

Intravitreal Aflibercept for Macular Edema Secondary to Branch Retinal Vein Occlusion in Chinese Patients

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Abstract

Purpose: To investigate the short-term efficacy and safety of intravitreal aflibercept in a case series of patients from Taiwan, China, with macular edema secondary to branch retinal vein occlusion (BRVO).

Methods: A total of 32 patients with macular edema associated with BRVO, without prior macular laser or other intervention, were enrolled consecutively from September 2013 to February 2015. The cases received single 2 mg injections of intravitreal aflibercept. Primary outcome measures included changes in central foveal thickness (CFT; 1 mm increments by spectral-domain optic coherence tomography) and best corrected visual acuity (BCVA), determined at 1, 2, and 3 months after the injection. Complications after injections were recorded. The changes in CFT and BCVA were compared with Wilcoxon sign-rank tests.

Results: The CFT was significantly reduced and the BCVA was significantly improved at 1, 2, and 3 months after injection (all $P < 0.05$). Tomography findings revealed no recurrence within 3 months. No systemic thromboembolic events, elevated intraocular pressure, retinal detachment, or infectious endophthalmitis occurred following injection.

Conclusion: Single intravitreal aflibercept may be useful in treating macular edema associated with BRVO within 3 months. No adverse systemic or ocular effects were found in this case series. (*Eye Science* 2015; 30:63–66)

Keywords: intravitreal injection; aflibercept; macular edema;

branch retinal vein occlusion; vascular endothelial growth factor

Introduction

Branch retinal vein occlusion (BRVO) is a common sight-threatening retinal vascular disorder, with macular edema as the main cause of visual impairment^{1,2}. Vascular endothelial growth factor (VEGF) plays an important role in the pathogenesis of macular edema in BRVO³. Intravitreal injections of anti-VEGF factors, including ranibizumab⁴, bevacizumab⁵, and pegaptanib⁶ are effective as treatments for macular edema resulting from BRVO. Aflibercept (Eylea, Regeneron Pharmaceuticals, Inc., and Bayer Pharma AG, Berlin, Germany) is a decoy receptor fusion protein, composed of the second domain of human VEGF receptor 1 and the third domain of VEGF receptor 2, which are fused to the Fc domain of human IgG1⁷⁻¹¹. Aflibercept can downregulate both VEGF-A, VEGF-B, and placental growth factor, which are synergistic for pathologic angiogenesis. The binding affinity of VEGF is higher for this drug than for ranibizumab and bevacizumab⁷.

Aflibercept displays a prolonged VEGF inhibition in comparison with the other VEGF-antagonists (ranibizumab and bevacizumab) in retinal pigment epithelium/choroid organ cultures⁸. Intravitreal aflibercept is beneficial for treating neovascular age-related macular degeneration⁹, diabetic macular edema¹⁰, and

macular edema caused by central retinal vein occlusion (CRVO)^{11,12}. The VIBRANT study, a randomized controlled trial of patients in North America and Japan, demonstrated intravitreal aflibercept was effective for managing patients with macular edema associated with BRVO in North America and Japan¹³. Similar efficacy and safety data are lacking for Chinese patients with macular edema secondary to BRVO treated by intravitreal aflibercept. In this case series, we reported the clinical results of intravitreal aflibercept treatment of macular edema in Chinese patients with BRVO in Taiwan.

Materials and methods

From September 2013 to February 2015, 32 eyes of 32 patients with macular edema associated with BRVO were included consecutively. Macular edema was defined as central foveal thickness $> 300 \mu\text{m}$ measured by spectral-domain optical coherence tomography (SD-OCT), using cross-line scan through the fovea in all patients. The patients had no prior ocular surgery, trauma, or laser histories. They had no abnormal ocular conditions. All the cases had systemic hypertension under medical treatment. No patient had diabetes mellitus, history of thromboembolic events, known coagulation abnormalities or current use of anticoagulative medication other than aspirin, or other major systemic diseases. All patients were treatment naïve. The procedures were performed at the Far Eastern Memorial Hospital by one surgeon (Wang JK). The off-label use of the drug and its potential risks and benefits were discussed extensively with all patients. All participants gave written informed consent before the injections.

The cases were examined using best corrected visual acuity (BCVA) using the Snellen chart (converting into ETDRS letters according to the prior publication)¹⁴, intraocular pressure (IOP) via pneumotonometer (Topcon, Tokyo, Japan), biomicroscopy of the fundus and anterior segment, and macular SD-OCT (RTVue, Optovue, San Francisco, USA) before the procedure. All injections were performed on the day after diagnosis. Following topical anesthesia and disinfection of the eyelid and conjunctiva, aflibercept (2 mg in 0.05 mL) was injected into the vitreous cavity using a 30-gauge nee-

dle inserted through the inferotemporal pars plana, 3.5 mm posterior to the limbus. After the procedure, tetracycline ointment was placed into the conjunctival sac. The eye was patched for one hour and then the patch was removed. The patient was instructed to instill one drop of 0.3% norfloxacin into the injected eye four times daily for one week.

Primary outcome measures included IOP, changes in central foveal thickness (CFT) in 1 mm increments by SD-OCT, and BCVA, all measured at 1, 2, and 3 months after the injection. The follow-up SD-OCT scans used using the baseline scan as a reference. Visual testing was done in the same room at each visit. Complications after injections were recorded. The changes in CFT and BCVA were compared with the Wilcoxon sign-rank test.

Results

The mean BCVA was 52.7 ± 16.1 letters before injections; this significantly increased to 62.3 ± 12.5 ($P = 0.01$), 63.8 ± 13.4 ($P = 0.007$), and 69.1 ± 7.68 letters ($P = 0.001$) at 1, 2, and 3 months, respectively, after injections. The change in the BCVA is shown in Figure 1A. A mean gain of 16.3 letters was noted 3 months following the single aflibercept injection. Of 12 patients, 7 (58.3%) gained ≥ 15 letters at 3 months from baseline. All patients had an improvement of at least 5 letters at 3 months, and

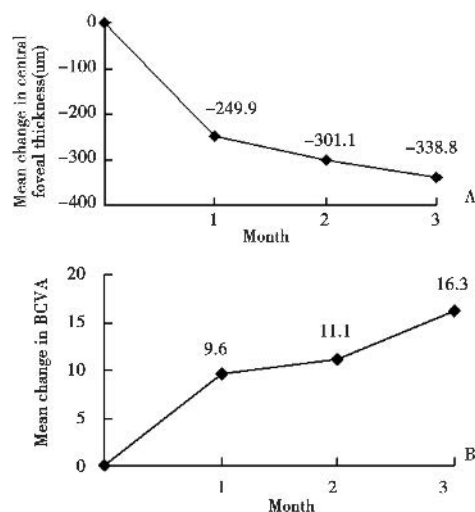


Figure 1 Changes in (A) central foveal thickness and (B) BCVA before and after intravitreal injection of aflibercept in patients with macular edema secondary to BRVO.

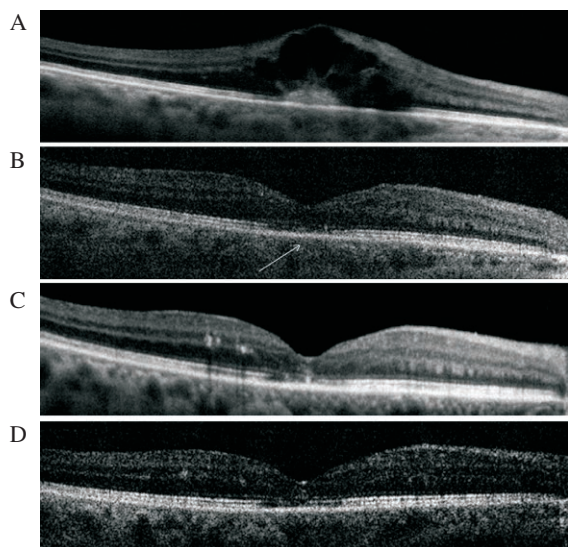


Figure 2 (A) A 69-year-old male patient had cystoid macular edema, secondary to branch retinal vein occlusion, in the right eye, with BCVA as 20/60 and central foveal thickness (CFT) up to 572 μm . (B) His BCVA improved to 20/50 and CFT decreased to 229 μm one month following a single intravitreal injection of aflibercept. (C) His BCVA further increased to 20/40 and CFT was maintained at 234 μm two months after the aflibercept treatment. (D) His BCVA improved to 20/30 and CFT remained stable at 224 μm three months after the intraocular aflibercept injection. The inner segment/outer segment line of photoreceptor (indicated by the arrow) remained disrupted from month 1 to month 3.

66.6% of patients had at least 20/40 in BCVA at 3 months. The CFT was $593.4 \pm 190.5 \mu\text{m}$ before injections; this significantly decreased to 343.5 ± 131.7 ($P = 0.0002$), 292.4 ± 91.5 ($P < 0.0001$), and $254.6 \pm 29.7 \mu\text{m}$ ($P = 0.0001$) at 1, 2, and 3 months, respectively, after injections. The changes in the CFT are shown in Figure 1B. No recurrence was indicated, based on the CFT changes, during 3-month follow-up. No epiretinal membrane or vitreomacular traction was found in any case. No ocular or systemic adverse events were reported.

Figure 2 describes the case of a 69-year-old man with cystoid macular edema, secondary to BRVO, who was successfully treated using a single injection of intravitreal aflibercept.

Discussion

The standard of care for macular edema in BRVO has been dictated by the Branch Vein Occlusion Study, which recommended grid laser photocoagu-

lation². However, visual improvement following macular grid laser is limited, with mean visual gains of only 1.33 lines reported after a three-year follow-up². Anti-VEGF intraocular injection is a new and promising treatment modality that results in noticeable functional and anatomical improvement.

Ranibizumab is an antibody fragment with a high binding affinity towards all forms of VEGF. In the BRAVO trial, six monthly intravitreal injections of ranibizumab (0.5 mg) resulted in a gain of 18.3 letters in patients with BRVO-associated macular edema⁴; 61% of the ranibizumab-treated eyes gained ≥ 15 letters from baseline⁴, while 64% of the ranibizumab-treated patients had at least 20/40 in BCVA at month 6⁴.

Bevacizumab is a full-length monoclonal antibody that inhibits all VEGF isoforms. The Pan American Collaborative Retina Study Group conducted a study using intravitreal bevacizumab to treat macular edema following BRVO. The 2-year results demonstrated that injection of bevacizumab (1.25 mg) resulted in a gain of 3.8 ETDRS lines, and 68% of bevacizumab-treated eyes gained \geq three ETDRS lines⁵. The percentage of bevacizumab-treated patients who had at least 20/40 in BCVA was 55%⁵.

Pegaptanib is an aptamer that binds to the isoform 165 of VEGF. A prior study showed the one-year outcome of intravitreal pegaptanib to be an increase of 14 letters in patients with BRVO-associated macular edema; while 55% of pegaptanib-treated eyes gained ≥ 15 letters from baseline⁶.

Several previous anti-VEGF treatments reported that improvements in visual acuity were accompanied by statistically significant reductions in foveal thickness^{4,6}. Ocular or systemic adverse events from different intravitreal anti-VEGF agents were rare^{1,4,6}. The VIBRANT study, a randomized controlled trial conducted in North America and Japan¹³, compared the efficacy of intravitreal aflibercept (2 mg) and the macular grid laser in 183 patients with macular edema associated with BRVO. After monthly injections for six months, the aflibercept group gained a mean of 17.0 letters, which was a significantly better improvement over the laser group that showed only a mean improvement of 6.9 letters. The proportion of injected eyes that gained more than 15 letters

from baseline at week 24 was 52.7%. The decrease in macular thickness was more prominent in the aflibercept group than in the laser group, without any accompanying adverse ocular or systemic events.

The present study showed a mean gain of 16.3 letters at 3 months following the single aflibercept injection in these Chinese cases from Taiwan; 58.3% of the patients gained ≥ 15 letters at 3 months from baseline, while 66.6% of the patients had at least 20/40 in BCVA at 3 months. A significant decrease in CFT was also noted. The efficacy of aflibercept for anatomical and functional recovery was similar to that reported for other anti-VEGF agents used as treatments for macular edema associated BRVO, and better than the sham group or laser only treatments described in previous studies^{4,6,13}. The improvement in visual acuity and macular thickness in the present observational report was also comparable to the aflibercept group in the previous VIBRANT study. No recurrence was evident based on the CFT changes in this short-term follow-up. No adverse ocular or systemic events were reported. However, the limitations of the present study are its small case number, short follow-up period, and the lack of a comparison group. We require longer follow-up, larger case numbers, and a comparison group to confirm the efficacy of aflibercept for macular edema secondary to BRVO in Chinese patients.

We conclude that a single intravitreal injection of aflibercept may be useful in treating Chinese patients with macular edema secondary to BRVO, based on short-term follow-up that showed no noticeable recurrence. No serious adverse systemic or ocular effects were found in this Chinese case series.

Conflict of interest

The authors have no proprietary or commercial interest in any materials discussed in this article. The authors declare no financial support or conflicts of interest.

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