• Clinical Research •

Off-label intravitreal brolucizumab and bevacizumab for chronic central serous chorioretinopathy

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Abstract

● **AIM:** To compare the intravitreal brolucizumab and bevacizumab injections for chronic central serous chorioretinopathy (cCSC).

● **METHODS:** Patients with cCSC were classified into bevacizumab and brolucizumab group. The proportion of complete resolution of subretinal fluid (SRF), best-corrected visual acuity (BCVA), central macular thickness (CMT), and subfoveal choroidal thickness (SFCT) were compared between the two groups.

● **RESULTS:** A total of 40 eyes from 40 patients with aged 34-59y were enrolled in the study. Twenty eyes in bevacizumab group (17 males) and 20 eyes (18 males) in brolucizumab group. Comparing the proportion of complete resolution of SRF, the brolucizumab group was statistically significantly higher than the bevacizumab group (P<0.05). In 1mo, CMT was significantly reduced in the brolucizumab group compared to the bevacizumab group (265±69 *vs* 319±70 μm; P=0.021). However, there was no significant difference in CMT between the two groups at 2 and 3mo (P>0.05).

● **CONCLUSION:** Brolucizumab is anatomically and functionally superior to bevacizumab in the treatment of patients with cCSC.

● **KEYWORDS:** brolucizumab; bevacizumab; central serous chorioretinopathy

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INTRODUCTION

Central serous chorioretinopathy (CSC) is a disease characterized by the presence of serous retinal detachment resulting from dysfunction of the retinal pigment epithelium (RPE) and choroid[1]. This condition primarily affects individuals between the ages of 30 and 50y. CSC has also been reported to occur more frequently in males than in females[2]. A full understanding of the pathogenesis of CSC remains elusive, but abnormalities within the choroidal layer are believed to play a major role[3]. Venous congestion, ischemia, and inflammation are hypothesized to contribute to choroidal hyperpermeability, resulting in RPE damage and serous retinal detachment[4].

Acute CSC usually resolves spontaneously within 3mo. Approximately 10% of patients diagnosed with acute CSC progress to a chronic course[4]. In chronic CSC (cCSC), persistent serous retinal detachment can result in permanent vision loss due to damage to RPE cells and photoreceptor cells. Treatment modalities including focal laser photocoagulation, photodynamic therapy (PDT), and intravitreal anti-vascular endothelial growth factor (VEGF) injection may be required if acute CSC does not resolve spontaneously within 3mo[5]. Cells in the retina and choroid produce VEGF, which increases vascular permeability and causes edema. Therefore, anti-VEGF agents are commonly used to alleviate choroidal leakage in CSC. It has been reported that intravitreal administration of bevacizumab (Avastin; Genentech Inc., San Francisco, CA, USA) in patients with CSC results in positive outcomes including visual improvement and reduction of neurosensory detachment and generally exhibits a favorable safety profile with limited side effects[6]. Some have evaluated the effectiveness of injecting anti-VEGF drugs into the eye to treat CSC, but the results of these treatments for CSC have varied. Anti-VEGF treatments appear to lack the ability to induce complete resorption of subretinal fluid (SRF) as effectively as PDT, as they do not completely address the leakage problem of hyperpermeable choroidal vessels. In contrast to the inconsistent results of anti-VEGF injections, PDT consistently provides excellent results[7]. PDT affects the choroidal

capillaries and acts directly on the choroidal circulation to reduce hyperpermeability. Therefore, PDT is often considered a suitable treatment for patients with cCSC. However, PDT requires specific tools, such as a PDT laser machine, and can lead to complications such as loss of tissue in the choroid and retina, new abnormal blood vessels in the choroid, and reduced blood supply to the choroid[8]. Therefore, we cannot rule out anti-VEGF injection into the eye as a possible treatment for CSC patients.

Brolucizumab, a humanized antibody to VEGF, interferes with the biological activity of vascular endothelial growth factor A (VEGF-A). In 2019, brolucizumab, the newest agent to inhibit VEGF, was approved for the treatment of neovascular age-related macular degeneration (nAMD)[9]. In 2022, brolucizumab was approved by US Food and Drug Administration for the treatment of diabetic macular edema (DME)[10]. Chakraborty *et al*[11] reported severeal cases that positive outcomes after off label intravitreal injection (IVI) of brolucizumab for recalcitrant macular edema due to central retinal vein occlusion. Kelkar *et al*[12] also reported severeal cases that therapeutic effect following off label intravitreal brolucizumab injection in patient with pseudophakic cystoid macular edema. Brolucizumab has several theoretical advantages over other anti-VEGF agents. Due to its smaller molecular structure and superior VEGF binding affinity, brolucizumab may exhibit enhanced retinal penetration compared to other anti-VEGF compounds[13]. Considering the molecular weight of each, brolucizumab, unlike conventional anti-VEGF antibodies, has a small molecular weight, can penetrate more deeply, and has a structure capable of binding 2:1, so it can be more effective in cCSC.

We would like to suggest that intravitreal brolucizumab injection may be an effective treatment option for cCSC cases that are resistant and unresponsive to intravitreal bevacizumab. This study was to compare the differences between intravitreal brolucizumab and bevacizumab injections for the treatment of cCSC.

PARTICIPANTS AND METHODS

Ethical Approval This study was conducted with Institutional Review approval from the Hospital Board in accordance with the Declaration of Helsinki (CHSN 2021-12-012). Written informed consent was obtained from all participants.

Study Design After a retrospective review of their medical records, 40 patients diagnosed with cCSC were included in the study from January 2022 to December 2023. All patients underwent a thorough medical history review, best-corrected visual acuity (BCVA) evaluation, slit lamp examination, color fundus imaging, fluorescein angiography, and optical coherence tomography (OCT; Cirrus OCT, courtesy of Carl Zeiss Inc., Dublin, CA, USA). CSC was identified based on findings of serous retinal detachment on fundus examination, characteristic vascular leakage on fluorescein angiography, and detection of SRF through OCT. cCSC is characterized by serous retinal detachment on OCT and that is symptomatic or lasts longer than 3mo. We excluded individuals according to the following conditions: 1) the presence of other ocular disease such as age-related macular degeneration (AMD), polypoidal choroidal vasculopathy, diabetic retinopathy, pathological myopia and retinal vein occlusion; 2) previous PDT and intravitreal anti-VEGF treatment; 3) had ocular surgery within the past 12mo.

According to the treatment method, 20 eyes were classified into bevacizumab group and brolucizumab group. All patients received a single dose of bevacizumab or brolucizumab. In a sterile operating room, a local anesthetic was applied, the injection site was disinfected with a 5% povidone-iodine solution, and a 30-gauge needle was inserted to the vitreous cavity. Then, 0.05 mL (2.5 mg) of bevacizumab (Avastin®; Genentech Inc., San Francisco, CA, USA) or 0.05 mL (6 mg) of brolucizumab (Beovu®, Novartis, Basel, Switzerland) was injected. The patient received antibiotic eye drops 4 times a day for 1wk after injection. The proportion of complete resolution of SRF in all patients at 1, 2, and 3mo was investigated. All patients were followed up for BCVA, color fundus imaging, and OCT at 1, 2, and 3mo after baseline. OCT was used to measure the thickness of the central macular region and submacular choroid. Subfoveal choroidal thickness (SFCT) and measurements of fovea and subfovea height included using digital caliper functions to assess the distance between the inner border of the choroid–sclera interface and the hyperreflective RPE, as well as between the hyperreflective RPE and the outer segments of photoreceptors located below the fovea. Brolucizumab was observed for 3mo after a single injection, and bevacizumab was injected at 1mo intervals until the SRF was absorbed and then injected according to the *pro re nata* (PRN) protocol according to OCT findings. If SRF persisted for up to 3mo, rescue treatment using PDT was performed. The occurrence of adverse reactions was observed at 1mo after every injections.

Statistical Analysis Statistical analysis was performed using SPSS ver.19.0 (SPSS, Inc., Chicago, IL, USA), and the Wilcoxon signed rank test and Mann-Whitney *U* test were used for comparison between groups. A *P*-value of 0.05 or less was considered statistically significant.

RESULTS

A total of 40 eyes from 40 patients were enrolled in the study. The number of eyes was 20 eyes in the bevacizumab group (17 males, 3 females) and 20 eyes (18 males, 2 females) in the brolucizumab group. Table 1 provided an overview of the baseline characteristics of patients in both study groups.

Notably, no significant differences were observed between the two groups in terms of age, gender, BCVA, central macular thickness (CMT), and SFCT. The average age of the brolucizumab group was 47.8±6.82y, and the average age of the bevacizumab group was 49.15±6.37y (*P*=0.522). Mean initial BCVA (logMAR) at diagnosis was 0.31±0.16 in the brolucizumab-treated group and 0.29±0.16 in the bevacizumab-treated group (*P*=0.698). At diagnosis, mean initial CMT was 426±99 μm in the brolucizumab group and 438±113 μm in the bevacizumab group (*P*=0.729), and mean initial SFCT was 377±129 μm in the brolucizumab group and 357±123 μm in the bevacizumab group (*P*=0.608). There was no significant difference in any of them.

Table 2 provided an overview of the proportion of complete resolution of SRF in both study groups at follow-up visits. At 1mo, SRF had completely resolved in 90% of cases in the brolucizumab injection group. In contrast, the bevacizumab injection group remained at 50%, and there was a statistical difference between the two groups (*P*=0.022). At 2mo, there was no additional cases in which SRF was completely resolved in the brolucizumab injection group, and there were 2 additional cases in which SRF was completely resolved in the bevacizumab injection group. At 3mo, there was no additional case in which SRF was completely resolved in the brolucizumab injection group, there was 1 additional case in which SRF was completely resolved in the bevacizumab injection group. In all cases which SRF was not completely resolved at 3mo, rescue treatment using PDT was performed.

Table 3 summarized the visual gain for both groups. BCVA (logMAR) at 1, 2, and 3mo after each injection showed that visual acuity improved 1mo after injection in both groups and was maintained until 3mo thereafter. There was no statistically significant difference in the BCVA between the two groups.

Tables 4 and 5 provided a comprehensive summary of the anatomical findings observed in both groups. Looking at the CMT of the two groups over time, it was found that the average CMT of the brolucizumab groups was significantly lower than that of the bevacizumab group at 1mo (*P*=0.021; Table 4). However, there was no significant difference in CMT between the two groups at 2mo (*P*=0.275) and 3mo (*P*=0.417). It was showed that there was no statistically significant difference in the average SFCT between the two groups during the follow-up period after injection (Table 5). No ocular or systemic side effects was noted in this study.

Table 1 Clinical characteristics of eyes with cCSC mean±SD

Characteristics	Brolucizumab	Bevacizumab	*P*
Patients (*n*)	20	20	
Male/female	18/2	17/3	0.633
Age (y)	47.8±6.82	49.15±6.37	0.522
Mean BCVA (logMAR)	0.31±0.16	0.29±0.16	0.698
Mean CMT (μm)	426±99	438±113	0.729
Mean SFCT (μm)	377±129	357±123	0.608

cCSC: Chronic central serous chorioretinopathy; BCVA: Best corrected visual acuity; CMT: Central macular thickness; SFCT: Subfoveal choroidal thickness; SD: Standard deviation.

Table 2 Proportion of complete resolution of SRF in the groups at follow-up visits *n* (%)

Follow-up	Brolucizumab (*n*=20)	Bevacizumab (*n*=20)	*P*
Baseline	0	0	
1mo	18 (90)	10 (50)	0.022
2mo	18 (90)	12 (60)	0.039
3mo	18 (90)	13 (65)	0.042

SRF: Subretinal fluid.

Table 3 BCVA in the groups at follow-up visits mean±SD, logMAR

Follow-up	Brolucizumab (*n*=20)	Bevacizumab (*n*=20)	*P*
Baseline	0.31±0.16	0.29±0.16	0.698
1mo	0.17±0.15	0.20±0.13	0.442
2mo	0.16±0.13	0.18±0.16	0.596
3mo	0.17±0.14	0.18±0.17	0.757

BCVA: Best-corrected visual acuity; SD: Standard deviation.

Table 4 CMT in the groups at follow-up visits mean±SD, μm

Follow-up	Brolucizumab (*n*=20)	Bevacizumab (*n*=20)	*P*
Baseline	426±99	438±113	0.729
1mo	265±69	319±70	0.021
2mo	262±71	281±65	0.275
3mo	261±67	277±64	0.417

CMT: Central macular thickness; SD: Standard deviation.

Table 5 SFCT in the groups at follow-up visits mean±SD, μm

Follow-up	Brolucizumab (*n*=20)	Bevacizumab (*n*=20)	*P*
Baseline	377±129	357±123	0.608
1mo	336±118	351±114	0.682
2mo	348±118	353±107	0.891
3mo	340±111	363±112	0.470

SFCT: Subfoveal choroidal thickness; SD: Standard deviation.

DISCUSSION

In the current study, we investigated the clinical outcomes of patients with cCSC who received IVI of either brolucizumab or bevacizumab. To our knowledge, this represents the first study to contrast the results of brolucizumab and bevacizumab in individuals diagnosed with cCSC. Acute CSC is considered a spontaneously reversible disease, whereas cCSC requires treatment. Results obtained by indocyanine-green angiography (ICGA) in CSC indicate that the choroid is involved in the pathophysiology, as evidenced by delayed choroidal perfusion, increased choroidal vascular permeability, and choroidal vein dilatation[14]. Several studies utilizing enhanced depth-of-field imaging OCT have demonstrated that eyes affected by CSC exhibit significantly greater SFCT when compared to unaffected

eyes or healthy individuals serving as normal controls[15]. PDT affects the choroidal capillaries and acts directly on the choroidal circulation to reduce hyperpermeability[8]. Patients diagnosed with cCSC who received PDT treatment with a 50% dose reduction showed a marked reduction in choroidal thickness, as reported in previous studies[16]. Although focal laser photocoagulation and PDT have proven efficacious in the management of cCSC, these therapeutic approaches can cause permanent damage, including changes in the RPE, excessive hypoperfusion of choriocapillaries, and secondary choroidal neovascularization. This has led to the search for safer and more effective treatments with fewer side effects than PDT or focal laser photocoagulation[17].

VEGF is known to induce vascular permeability, but the direct role of VEGF in CSC is uncertain. It is hypothesized that factors such as choroidal lobular ischemia, choroidal venous congestion, and hyperpermeability of choroidal vessels may collectively contribute to the condition of CSC patients[18]. Choroidal ischemia in CSC can increase VEGF levels. It has been reported that VEGF levels may be increased in some patients with cCSC[19]. Administration of anti-VEGF therapy in CSC may contribute to SRF reduction. This effect is likely due to the ability of the therapy to reduce choroidal vascular hyperpermeability due to its perceived antipermeable properties. There have been several reports that intravitreal anti-VEGF injection is an effective treatment for CSC. Intravitreal bevacizumab injection has effects on reducing choroidal vascular hyperpermeability, improving visual acuity and reducing SRF[20]. Tekin *et al*[21] reported a shorter resolution time of SRF using ranibizumab over bevacizumab in acute CSC. Altun *et al*[22] reported that ranibizumab could be a potentially effective alternative for patients with bevacizumab-resistant CSC in the acute or early chronic phase. A study conducted by Pitcher *et al*[23] showed that multiple injections of aflibercept significantly reduced SFCT in patients with cCSC. Although the clinical results of bevacizumab and ranibizumab in the treatment of cCSC were considered acceptable, prospective comparative studies showed a lack of efficacy when compared to anatomical resolution achieved through low fluence PDT[24]. Anti-VEGF drugs such as bevacizumab and ranibizumab appear to lack the ability to induce complete resorption of SRF as effectively as PDT, as they do not completely address the leakage problem of hyperpermeable choroidal vessels. Currently, PDT is the preferred treatment for cCSC, but intraocular injection of anti-VEGF may be a viable alternative.

Recently, research on brolucizumab, a exudative AMD treatment, is underway. Brolucizumab is designed to attach to and block a substance called VEGF-A[9]. Brolucizumab consists of the variable domain of a monoclonal antibody (mAb) linked to a short peptide that provides the necessary stability[10]. The lack of an Fc region and the small molecular size of single-chain variable antibody fragments (scFvs) are advantageous from a pharmacokinetic and manufacturing point of view[9]. Brolucizumab showed a significantly greater ability to bind the VEGF-A isoform when compared to bevacizumab[25]. Brolucizumab showed strong binding to all VEGF-A variants and slightly greater affinity compared to aflibercept or ranibizumab when tested using the same assay under the same conditions. Also, it has a lower molecular weight compared to other VEGF injections, so it can show a more effective response. It is currently the lowest molecular weight (26 kDa) VEGF binding compound. Bevacizumab (Avastin®) is an IgG1 antibody with a molecular weight of 149 kDa, aflibercept is a fusion protein of 97 to 115 kDa, and ranibizumab is an antibody fragment with a molecular weight of 48 kDa[26]. A denser structure allows faster dispersal across all layers of the retina.

We suggest that the increased effect of brolucizumab may be due to its ability to penetrate retinal tissue at higher concentrations due to its smaller size. Brolucizumab, a new anti-VEGF drug, is known to have a higher VEGF binding capacity than ranibizumab and aflibercept. Clinical studies have shown that brolucizumab induces greater reductions in SFCT in eyes affected with nAMD compared to ranibizumab and aflibercept[27]. In addition, available evidence suggests that brolucizumab not only produced additional reductions in choroidal and retinal thickness, but also showed efficacy in patients with AMD who had inadequate response to prior treatment with ranibizumab or aflibercept[28]. These results suggest that brolucizumab may have more pronounced effects on the choroidal vasculature compared to previous anti-VEGF drugs. Given the positive results observed in studies highlighting the efficacy of brolucizumab in reducing leakage of hyperpermeable choroidal vessels in AMD, it is reasonable to explore the potential application of brolucizumab in CSC treatment. Given its superior efficacy and effects on the choroidal vasculature, brolucizumab has potential as a therapeutic option for managing CSC-related fluid leakage.

To compare the effect of anti-VEGF injection on the eyeball with its ability to reach hyperpermeable lesions in the choroidal vessels of CSC patients, OCT was used to evaluate CMT[29]. In the group administered with brolucizumab, the most decreased at 1mo after injection, and it was confirmed that the decrease was greater than that in the group administered with bevacizumab. Brolucizumab was thought to have faster improvement due to its penetrability. When submacular choroidal thickness was compared to compare the effect on choroidal vascular permeability, it was confirmed that the brolucizumab-treated group slightly decreased at

1mo. In the case of the bevacizumab injection group, there was no significant difference from the initial period. However, although there was no statistical significance, the fact that there was an initial change compared to the bevacizumab injection group suggests that additional research is needed whether it is due to differences in molecular weight and binding force. As a result, the brolucizumab group showed similar or better BCVA improvement than the bevacizumab group. Therefore, brolucizumab is used in the cCSC group and can be used for treatment because it is superior to bevacizumab and can show similar results.

IVI brolucizumab is associated with intraocular inflammation (IOI). In the HAWK and HARRIER studies, the incidence of IOI was 4% for brolucizumab compared to 1% for aflibercept[30]. The American Society of Retina Specialists (ASRS) issued an alert in February 2020 after reports of 14 cases of retinal vasculitis, 11 of which were obstructive vasculitis, following the use of IVI brolucizumab. In postmarketing, the incidence of retinal vasculitis+/retinal vessel occlusion was 15.31 per 10 000 injections (through 12 February 2021)[31]. However, no anterior or posterior segment inflammation occurred during the 12-week follow-up in our series. Also, no patients reported any systemic side effects. However, our series is too small for a short follow-up of 12wk. Therefore, there is insufficient authority to determine the risk of systemic adverse events. The risk of IOI may be higher due to more frequent injections in AMD or DME, but the risk of IOI may be lower due to less frequent injections in CSC.

A limitation of this study is that it is a single-center retrospective study. The number of patients was relatively small and the observation period was short.

In conclusion, we would like to suggest that intravitreal brolucizumab injection may be an effective treatment option for CSC cases that are resistant and unresponsive to intravitreal bevacizumab, especially in the chronic phase. Intravitreal brolucizumab injection may be effective in achieving rapid resolution of serous detachment in patients with cCSC. Reducing the duration of serous retinal detachment reduces the risk of photoreceptor degeneration and prevents permanent vision loss. Further prospective comprehensive studies are needed to determine the long-term benefits and risks of brolucizumab injection for the treatment of cCSC.

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