International Journal of Medical Ophthalmology

E-ISSN: 2663-8274
P-ISSN: 2663-8266
www.ophthalmoljournal.com
IJMO 2024; 6(2): 48-50
Received: 08-07-2024
Accepted: 13-08-2024

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Brolucizumab induced vasculitis-worsening inflammation with Brolucizumab re-challenge

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DOI: https://doi.org/10.33545/26638266.2024.v6.i2a.204

Abstract
We present a case of Brolucizumab induced intraocular inflammation with occlusive vasculitis that worsened with Brolucizumab re-challenge. A 68-year-old lady, with no comorbidity was diagnosed with left eye (LE) polypoidal choroidal vasculopathy (PCV) with initial visual acuity of 1/60. Patient had previously received multiple doses of other anti-vascular endothelial growth factor (anti VEGF) injections in left eye and was switched to Brolucizumab.
After second dose, vision in left eye improved to 3/60 but patient was incidentally diagnosed to have Brolucizumab induced retinal vasculitis on routine examination. The patient had inferior arterial occlusion without any vitritis/anterior segment inflammation. Patient was successfully treated with short course of topical and oral steroids combination.
Brolucizumab re-challenge was given to the patient under steroid cover. 1 week after third dose, patient complained of acute diminution of vision. On examination, vision in the left eye dropped to hand movements (HM). The left eye developed diffuse anterior episcleritis and fundus examination showed +2 vitritis and worsening of vasculitis. After ruling out infective etiologies, the patient was again started on systemic steroids. Satisfied with recovery, the patient abruptly stopped the medication herself at 2 weeks that worsened the inflammation. She underwent extensive systemic work up to rule out any other infective/inflammatory foci. The patient was again started on oral Prednisolone 80 mg/d with topical steroids which was slowly tapered over 2 months resulting in resolution.
Although Brolucizumab associated intraocular inflammation responds well to steroid therapy and have a short course, the intraocular inflammation (IOI) worsened following re-challenge and was associated with a more protracted course of episcleritis and vasculitis in our case.

Keywords: Brolucizumab, anti-VEGF, retinal vasculitis, episcleritis, intraocular inflammation

Introduction
Intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy is the standard of care for management of neovascular age related macular degeneration (nARMD) and polypoidal choroidal vasculopathy (PCV). Brolucizumab, one of the newer FDA-approved drugs, due to smaller molecular size, provides higher molar equivalent dose as compared to other agents responsible for good clinical efficacy and long duration [1-4]. However, the higher molar equivalent dose and better target tissue penetration, along with post translational protein modification has been hypothesized to be responsible for higher incidences of intraocular inflammation as compared to other agents (1.4–2.2% vs 0–0.3%, respectively) [3]. Although the Brolucizumab induced ocular inflammation hinders its widespread clinical use, the inflammation is short lived with good response to systemic steroids. Diseases like ARMD and PCV may warrant a continued anti-VEGF therapy, which requires re-challenge with either a different/same anti-VEGF molecule. Current evidence suggests that suggests that intravitreal anti VEGF re-challenge under steroid cover does not worsen ocular inflammation [5, 6]. However, we report a case of Brolucizumab induced ocular inflammation (retinal vasculitis and episcleritis) worsening with Brolucizumab re-challenge for persistent choroidal neovascular activity.

Case report
A 68-year-old Indian lady, with no comorbidity was diagnosed with right eye (RE) dry ARMD and LE PCV with initial visual acuity: RE 6/12 and LE 1/60 (Figure 1). The patient had suboptimal response to 2 doses of bevacizumab, 6 doses of ranibizumab and 3 doses aflibercept after which patient was switched to Brolucizumab.

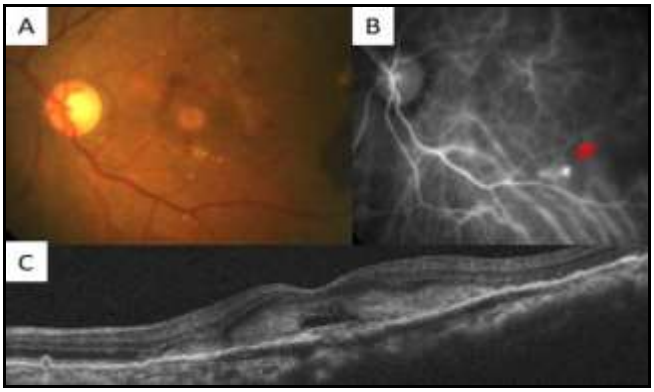

Fig 1: (A) Baseline color photograph (B) indocyanine green angiogram showing polyp (arrow) (C) baseline OCT macula with with subretinal and intraretinal fluid with subretinal hyperreflective material (SHRM).

Two weeks after the second dose, the LE visual acuity improved to 3/60 but routine examination revealed Brolucizumab induced retinal vasculitis without significant vitritis or anterior segment inflammation (Figure 2 b). The patient was successfully managed with topical and systemic steroids. After necessary discussion with the patient, third dose of brolucizumab was administered as re-challenge under low dose steroid cover (oral prednisolone 30 mg).

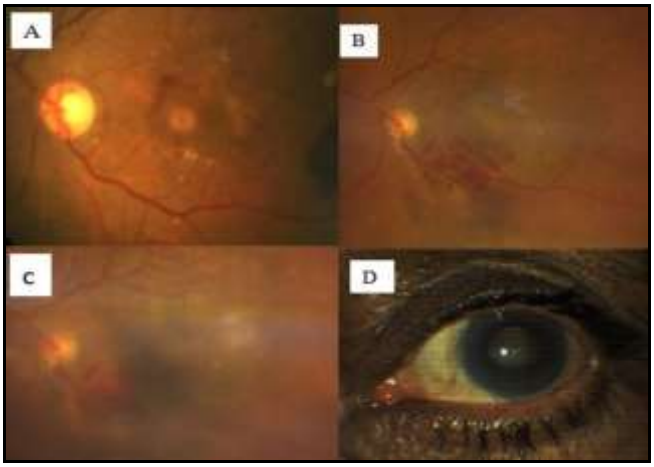

Fig 2: Time sequence of Clinical photographs (a)Baseline (b) Post 2nd dose Brolucizumab with inferior arterial occlusion (arrow) and superficial haemorrhages (*) (c) Worsening vitritis and vasculitis after 3rd dose (d) Associated episcleritis.

One week after third dose, patient complained of acute diminution of vision. On examination, left eye vision dropped from 3/60 to hand movements (HM). There was mild episcleritis with +1 AC (anterior chamber) flare and +1 AC cells. On posterior segment evaluation, grade 2 vitritis and worsening of inferior retinal arterial occlusive vasculitis was noted. No patches of retinitis or vitreous exudates were seen (Figure 2c).

Once routine inflammatory and common infective etiologies were ruled out, the patient was treated with 1% topical prednisolone and short course of oral steroids (prednisolone 80 mg/day) which was to be tapered over next 1 month.

However, the patient satisfied with good response, stopped oral steroids suddenly in 2 weeks and came back with a flare up of episcleritis. An extensive systemic work was done including C-reactive protein, erythrocyte sedimentation rate, c-ANCA, p-ANCA, angiotensin converting enzyme, lysozyme, Quantiferon Gold, syphilis screen, herpes simplex and varicella zoster IgG-IgM, blood culture, urine-analysis and chest-abdomen-pelvis imaging. Other than raised CRP and ESR, all other tests were negative or within normal limits. Topical-systemic steroid combination (80 mg/day) was again initiated with slow taper. After 2 months, the left eye visual acuity improved to 3/60 along with resolution of episcleritis and IOI (Figure 3).

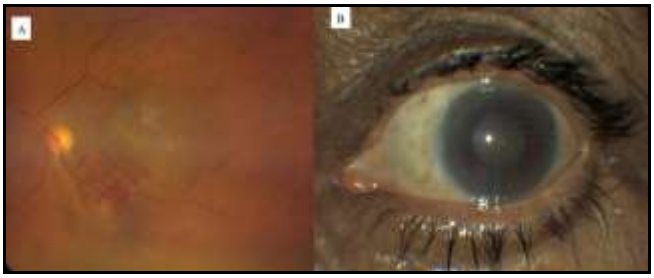

Fig 3: At final follow up under immunosuppression: (a) resolved vitritis and vasculitis (b) resolved episcleritis

Discussion

Brolucizumab, one of the recently approved anti-VEGF molecule for neovascular age related macular degeneration, is different from its predecessors in some aspects. It has the smallest size amongst all other agents with molecular mass of 26 kDa which enables it to have a better ocular tissue penetration and higher molar equivalent dose as compared to Aflibercept (12 times) and Ranibizumab (22 times).

However, the same reasons are also considered responsible for Brolucizumab associated intraocular inflammation and retinal vasculitis. The smaller size of molecules enables it to unfold and expose new epitope sites inciting immunogenic response further enhanced by post translational protein modification [7].

But most of the patients tend to have a shorter inflammatory course, with good response to local/systemic steroids. We present an interesting case of intraocular inflammation associated with second dose of Brolucizumab that worsened with re-challenge and needed a more protracted course of systemic steroids for management.

A post-hoc analysis of the phase-3 HAWK and HARRIER trials by an independent safety review committee shows an incidence of ocular inflammation of 4.6%, ranging from mild intraocular inflammation (IOI) to vascular occlusions (2.1%) [5, 7]. Most of these IOI were categorized as mild to moderate and were treated with a course of topical corticosteroid/anti-infective agents.

Hypersensitivity reactions to anti-VEGF agents have been reported in literature, mostly type 4 (due to the agent) or type 1 (to substance used in injection) [8]. Of the recognized types of hypersensitivities, type IV is the most delayed in onset and requires repeat exposure to antigen. There is also a possible role of humoral immunity in form of anti Brolucizumab antibodies that may contribute to type 3 hypersensitivity reaction [7]. During HAWK and HARRIER trial, 36%-52% patients had pre-existing anti-Brolucizumab antibodies and 53%-67% of patients had treatment emergent with 25% patients showing boosted levels with repeated exposure [5]. The presence of treatment naïve antibodies may explain cross reactivity of antibodies following previous anti-VEGF exposure.

In a recent multicenter study conducted in Indian population, incidence of Brolucizumab associated inflammation was reported around 1.3%. The intraocular inflammation occurred after the first dose in 15%, after the

second dose in 46% eyes, and 39% eyes after the third dose [6]. This emphasizes on potential increased risk of Brolucizumab associated inflammation in patient with multiple previous injection as compared to treatment naïve patients.

Re-challenge is a pharmacological concept which means that a previously discontinued drug is restarted [9]. Currently, ASRS reST committee recommends that anti-VEGF re-challenge should only be given once the inflammation resolves and with a non-brolucizumab agent (7). In a study brolucizumab induced IOI, 69% eyes underwent re-challenge out of which 63% eyes received a non-Brolucizumab molecule with none of the eyes showing recurrence of intraocular inflammation [5]. However, there is evidence in current literature where intraocular inflammation can recur even when a different agent like ranibizumab is used as a rechallenge [7].

Although, it is advisable to use other anti-VEGF molecules in re-challenge, there is some evidence in existing literature where brolucizumab re-challenge under steroid cover (subtenon) did not cause worsening of intraocular inflammation [5].

In study on Brolucizumab associated ocular inflammations, repeat Brolucizumab injection was given in 6% patients with no recurrence of inflammation [5]. In 3 eyes, Brolucizumab re-challenge under steroid cover did not worsen intraocular inflammation and authors concluded that possibly the ocular inflammation was idiosyncratic in nature and possibly related to contaminant in formulation that vary from vial to vial. Due to small number of reported cases, we cannot draw conclusions for safety profile of Brolucizumab re-challenge.

Given the timely manner of the occurrence and exclusion of other possibilities, our patient possibly developed delayed hypersensitivity to Brolucizumab. The patient had received multiple anti-VEGF injections previously without any intraocular inflammation. We believe there was delayed hypersensitivity reaction to our second Brolucizumab injection that worsened with re-challenge even if it was administered under low dose steroid cover once initial IOI resolved. However, we did not do titers for anti-Brolucizumab antibody before or after re-challenge.

Conclusion

Delayed hypersensitivity to intravitreal anti-VEGF agents is a known phenomenon but has a higher risk in patients recieving multiple previous injections . While nature of disease like age related macular degeneration may necessiate repeat injection post brolucizumab associated inflammaton, care must be taken to do it under cover of subtenon steroid injection or high dose of oral steroids with slow taper. It is preferable to use a non-brolucizumab anti-VEGF agent in case of re-injection. However, in case of refractory disease to other antiVEGF agents, Brolucizumab rechallenge can be given with adequate immunosupression, slow taper and frequent follow ups. Inadequate immunosupression and fast taper can lead to flare up of ocular/systemic inflammation.

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflict of Interest

Not available

Financial Support

Not available

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How to Cite This Article
Kumar P, Velagala AR, Pillai GS. Brolucizumab induced vasculitis-worsening inflammation with Brolucizumab re-challenge. International Journal of Medical Ophthalmology. 2024;6(2):48-50.