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COMMENT

Brolucizumab—early experience with early extended interval regime in chronic centre involved diabetic macular oedema

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Brolucizumab (Beovu, Novartis, Basel, Switzerland) is the newest anti-vascular endothelial growth factor (anti-VEGF) drug. It was approved for the treatment of neovascular age-related macular degeneration (nAMD) on the basis of HAWK and HARRIER phase 3 trial results [1]. Preliminary results of KITE and KESTREL trials have shown positive outcomes of brolucizumab in centre involved diabetic macular oedema (CiDMO) [2]. Multiple studies related to brolucizumab use in nAMD have been published [3–5]. To the best of our knowledge, experience in cases of DMO has not been explored. Here we report the early clinical outcomes regarding safety and efficacy after off label brolucizumab administration in chronic non responding cases of DMO.

A retrospective, consecutive, interventional, uncontrolled, single-centre study was conducted. Institutional Review Board approval was obtained, and the investigators adhered to the tenets of the Declaration of Helsinki. All patients were treated with intravitreal brolucizumab 6 mg between November 2020 and May 2021. After receiving the first brolucizumab injection, the next injection was given when the visual acuity declined by one Snellen line or when the central foveal thickness (CFT) increased by 30%. Eyes with structural changes other than CiDMO and patients with vitreoretinal interface diseases were excluded. Each patient underwent best-corrected visual acuity (BCVA) measurement with a Snellen chart (converted to LogMAR for analysis), CST with spectral-domain optical coherence tomography (SD-OCT) and intraocular pressure (IOP) measurement along with complete ophthalmic examination at baseline and at the last follow-up after brolucizumab injection. Descriptive statistics including mean and standard deviation (SD) were calculated for continuous variables. A paired sample t-test was used to measure the mean differences between pre and post-injection values. All the statistical comparisons were made from the baseline visit.

Thirteen eyes of 13 patients were included in this study. The patients received a total of 25 injections. All patients except one received 2 injections. The mean age was 52.9 ± 4.6 years and 61.5% were males. The mean follow-up period was 24.6 ± 4.05 weeks after the first injection of brolucizumab. All the eyes were previously treated with either single or a combination of other intravitreal anti-VEGFs and steroids (bevacizumab, ranibizumab, aflibercept, triamcinolone, dexamethasone implant). The mean number of previous injections (anti-VEGF and steroids) was 15.07 ± 4.3. Ten patients were on anti-glaucoma medications. Eight eyes had history of laser either pan retinal photocoagulation (PRP) or focal laser or both. Nine patients were diagnosed as moderate non proliferative diabetic retinopathy (NPDR) and 4 patients had stable proliferative diabetic retinopathy (PDR). Seven patients had controlled hypertension (HTN) along with diabetes mellitus (DM) and one patient had hypothyroidism along with HTN and DM. Subfoveal exudates were present in 4 eyes.

Immediate data prior to the first brolucizumab injection was considered as the baseline, and the subsequent data after brolucizumab injection were included in the analysis.

KEY OUTCOMES

Visual acuity

All 13 eyes completed the monthly follow-up till 12 weeks. Amongst these eyes, mean BCVA at baseline was 0.53 ± 0.08 LogMAR (20/63) which improved significantly to 0.40 ± 0.12 LogMAR (20/50) at 4 weeks ($p = 0.0075$; CI 95%0.036 to 0.210), 0.39 ± 0.12 LogMAR (20/50) at 8 weeks ($p = 0.0031$; CI 95% 0.052 to 0.225), 0.39 ± 0.12 LogMAR (20/50) at 12 weeks ($p = 0.0031$; CI 95% 0.052 to 0.225). Twelve eyes completed 16 weeks follow-up after the 1st brolucizumab injection. In these twelve eyes, BCVA at baseline was 0.52 ± 0.08 LogMAR (20/63) and 0.48 ± 0.09 LogMAR (20/63) at 16 weeks after the 1st brolucizumab injection ($p = 0.27$; CI 95% −0.035 to 0.118) (Fig. 1).

Nine eyes completed 12 weeks follow-up after the 2nd brolucizumab injection. In these nine eyes, BCVA at baseline was 0.52 ± 0.09 LogMAR (20/63) and 0.5 ± 0.15LogMAR (20/63) at 12 weeks after the 2nd brolucizumab injection. ($p = 0.71$; CI 95% 0.104 to 0.149).

Disease activity

Amongst the 13 eyes that completed 12 weeks follow up after the 1st brolucizumab injection, mean CST at baseline was 402 ± 60.1 microns which improved significantly to 273.33 ± 25.8 microns at 4 weeks ($p = 0.0001$; CI 95% 101.39 to 173.85), 263.55 ± 22.01 at 8 weeks ($p = 0.0001$; CI 95% 113.57 to 184.28), 295.11 ± 13.38 at 12 weeks ($p = 0.0001$; CI 95% 92.53 to 160.08) compared to baseline. In the twelve eyes that completed 16 weeks follow-up after the 1st brolucizumab injection, CST at baseline was a 419 ± 60.3 micron which was 378.3 ± 29.8 microns at the end of 16 weeks ($p = 0.0305$; CI 95% 5.51 to 101.33) (Figs. 2 and 3).

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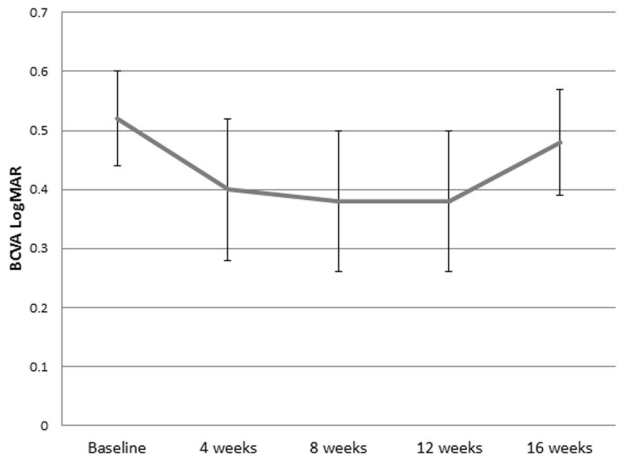

Fig. 1 Change in BVCA. BCVA change during 16 weeks follow up after first brolucizumab injection in 12 patients.

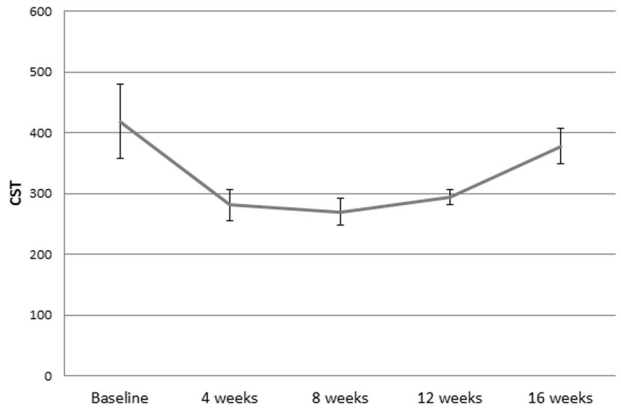

Fig. 2 Change in CST. CST change during 16 weeks follow up after first brolucizumab injection in 12 patients.

Nine eyes completed 12 weeks follow up after the 2nd brolucizumab injection. In these nine eyes, CST at baseline was 402 ± 60.1 microns and improved to 295.1 ± 13.3 microns at 12 weeks after the 2nd brolucizumab injection ($p = 0.0001$; CI 95% 63.35 to 150.42).

Proportion of patients on 16 weeks regime-

Amongst the patients who completed 16 weeks follow up after the 1st brolucizumab, 91.6% of patients could achieve 16 weeks treatment free interval. One patient (8.3%) was injected at 12 weeks follow up as the patient would not be able to report for the 16 weeks review, and moreover the CMT increased by 87 micron and hence the decision to inject early. Mean number of injections were 2.07 ± 0.49 during the mean follow up of 24.6 ± 4.05. Two eyes (22.2%) received repeat injections at 12 weeks amongst the nine eyes that completed 12 weeks follow up after the 2nd brolucizumab.

Safety

In this study, none of the eyes reported any signs of inflammation, vasculitis, or any other ocular or systemic adverse effects.

To summarise, early off label experience in this limited series of cases demonstrated that brolucizumab was safe and effective in extending treatment interval between 12–16 weeks. According to the Phase 3 data of KITE and KESTREL, brolucizumab is associated with intraocular inflammation (IOI) and retinal vascular occlusion as an adverse event in cases of DMO [2]. In our study, we did not find any case of anterior or posterior segment inflammation including occlusive retinal vasculitis. However, given the reported rates, our series is too small to make any definitive statements regarding safety. IOI and retinal vasculitis with vascular occlusion as an adverse event has not yet been understood. [6–8] We have proposed antidrug antibody (ADA) as a major culprit along with Type 3 immune reaction [6].

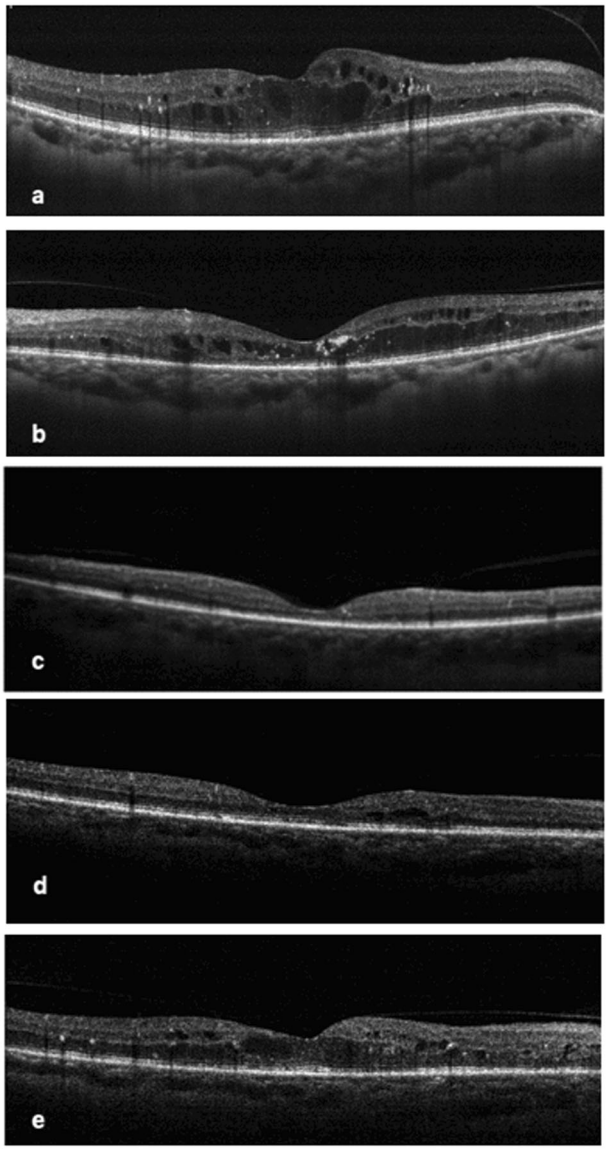

Fig. 3 Representative Example. Representative case of CiDMO showing change in central subfield thickness (CST) from baseline (a) to 4 weeks (b), 8 weeks (b), 12 weeks (c) and 16 weeks after 1st injection of brolucizumab.

There are limitations to the study due to its small sample size, absence of a control group, and short follow-up. Furthermore, all the eyes were previously treated with a significant number of other anti-VEGF injections and steroids. Hence, these results cannot be directly extrapolated to treatment naïve eyes. Detailed results of KITE and KESTREL will help us understand the efficacy and safety of brolucizumab in DMO. Real world studies with large sample size and long-term follow-up with a comparison arm will be needed to better understand the anatomic efficacy and durability benefits of brolucizumab along with the safety profile to define the optimal use of brolucizumab in cases of DMO.

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AUTHOR CONTRIBUTIONS

AS: conception, analysis, drafting, integrity check, final approval. DC, SM, NP and NK: drafting, analysis, integrity check.

COMPETING INTERESTS

DC: CONSULTANT: for Novartis, Bayer, Intas. AS: CONSULTANT: for Novartis, Allergan, Bayer, Intas and Lupin. The remaining authors declared no competing interests.

ADDITIONAL INFORMATION

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