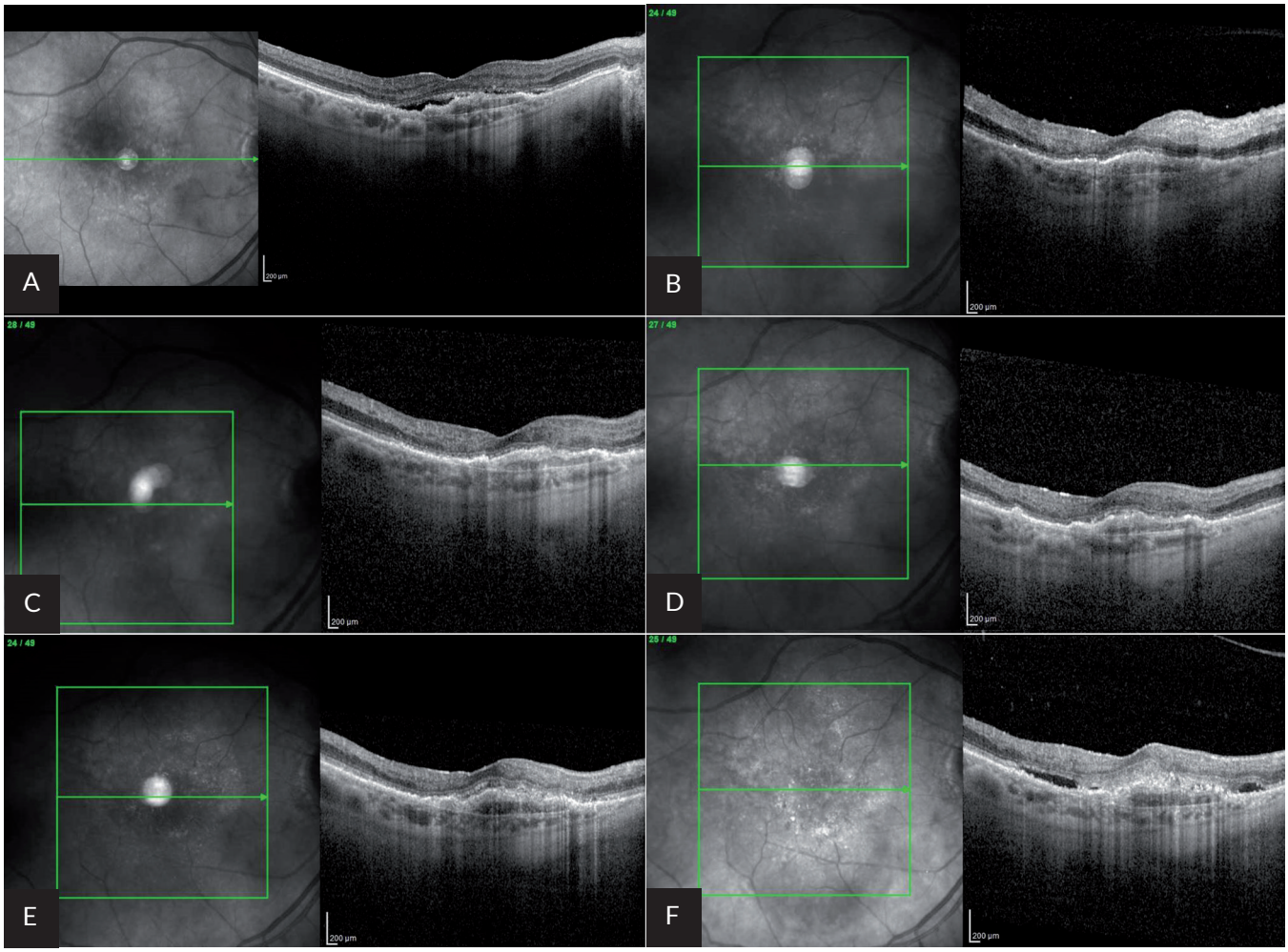

Figure 3. Optical coherence tomography (OCT) of the right eye. **A.** Before brolucizumab injection; subretinal fluid present. **B.** At 2 months of brolucizumab injection, on the day of presentation to the Clinic with ORV symptoms. **C.** At one week of steroid therapy onset. **D.** At 3 weeks of steroid therapy onset. No signs of neovascularization, significant resolution of perifoveal hyperreflectivity. **E.** At one month of steroid therapy onset and 3 months after brolucizumab administration. Visible subretinal fluid (gradual relapse of disease activity) and progression of retinal pigment epithelial detachment (PED) parameters. **F.** At 4 months of brolucizumab administration; clearly visible subretinal fluid

Based on the clinical picture, imaging findings, and similar clinical cases reported by the American Society of Retinal Specialists (ASRS), the patient was diagnosed with a complication of intravitreal brolucizumab, i.e. brolucizumab-associated retinal vasculitis (BARV) with IOI. Local and systemic steroid therapy was started. Periocular prednisolone acetate, topical dexamethasone 0.1% (eye drops, initially at 1-hour intervals, then five times daily), along with a non-steroidal anti-inflammatory drug and mydriatics were included. Intravenous steroid therapy with methylprednisolone 2 × 500 mg per day was initiated, reaching a total dose of 3 g. Then, oral steroid therapy with prednisone was continued at an initial dose of 40 mg per day, which was gradually reduced by 5 mg in the weeks that followed.

One week after the diagnosis of BARV, right VA improved to Snellen 0.3. Slit-lamp examination revealed no inflammatory cells in the AC of the right eye, with reduced inflammatory exudate in the vitreous chamber. Ophthalmoscopy and colour fundus photography of the right eye showed gradual regression of perivascular sheathing (Fig. 1). Fluorescein angiography (FA) showed reduced vascular leakage with segmental perivascular pigment stasis, delayed arteriolar filling with partial improvement of retinal perfusion compared to baseline (Fig. 2), and no pigment leakage on the optic disc. SD-OCT showed no signs of active wAMD (Fig. 3).

Six weeks after BARV diagnosis, right visual acuity stabilized at 0.4 Snellen. Right eye FA showed no vascular leakage, delayed and partial filling of the temporal branches of the central retinal artery, nonperfusion zones in the temporal quadrants, and a dark, ischemic optic disc (Fig. 2). Ophthalmoscopy and colour fundus photography at subsequent follow-ups showed resolution of inflammatory opacities in the vitreous body, optic disc oedema, and cotton wool spots, partial arterial revascularization with segmental blood column restoration in the affected vessels, as well as persistent intraretinal haemorrhages (Fig. 1). Analysis of the thickness of the right retinal nerve fibres showed their secondary, sectoral thinning within the optic disc (Fig. 4). A scotoma was detected in the right eye, covering the upper half of the visual field (Fig. 5).

After BARV diagnosis, right eye intravitreal therapy was discontinued. Subsequent follow-up examinations, con-

ducted 3 and 4 months after brolucizumab administration, showed a decrease in right VA to Snellen 0.16. Right macular SD-OCT revealed recurrence of wAMD activity, with the presence of subretinal fluid and increased pigment epithelial detachment (PED) parameters (Fig. 3). The patient was qualified to resume anti-VEGF therapy with a medication other than brolucizumab.

Discussion

Sterile intraocular inflammation (SII) following anti-VEGF treatment is characterized by acute onset and intraocular involvement in the absence of an infectious agent. Reported incidence rates vary across studies, ranging from 0.02% to 0.37% [8, 9]. Symptoms of SII typically appear within 24 hours to seven days following intravitreal injection [10–12]. The most common manifestations include blurred vision, floaters, and mild to moderate ocular pain, with photophobia occurring less frequently [12, 13]. Although visual acuity typically recovers to an average of 20/55 after resolution of SII following treatment, which may involve topical and systemic steroids, mydriatics, antibiotics, and, in severe cases, pars plana vitrectomy (PPV), approximately 15% of cases result in permanent vision loss of two lines or more, often associated with advanced inflammation with fibrin deposits and older age [12, 14].

Brolucizumab-associated SII does not significantly differ in terms of symptoms, treatment, or therapeutic outcomes from inflammations observed after other anti-VEGF agents [14]. However, data from clinical practice indicate that it has a more delayed course. In cases without vascular involvement, symptoms typically appear an average of 24 days post injection [15]. Brolucizumab has a higher rate of SII (>4%) compared to other anti-VEGF therapies. This may be due to higher serum levels of anti-brolucizumab antibodies in patients undergoing therapy compared to other anti-VEGF medications [2, 15]. The HAWK and HARRIER trials found that these antibodies were present in 36 to 52% of patients even before initiation of brolucizumab therapy, increasing to 53–67% once the treatment was started [2, 15]. Higher rates of SII were observed among individuals with these antibodies (6%) compared to those without (2%) [15].

In February 2020, i.e. a few months after FDA approval of brolucizumab, the ASRS announced receiving over a dozen BARV case reports. More than two-thirds of these were considered ORVs, which were associated with significant VA loss [16, 17]. These reports, along with case studies from routine clinical practice, prompted Novartis Pharma AG to establish a committee to monitor brolucizumab safety data. A post hoc analysis of HARRIER and HAWK [18] found that among 1,088 eyes treated with brolucizumab, 36 cases (3.3%) developed 'probable or definite' retinal vasculitis. Vasculitis coexisted with IOI in 24 of these 36 cases (67%). The rates of BARV (3.3% and 2.1%, respectively, for the individual studies) and vascular occlusion were significantly higher than those reported in the original HARRIER and HAWK trials. However, despite the actual risk of vision loss associated with these events, the overall rate of moderate to severe visual acuity loss (≥15 ETDRS letters) was comparable between brolucizumab (7.4%) and aflibercept (7.7%) treatment groups [2, 4, 18].

The aetiology of brolucizumab-related retinal vasculitis remains unknown. It is unlikely that the molecule itself directly causes inflammation, particularly since it lacks an Fc region and does not activate the complement system or antibody-mediated cytotoxicity mechanisms [19].

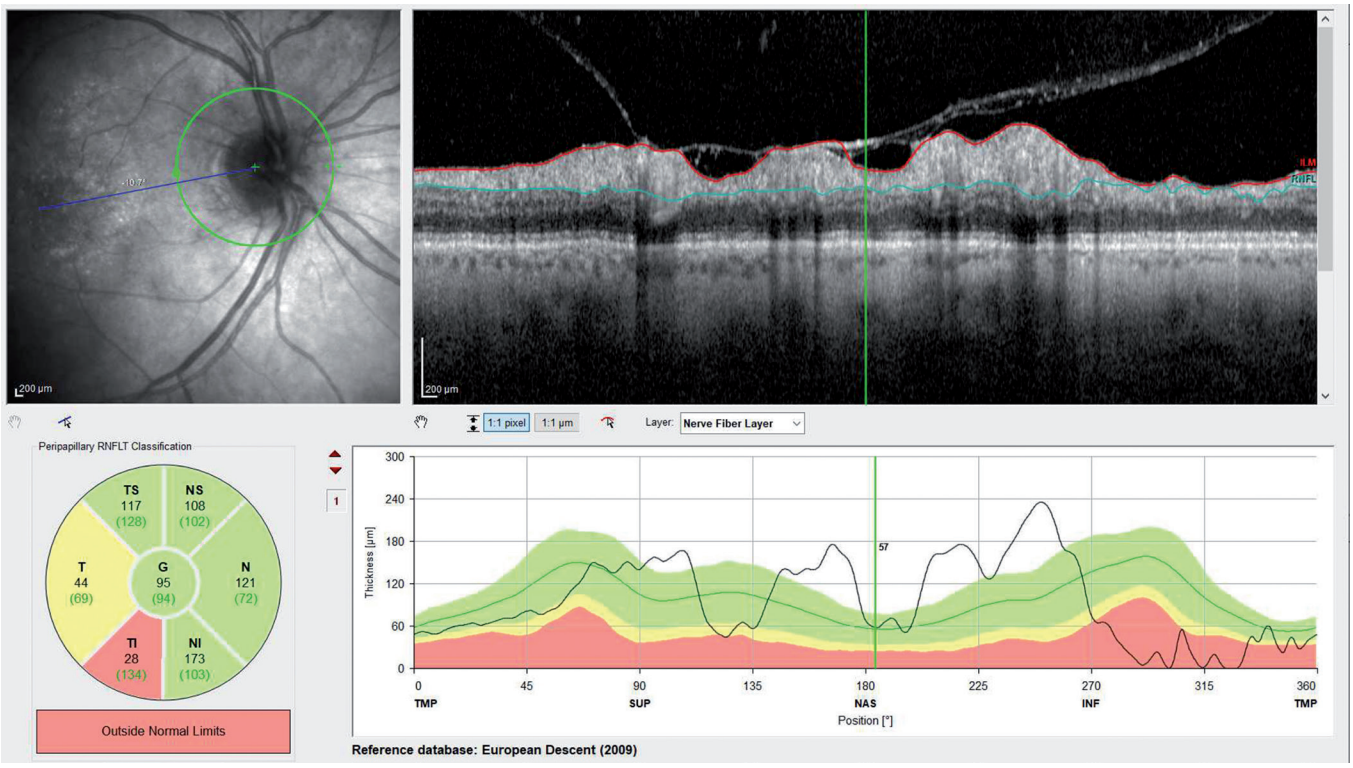

Figure 4. OCT of the right optic nerve. Evident sectoral loss of nerve fibres in the lower part

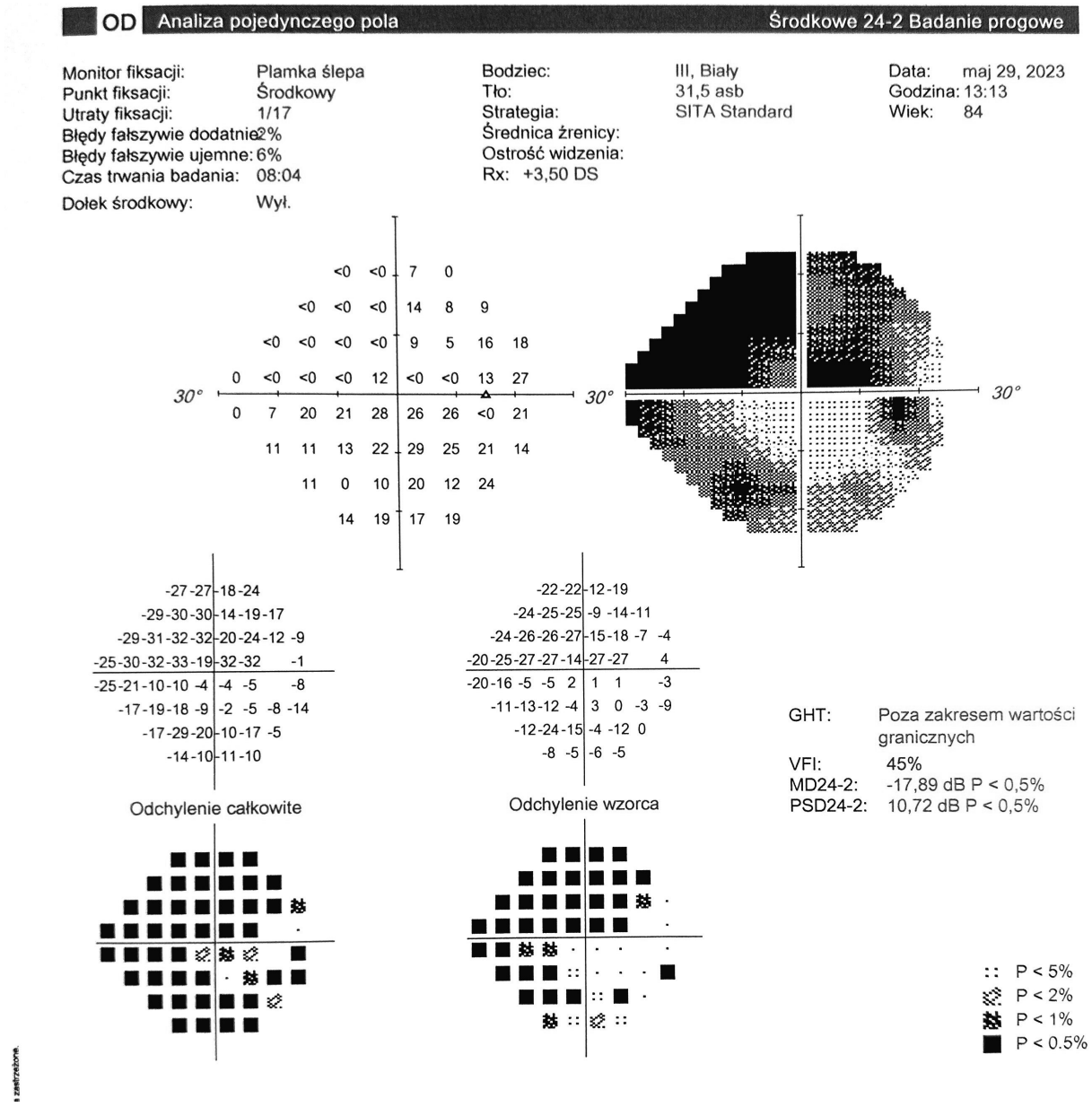

Figure 5. Visual field test for the right eye. Evident limitation of the visual field, mainly in the upper quadrants

Although impurities related to drug manufacturing, storage, or delivery are known to contribute to SII, this is unlikely to account for the majority of BARV cases given that symptom onset is often delayed and most cases are very rare. One hypothesis suggests that brolucizumab's smaller molecular weight may allow for deeper retinal penetration and increased VEGF inhibition. In the presence of concomitant inflammation, this could additionally diminish vascular perfusion and increase ischaemia, especially in eyes with reduced retinal blood flow at baseline [6, 17]. Alternatively, BARV may arise from the already mentioned anti-brolucizumab antibodies [2, 15]. In the presence of anti-drug antibodies, systemic monoclonal antibody therapy, including anti-VEGF agents, e.g. in the treatment of cancer, induces type III hypersensitivity reaction leading to vasculitis [20]. BARV may represent a similar reaction wherein intravascular deposition of IgG/IgM complexes causes vasculitis and vascular occlusion. This mechanism would be similar to the pathogenesis of haemorrhagic occlusive retinal vasculitis (HORV), which is seen in some patients who receive intraocular vancomycin and have been exposed to vancomycin previously [21].

Currently, histopathological studies related to HORV also suggest possible involvement of a type IV hypersensitivity reaction primarily involving T cells [22]. A case report with an analysis of a vitreous sample collected during vitrectomy in a patient with BARV showed the presence of CD3, CD4, CD8 and CD68 proteins. These findings indicate the presence of T cells and histiocytes, suggesting a type IV hypersensitivity reaction [23]. The observed coincidence of the presence of B and T cells may indicate a mixed type III and IV response [23, 24]. The time of BARV symptom onset also suggests a delayed hypersensitivity reaction, in which repeated exposure to the drug may result in a more rapid immune response. In the reported BARV case series, symptoms appeared on average between 30 and 53 days after injection [6, 15]. However,

Baumal et al. found that retinal vasculitis occurred earlier in patients who received more than one brolucizumab injection [6]. Additional factors, such as HLA subtype, immune status, comorbidities, or previous exposure to compounds structurally similar to brolucizumab, may also play a role in the pathogenesis of BARV [6].

Previous studies suggest that BARV is more common in women (88–100%), with an average age of 77 to 79 years. Most cases (92–96%) occur in Caucasians [6, 15]. Cardiovascular diseases (CVDs), such as hypertension, cardiac arrhythmias, as well as diabetes mellitus, and previous pneumonia may be risk factors for BARV. All ORV patients included in the HARRIER and HAWK trials had a medical history of CVD [18]. Similar findings have been reported in retrospective case series [4, 6]. Cancer or autoimmune disorders (e.g. multiple sclerosis, Graves disease or Raynaud's syndrome) were rarely reported [4, 6]. Symptoms of inflammation appear within 7 to 56 days after the last administration of brolucizumab [4, 6, 16, 17]. Blurred vision (58–62%), floaters (46–67%), redness (19%), pain (17–31%), and scotoma (12–25%) are the hallmark symptoms [4, 6, 16–17]. Visual acuity usually deteriorates, from an average of 20/53 at the time of brolucizumab administration to a mean of 20/191 at diagnosis [6]. IOI is usually present (92–100% of cases). Inflammation may be localized to the AC (0–31%), vitreous body (27%), or both (35–73%) [4, 16, 17]. Additionally, fine keratic precipitates, conjunctival injection, and Descemet folds have also been observed. No cases of hypopyon have been reported. Clinical signs of vasculitis are typically, though not always, present at the time of diagnosis. A minority of patients may present with recurrent IOI with vascular involvement, even if corticosteroids were started and the intraocular inflammation has decreased [25]. Vasculitis can involve arteries, veins, and capillaries. Both large- and small-calibre retinal arteries can be affected, showing narrowing, occlusion, and perivascular sheathing. Symptoms of retinal ischemia include retinal whitening, cotton wool spots, intraretinal haemorrhage, and pericentral acute middle maculopathy. Vascular occlusion accompanies inflammation in 67–85% of cases [6, 15].

The presented clinical case of BARV with IOI aligns with the known risk factors for this complication, as reported in the literature and mentioned above. Typical symptoms also emerged within a characteristic delayed time frame following brolucizumab injection. Both the anterior segment and the vitreous body of the eye were involved. The inflammation was sterile; however, infectious causes (infection-related symptoms typically arise within 3–4 days of drug administration, whereas aseptic reactions to brolucizumab usually manifest after several weeks) and systemic diseases that can cause vasculitis should always be considered in the differential diagnosis of IOI. Diagnostic tools, including FA, SD-OCT and wide- field imaging, allowed for the detection of ORV hallmarks, as well as for a precise assessment of the distal retinal periphery. Wide-field imaging is crucial in this complication, as signs of vasculitis may be subtle, scattered, and located just beyond the central posterior pole. In the presented case, the inflammatory changes were accompanied by a significant decline in visual acuity. The most prognostically concerning findings were ischemic changes in critical visual areas of the posterior pole, specifically the peripapillary region and macula, characterized by limited perfusion and secondary blurring of the papillary retinal lamellar structure.

Treatment of IOI, whether or not accompanied by vasculitis, should be prompt and aggressive. In cases of inflammation limited to the anterior chamber with preserved visual function, intensive topical corticosteroids (with sub-Tenons steroid injections) may be sufficient. Simultaneous monitoring of the posterior segment is essential. Inflammatory reaction involving the vitreous body is an indication for systemic steroids, initially at high intravenous doses, followed by oral maintenance therapy for a period of usually 6–12 weeks [6, 15, 16, 26–29]. In cases with significant vitreous involvement, PPV may be considered [28]. Case studies of BARV have shown that visual function may improve in some patients following steroid therapy [6, 15–17, 21–29], although not always to the pre-brolucizumab level. Wykoff et al. (2023) reviewed a total of 19 publications (70 eyes) on BARV. Of the eyes assessed for pre- and post-event VA, 22/42 eyes (52.4%) showed unchanged (±0.08 logMAR) or improved VA compared with the last recorded pre-event assessment, whereas 15/42 eyes (35.7%) showed ≥0.30 logMAR VA reduction (≥15 letters). Patients showing no VA loss were on average slightly younger and had higher rates of nonocclusive events [30].

In the presented case with vitritis, intensive local and systemic steroid therapy was initiated immediately upon the patient's presentation. During the first week of treatment, marked functional improvement and reduction of inflammation were achieved. After six weeks of therapy, Snellen VA of 0.4 was noted, which is two lines lower compared to the pre-brolucizumab values. Despite resolution of active inflammation and partial retinal revascularization, long-term follow-up revealed persistent consequences of prior ischemia in the form of optic nerve atrophy and visual field defect. In our view, ischemia secondary to BARV should be regarded as one of the most significant risk factors for permanent functional impairment following this complication.

Given the risk of adverse events such as BARV, the question arises as to how the associated risk of vision loss can be minimized. Patients should be educated about the potential symptoms of IOI following brolucizumab administration and advised to report to the clinic immediately upon experiencing any concerning symptoms [26, 27]. In the presented case, the patient reported a few days after symptom onset, delaying the initiation of appropriate treatment. Available data indicate that IOI symptoms following brolucizumab injection may occur over a broad time interval. Additional monitoring follow-ups between brolucizumab injections are not recommended; however, special emphasis should be placed on patient education. Before each subsequent brolucizumab injection, a thorough ophthalmological examination should be performed using a slit lamp (following pupil dilation) and vitreous assessment to detect inflammatory cells and subtle peripheral vascular occlusions. Most IOI cases (74%) in HAWK and HARRIER trials were detected within the first 6 months of treatment, with only 14% occurring between

6 and 12 months and another 12% after 12 months [4]. Therefore, ophthalmologists should remain vigilant for signs of inflammation, even beyond the first six months of therapy.

In the presented case, several months after BARV onset and following the resolution of inflammation, further significant decline in right eye VA was observed. Thorough diagnosis using wide-field imaging ruled out the recurrence of inflammation. VA deterioration was due to activation of wAMD, as confirmed by SD-OCT. The patient was qualified to resume anti-VEGF therapy, but with a different agent. This is one of the elements of prophylaxis. Furthermore, simultaneous administration of brolucizumab to both eyes should be avoided [31]. Ongoing treatment of wAMD in our patient is being closely monitored.

Conclusions

Brolucizumab is widely used worldwide for wAMD and diabetic macular oedema. Its efficacy and adverse events are continuously monitored through current literature [30, 32–34]. When qualifying patients for intravitreal brolucizumab injections and during treatment monitoring, it is important to remain aware of a rare yet vision-threatening complication in the form of retinal vasculitis, which often coexists with intraocular inflammation. Patient education, early diagnosis and prompt initiation of appropriate treatment can prevent severe vision loss in most cases. However, ischemia accompanying vasculitis may lead to permanent morphological changes in the retinal nerve fibres and, consequently, reduced field of vision.

References

1. Dugel PU, Jaffe GJ, Sallstig P, et al. Brolucizumab versus aflibercept in participants with neovascular age-related macular degeneration: a randomized trial. Ophthalmology, 2017; 124: 1296–1304. doi: 10.1016/j.ophtha.2017.03.057
2. Dugel PU, Koh A, Ogura Y, et al.; HAWK and HARRIER Study Investigators. HAWK and HARRIER: Phase 3, Multicenter, Randomized, Double-Masked Trials of Brolucizumab for Neovascular Age-Related Macular Degeneration. Ophthalmology, 2020; 127: 72–84. doi: 10.1016/j.ophtha.2019.04.017
3. Nguyen QD, Das A, Do DV, et al. Brolucizumab: evolution through preclinical and clinical studies and the implications for the management of neovascular age-related macular degeneration. Ophthalmology, 2020; 127: 963–976. doi: 10.1016/j.ophtha.2019.12.031
4. Dugel PU, Singh RP, Koh A, et al. HAWK and HARRIER: Ninety-Six-Week Outcomes from the Phase 3 Trials of Brolucizumab for Neovascular Age-Related Macular Degeneration. Ophthalmology, 2021; 128: 89–99. doi: 10.1016/j.ophtha.2020.06.028. Erratum in: Ophthalmology, 2022; 129: 593–596. doi: 10.1016/j.ophtha.2022.02.022
5. Kumar A, Ferro Desideri L, Ting MYL, Anguita R. Perspectives on the currently available pharmacotherapy for wet macular degeneration. Expert Opin Pharmacother, 2024; 25: 755–767. doi: 10.1080/14656566.2024.2354921
6. Baumal CR, Spaide RF, Vajzovic L, et al. Retinal vasculitis and intraocular inflammation after intravitreal injection of brolucizumab. Ophthalmology, 2020; 127: 1345–1359. doi: 10.1016/j.ophtha.2020.04.017
7. Cox JT, Eliott D, Sobrin L. Inflammatory complications of intravitreal anti-VEGF injections. J Clin Med, 2021; 10: 98. doi: 10.3390/jcm10050981
8. Daien V, Nguyen V, Essex RW, et al.; Fight Retinal Blindness! Study Group. Incidence and outcomes of infectious and noninfectious endophthalmitis after intravitreal injections for age-related macular degeneration. Ophthalmology, 2018; 125 : 66–74. doi: 10.1016/j.ophtha.2017.07.005
9. Knickelbein JE, Chew EY, Sen HN. Intraocular inflammation following intravitreal injection of anti-VEGF medications for neovascular age-related macular degeneration. Ophthalmic Epidemiol, 2016; 23: 69–70. doi: 10.3109/09286586.2015.1122067
10. Wickremasinghe SS, Michalova K, Gilhotra J, et al. Acute intraocular inflammation after intravitreous injections of bevacizumab for treatment of neovascular age-related macular degeneration. Ophthalmology, 2008; 115: 1911–1915. doi: 10.1016/j.ophtha.2008.05.007
11. Shah CP, Garg SJ, Vander JF, et al.; Post-Injection Endophthalmitis (PIE) Study Team. Outcomes and risk factors associated with endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents. Ophthalmology, 2011; 118: 2028–2034. doi: 10.1016/j.ophtha.2011.02.034
12. Greenberg JP, Belin P, Butler J, et al.; Aflibercept Sterile Inflammation Research Group. Aflibercept-Related Sterile Intraocular Inflammation Outcomes. Ophthalmol Retina, 2019; 3: 753–759. doi: 10.1016/j.oret.2019.04.006
13. Agrawal S, Joshi M, Christoforidis JB. Vitreous inflammation associated with intravitreal anti-VEGF pharmacotherapy. Mediators Inflamm, 2013; 943409. doi: 10.1155/2013/943409
14. Hahn P, Chung MM, Flynn HW Jr, et al. Postmarketing analysis of aflibercept-related sterile intraocular inflammation. JAMA Ophthalmol, 2015; 133: 421–426. doi: 10.1001/jamaophthalmol.2014.5650
15. Witkin AJ, Hahn P, Murray TG, et al. Brolucizumab-associated intraocular inflammation in eyes without retinal vasculitis. J Vitreoretin Dis, 2021; 5: 326–332. doi: 10.1177/2474126420975303
16. Haug SJ, Hien DL, Uludag G, et al. Retinal arterial occlusive vasculitis following intravitreal brolucizumab administration, Am J Ophthalmol Case Rep, 2020; 18: 100680. doi: 10.1016/j.ajoc.2020.100680
17. Jain A, Chea S, Matsumiya W, et al. Severe vision loss secondary to retinal arteriolar occlusions after multiple intravitreal brolucizumab administrations. Am J Ophthalmol Case Rep, 2020; 18: 100687. doi: 10.1016/j.ajoc.2020.100687
18. Monés J, Srivastava SK, Jaffe GJ, et al. Risk of inflammation, retinal vasculitis, and retinal occlusion-related events with brolucizumab: post hoc review of HAWK and HARRIER. Ophthalmology, 2021; 128: 1050–1059. doi: 10.1016/j.ophtha.2020.11.011
19. Hansel TT, Kropshofer H, Singer T, et al. The safety and side effects of monoclonal antibodies. Nat Rev Drug Discov, 2010; 9: 325–338. doi: 10.1038/nrd3003

20. Baldo BA. Adverse events to monoclonal antibodies used for cancer therapy: Focus on hypersensitivity responses. Oncoimmunology, 2013; 2: e26333. doi: 10.4161/onci.26333
21. Witkin AJ, Shah AR, Engstrom RE, et al. Postoperative hemorrhagic occlusive retinal vasculitis: expanding the clinical spectrum and possible association with vancomycin. Ophthalmology 2015; 122: 1438–1451. doi: 10.1016/j.ophtha.2015.03.016
22. Todorich B, Faia LJ, Thanos A, et al. Vancomycin-associated hemorrhagic occlusive retinal vasculitis: a clinical-pathophysiological analysis. Am J Ophthalmol, 2018; 188: 131–140. doi: 10.1016/j.ajo.2018.01.030
23. Iyer PG, Peden MC, Suner IJ, et al. Brolucizumab related retinal vasculitis with exacerbation following ranibizumab retreatment: a clinicopathologic case study. Am J Ophthalmol Case Rep, 2020; 20: 100989. doi: 10.1016/j.ajoc.2020.100989
24. Sharma A, Kumar N, Parachuri N, et al. Understanding retinal vasculitis associated with brolucizumab: complex pathophysiology or occam's razor? Ocul Immunol Inflamm, 2022; 30: 1508–1510. doi: 10.1080/09273948.2021.1897628
25. Moisseiev E, Loewenstein A. Abicipar pegol–a novel anti-VEGF therapy with a long duration of action. Eye (Lond) 2020; 34: 605–606. doi: 10.1038/s41433-019-0584-y
26. Hikichi T. Three Japanese cases of intraocular inflammation after intravitreal brolucizumab injections in one clinic. Jpn J Ophthalmol, 2021; 65: 208–214. doi: 10.1007/s10384-021-00819-7
27. Kataoka K, Horiguchi E, Kawano K, et al. Three cases of brolucizumab-associated retinal vasculitis treated with systemic and local steroid therapy. Jpn J Ophthalmol, 2021; 65: 199–207. doi: 10.1007/s10384-021-00818-8
28. Holz FG, Iida T, Maruko I, Sadda SR. A consensus on risk mitigation for brolucizumab in neovascular age-related macular degeneration: patient selection, evaluation, and treatment. Retina, 2022; 42: 1629–1637. doi: 10.1097/IAE.0000000000003556
29. Antaki F, Vadboncoeur J. Retinal vasculitis after intravitreal injection of brolucizumab. Can J Ophthalmol, 2022; 57: e40. doi: 10.1016/j.jcjo.2021.04.004
30. Wykoff CC, Matsumoto H, Barakat MR, et al. Retinal vasculitis or vascular occlusion after brolucizumab for neovascular age-related macular degeneration: a systematic review of real-world evidence. Retina, 2023; 43: 1051–1063. doi: 10.1097/IAE.0000000000003769
31. Kessler LJ, Mayer CS, Bagautdinov D, et al. Bilateral Vasculitis after Single Intravitreal Brolucizumab Injection. Klin Monbl Augenheilkd, 2022; 239: 196–201. doi: 10.1055/a-1675-2829
32. Baumal CR, Sørensen TL, Karcher H, et al. Efficacy and safety of brolucizumab in age-related macular degeneration: a systematic review of real-world studies. Acta Ophthalmol, 2023; 101: 123–139. doi: 10.1111/aos.15242
33. Zubricky R, McCoy J, Donkor R, et al. Real-world frequency and management of ocular adverse events in eyes with neovascular age-related macular degeneration treated with brolucizumab. Ophthalmol Ther, 2023; 12: 2397–2408. doi: 10.1007/s40123-023-00741-w
34. Kilmartin DJ. Literature review and proposal of best practice for ophthalmologists: monitoring of patients following intravitreal brolucizumab therapy. Ir J Med Sci, 2023; 192: 447–456. doi: 10.1007/s11845-022-02929-8