American Academy of Ophthalmology
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Safety and Efficacy of Conbercept in Neovascular Age-Related Macular Degeneration

Results from a 12-Month Randomized Phase 2 Study: AURORA Study

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Purpose: To assess the safety and efficacy of multiple injections of 0.5 and 2.0 mg conbercept using variable dosing regimens in patients with neovascular age-related macular degeneration (AMD).

Design: Randomized, double-masked, multicenter, controlled-dose, and interval-ranging phase 2 clinical trial divided into a 3-month loading phase followed by a maintenance phase.

Participants: Patients with choroidal neovascularization secondary to AMD with lesion sizes of 12 disc areas or less and a best-corrected visual acuity (BCVA) letter score of between 73 and 24 were enrolled.

Methods: Patients were randomized 1:1 to receive either 0.5 or 2.0 mg intravitreal conbercept for 3 consecutive monthly does. After the third dose, each group was reassigned randomly again to monthly (Q1M group) or as-needed (pro re nata [PRN] group) treatment without changing the drug assignment.

Main Outcome Measures: The primary end point was the mean change in BCVA from baseline to month 3, with secondary end points being the mean change in BCVA, mean change in central retinal thickness (CRT), and safety at month 12.

Results: We enrolled 122 patients. At the primary end point at month 3, mean improvements in BCVA from baseline in the 0.5- and 2.0-mg groups were 8.97 and 10.43 letters, respectively. At month 12, mean improvements in BCVA from baseline were 14.31, 9.31, 12.42, and 15.43 letters for the 0.5-mg PRN, 0.5-mg Q1M, 2.0-mg PRN, and 2.0-mg Q1M regimens, respectively. At month 12, mean reductions in CRT in the 4 regimens were 119.8, 129.7, 152.1, and 170.8 μm, respectively. There were no significant differences for the pairwise comparisons between all study groups. The difference in the number of injections between the 2 PRN groups was not statistically significant. Treatment with conbercept generally was safe and well tolerated.

Conclusions: The significant gains in BCVA at 3 months were the same or better at 12 months in all conbercept dosing groups of neovascular AMD patients. During the 12 months, repeated intravitreal injections of conbercept were well tolerated in these patients. Future clinical trials are required to confirm its long-term efficacy and safety. *Ophthalmology 2014;121:1740-1747*

Age-related macular degeneration (AMD) is a progressive disease of the macula and the leading cause of irreversible blindness in industrialized countries.[1] Although it has not yet become the leading cause of blindness among the Chinese population, the prevalence of AMD is rising gradually as the population ages and the socioeconomic situation improves.[2] An epidemiologic investigation showed that 15.5% of the included Shanghai residents (≥50 years of age) had AMD and 11.9% of them had neovascular (exudative) AMD.[3] Neovascular AMD is characterized by the growth of abnormal new blood vessels under the retinal pigment epithelium, under the retina, or within the retina. When neovascularization arises from the choroid, these new blood vessels are referred to as choroidal neovascularization (CNV).[4] The pathophysiologic features of neovascular AMD are not fully understood, but it is known that vascular endothelial growth factor (VEGF) plays an important role in the proliferation and maintenance of this neovascularization. This fact has led to the development of therapeutic strategies to inhibit VEGF for the treatment of neovascular AMD.[5]

Between 2004 and 2006, three anti-VEGF drugs were introduced to ophthalmology after either receiving regulatory approval for the treatment of AMD or being used in an off-label manner. They exhibit important differences in their sites of activity, formulation methods, binding affinities, and biologic activities. Pegaptanib (Macugen; Eyetech Pharmaceuticals, Lexington, MA) is a ribonucleic acid aptamer that

blocks the main pathologic isoform of VEGF (known as VEGF165) and larger isoforms of VEGF by attaching to its heparin binding domain,[6] whereas ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA) and bevacizumab (Avastin; Genentech and Roche, Basel, Switzerland) are derived from a murine monoclonal antibody against VEGF-A; ranibizumab is an affinity-matured, humanized, monoclonal antigen binding fragment from the antibody and bevacizumab is a full-length, humanized, monoclonal antibody directed against VEGF-A. Both drugs function by blocking the same receptor binding domains of all VEGF-A isoforms.[7] In November 2011, aflibercept (Eylea; Regeneron, Tarrytown, NY; and Bayer, Leverkusen, Germany) was approved by the US Food and Drug Administration. This soluble decoy receptor is produced by combining all-human DNA sequences of the second binding domain of human VEGF receptor (VEGFR)-1 to the third binding domain of human VEGFR-2, which is then combined with the Fc region of human immunoglobulin G-1.[8] Aflibercept binds to all VEGF-A and VEGF-B isoforms, as well as to the highly related placental growth factor.

Similar to aflibercept, conbercept (KH902; Chengdu Kanghong Biotech Co., Ltd., Sichuan, China) consists of the VEGF binding domains of the human VEGFR-1 and VEGFR-2 combined with the Fc portion of the human immunoglobulin G-1. In addition to having high affinity for all isoforms of VEGF-A, it also binds to placental growth factor and VEGF-B. The structural difference between conbercept and aflibercept is that conbercept also contains the fourth binding domain of VEGFR-2. This fourth domain is essential for receptor dimerization and enhances the association rate of VEGF to the receptor.[9,10] Because this domain of VEGFR-2 has a lower isoelectric point, the addition of this domain to KH902 decreases the positive charge of the molecule and results in decreased adhesion to the extracellular matrix. Preclinical studies have demonstrated that conbercept shows strong antiangiogenetic effects by binding with high affinity and neutralizing VEGF-A, all its isoforms, and placental growth factor.[11]

Intravitreal administration of conbercept has been shown to successfully prevent lesion growth and leakage of CNV in a nonhuman primate model.[11,12] A phase 1 study also demonstrated that conbercept resulted in improvements in best-corrected visual acuity (BCVA), reduction in central retinal thickness (CRT), and a decrease in the area of CNV in patients with neovascular AMD.[13] The present study was designed to investigate the safety and efficacy of intravitreal injections of conbercept in patients with CNV secondary to AMD.

Methods

Study Design

The AURORA study was a 12-month, randomized, double-masked, controlled-dose, and interval-ranging phase 2 clinical trial and was designed as a superiority trial to assess the safety and efficacy of different dosing regimens of conbercept in patients with CNV secondary to AMD. At 9 sites in China, the safety and efficacy of different doses and different dosing regimens were compared after repeated intravitreal injections of conbercept. The primary end point was assessed at month 3, and the results of the maintenance phase were assessed at month 12. The major eligibility criteria included age 50 years or older, the presence in the study eye (1 eye per patient) of untreated active subfoveal or juxtafoveal CNV secondary to AMD, lesion size 12 disc areas or less in either eye, and BCVA letter scores in the study eye between 73 and 24. The BCVA score was based on the number of letters read correctly on the Early Treatment Diabetic Retinopathy Study visual acuity chart when assessed at a starting distance of 4 m. An Early Treatment Diabetic Retinopathy Study visual acuity score of 73 to 24 letters is approximately 20/40 to 20/320 in Snellen visual acuity. An increase in the BCVA letter score indicates improvement in visual acuity. Patients were excluded if any of the following were present: significant subfoveal atrophy or scarring; presence of other causes of CNV in either eye; history of previous AMD drug treatment (such as anti-VEGF drugs and steroids); previous laser therapy or other ocular operation, or both, in the study eye, such as macular translocation surgery, cataract surgery, vitrectomy surgery, glaucoma filtering operation, verteporfin photodynamic therapy, subfoveal focal laser photocoagulation, and transpupillary thermotherapy; active ocular inflammation or infection; uncontrolled diabetes mellitus; uncontrolled hypertension; history of cerebrovascular accident or myocardial infarction within 6 months; renal failure requiring dialysis or renal transplant; pregnancy or lactation; or history of allergy to fluorescein or povidone iodine. The trial was registered at www.clinicaltrial.gov under the identifier NCT 01157715.

Intervention

Eligible patients were randomized 1:1 to 0.5- or 2.0-mg treatment groups. Initially, all patients received monthly intravitreal injections of conbercept for a total of 3 injections. After the 3-month loading phase, patients were reassigned randomly to monthly (Q1M group) or as-needed treatments (pro re nata [PRN] group) with the same dose of conbercept given during the loading phase.

Patients randomized to the monthly regimen were treated monthly during the maintenance phase. Patients randomized to the PRN regimen were not re-treated unless any of the following was present in the study eye: a more than 100-μm increase in CRT compared with the lowest previous measurement; a loss of 5 or more BCVA letters compared with the best previous measurement; new, recurrent, or persistent subretinal or intraretinal fluid based on the review of all the optical coherence tomography (OCT) scans; new onset of classic neovascularization; new or persistent leakage on fluorescein angiography (FA); or new macular hemorrhage or hemorrhagic area of more than 50% of the disc area. Decisions about re-treatment were made on the basis of the investigator's evaluation of the BCVA, ophthalmic examination results, and images from OCT, FA, and fundus photography (FP). The investigator was masked to the assignment of dose in the PRN arms. Rescue therapy with another treatment was not offered as part of this study, so if a patient elected to receive any other therapy for their neovascular AMD, then they were asked to exit the study. The only approved anti-VEGF therapy in China is ranibizumab, and ranibizumab was not approved in China until 2012, which occurred well after the start of this study in 2010.

The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments, China good clinical practice regulations, and applicable institutional regulatory requirements. Before the initiation of the study, relevant institutional review boards and ethics committees from the respective study centers approved the research protocol and its amendments. All patients provided written informed consent for study participation.

Assessments

All patients were evaluated monthly. Evaluations included visual function, ocular assessments, adverse events using BCVA measured with the Early Treatment Diabetic Retinopathy Study chart (4-m starting distance), intraocular pressure measurements, slit-lamp examinations, and imaging with FP, OCT, FA, and indocyanine green angiography (ICGA). Fundus photography and OCT imaging were performed at every visit, whereas FA and ICGA were performed only at baseline and at months 3, 8, and 12. Optical coherence tomography was performed either with the Stratus OCT instrument (Carl Zeiss Meditec, Dublin, CA) or the Heidelberg Spectralis spectral-domain OCT instrument (Heidelberg Engineering, Heidelberg, Germany). The same type of OCT instrument used at baseline was used throughout the study. When the Stratus OCT was used, the following scan patterns were performed on both eyes and were centered on the fovea: two 7-mm posterior pole custom scans positioned 5° below horizontal from the temporal edge of the optic nerve toward the fovea (512 A-scans per B-scan), one 3-mm high-resolution cross-hair scan (512 A-scans per B-scan), one 6-mm high-resolution cross-hair linear scan (512 A-scans per B-scan), and 2 fast macular thickness map scans consisting of 6 radial linear scans (128 A-scans per B-scan). When the Heidelberg Spectralis spectral-domain OCT was used, the following scan patterns were performed on both eyes and were centered on the fovea: a single 30° horizontal section scan with an automatic real-time setting of 15 (1536 A-scans per B-scan) and a volume scan over a 20°×20° area consisting of 49 B-scans (512 A-scans per B-scan), with each B-scan separated by 120 μm, and an automatic real-time setting of 15. Either the Topcon TRC.50-DX or the Heidelberg HRA2 were used to perform FA and ICGA. Fundus photography was performed using the Topcon TRC.50-DX, Topcon TRC-50EX, and Zeiss FF 450 plus. The OCT, FA, ICGA, and FP images were graded at a central reading center (the Digital Angiography Reading Center, New York, NY). Adverse events (AEs) were recorded at each visit as well. Study visits were scheduled every 30±7 days.

Outcomes

The primary efficacy outcome was the mean change in BCVA score from baseline at month 3. Secondary outcomes at month 12 were the mean changes of BCVA score from baseline over time, the incidence rates of AEs over time, the mean changes in CRT on OCT imaging over time, the changes in leakage area on FA imaging, and the mean number of injections over time.

Statistical Methods

The full analysis dataset with all the patients who completed the month 12 visit was the dataset used for the primary efficacy analysis. Mean changes in BCVA from baseline at months 3 and 12 were assessed using the paired *t* test or rank-sum test with 95% confidence intervals. The chi-square test or Fisher test was used for the proportions of patients who gained more than 0 letters, gained at least 15 letters, and gained at least 30 letters or lost fewer than 15 letters. Other secondary end points, as well as demographic data at baseline, were evaluated using summary statistics.

The safety analysis set with all the patients who participated in the study was used for all safety and tolerability assessments. All the AEs, treatment-related AEs, incidence of AEs, and serious AEs (SAEs) were compared between groups using the chi-square test or Fisher exact method. All statistical tests were 2-sided. A *P* value less than 0.05 was considered statistically significant. All the above analyses were performed using SAS software version 9.1 (SAS Inc., Cary, NC). Adverse events were coded with the Medical Dictionary for Regulatory Activities (MedDRA 14.1; the International Federation of Pharmaceutical Manufacturers and Associations [IFPMA], Geneva, Switzerland).

Results

Characteristics of Patients

Between July 2010 and July 2012, 122 patients (0.5-mg group, n = 60; 2.0-mg group, n = 62) were randomized. One patient withdrew

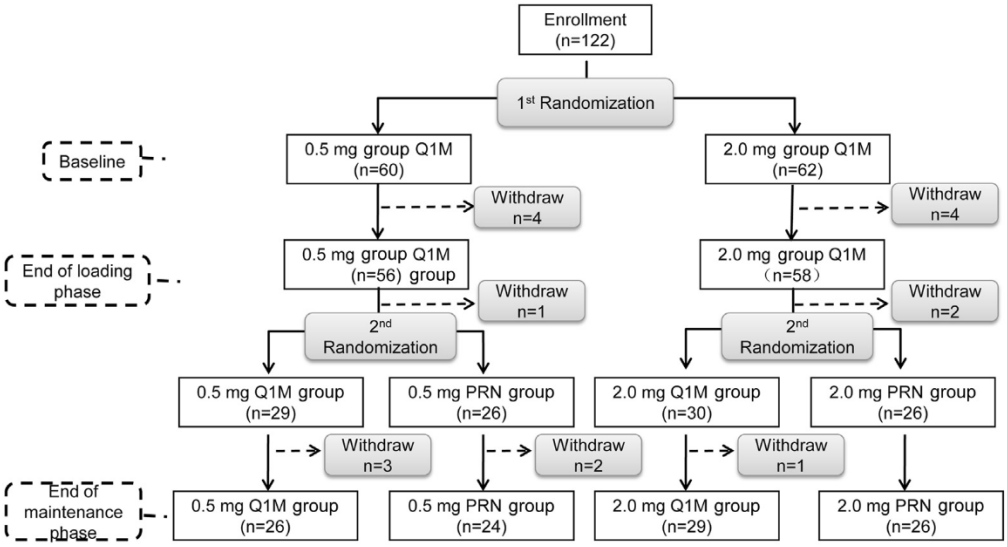

Figure 1. Diagram of participant flow in the AURORA study. Before the second randomization, 5 (8.3%) and 6 (9.7%) patients withdrew from the 0.5-mg monthly (Q1M) and 2.0-mg Q1M groups, respectively. At the end of maintenance phase, 3 (10.3%), 2 (7.7%), 1 (3.3%), and 0 (0%) patients prematurely discontinued the study in the 0.5-mg Q1M, 0.5-mg as-needed (pro re nata [PRN]), 2.0-mg Q1M, and 2.0-mg PRN groups, respectively. A total of 102 patients were included in the final analysis.

Table 1. Baseline Characteristics of the Study Population

Characteristics	0.5-mg Group		2.0-mg Group	
	As Needed (n = 26)	*Monthly (n = 29)*	*As Needed (n = 26)*	*Monthly (n = 30)*
Age (yrs)	64.50±8.89	69.66±8.26	66.08±9.27	63.53±7.55
Sex, no. (%)				
Male	13 (50.0)	19 (65.5)	16 (61.5)	22 (73.3)
Female	13 (50.0)	10 (34.5)	10 (38.5)	8 (26.7)
Study eye, no. (%)				
Right eye	14 (53.9)	13 (44.8)	15 (57.7)	17 (56.7)
Left eye	12 (46.2)	16 (55.2)	11 (42.3)	13 (43.3)
BCVA (letters)	46.58±14.54	50.79±12.87	47.62±13.73	48.87±14.66
CRT (μm)	291.54±183.35	310.90±138.45	330.36±121.24	335.50±152.39
CNV type, no. (%)				
Occult	5 (19.2)	12 (41.4)	10 (38.5)	7 (23.3)
Classic	4 (15.4)	6 (20.7)	5 (19.2)	5 (16.7)
Predominant classic	17 (65.4)	11 (37.9)	11 (42.3)	18 (60.0)
CNV area (mm^2)	8.07±8.07	8.40±6.14	9.75±6.50	7.74±6.91
Fluorescein leakage, no. (%)				
Yes	26 (100.0)	29 (100.0)	26 (100.0)	30 (100.0)
No	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leakage area (mm^2)	8.30±7.87	9.31±6.28	10.94±7.02	8.26±6.74

BCVA = best-corrected visual acuity; CRT = central retinal thickness; CNV = choroidal neovascularization.
Data are mean ± standard deviation unless otherwise indicated.

consent after the randomization and 1 patient was found to have angioid streaks, which was a condition among the exclusion criteria, leaving 120 patients who were treated and included in our analyses. Of these, 114 patients completed treatment in the 3-month loading phase. Reasons for withdrawal included an SAE (n = 1, reduced visual acuity score from 40 to 5), investigator decisions (n = 2), protocol deviation (n = 1), an inability to attend visits (n = 1), and a subject's request (n = 1). Before the second randomization, 3 patients exited the study. One withdrew consent and 2 had ocular AEs that included ocular inflammation and vitreous opacities, leaving 111 patients to continue treatment in the maintenance phase. Overall, 105 patients (86.1%) completed the 12-month study period (0.5-mg PRN, n = 24; 0.5-mg Q1M, n = 26; 2.0-mg PRN, n = 26; 2.0-mg Q1M, n = 29; Fig 1). The reasons why the 6 patients exited before the final month 12 visit included SAEs (n = 3; including 1 case of suspected drug-induced hepatitis, 1 case of hepatitis B, and 1 hepatic tumor), an investigator decision (n = 1; AMD progress in the fellow eye), an inability to attend visits (n = 1), and a subject's request (n = 1).

During the entire study, 10 patients were deemed ineligible because of protocol deviations. Eight of them failed to meet the study eye inclusion criteria, and the other 2 did not meet nonocular inclusion criteria. Overall, the randomized groups were well balanced with respect to baseline demographics and study eye characteristics (Table 1).

Efficacy

Treatment with conbercept produced significant improvements in BCVA in all treatment groups at both month 3 (the primary end point) and month 12 (Table 2). Most of the improvement occurred during the loading phase in the first 3 months. The mean changes in BCVA from baseline at month 3 were 8.97±13.08 letters for the 0.5-mg group ($P<0.0001$) and 10.43±10.65 letters for the 2.0-mg group ($P<0.0001$). Furthermore, these improvements were maintained or increased during the study. At month 12, mean changes in BCVA were 14.31±17.07 letters (0.5-mg PRN; $P = 0.0002$), 9.31±10.98 letters (0.5-mg Q1M; $P<0.0001$), 12.42±16.39 letters (2.0-mg PRN; $P = 0.0007$), and 15.43±14.70 letters (2.0-mg Q1M; $P<0.0001$) compared with baseline (Fig 2). The visual outcomes from the 2 dosing regimens were compared along with visual outcomes from all the study groups. No significant differences were observed between the dosing regimens and all study groups using pairwise comparisons ($P>0.05$).

At month 12, the proportions of patients gaining 15 letters or more were 50.0%, 31.0%, 42.3%, and 46.7% for the 0.5-mg PRN, 0.5-mg Q1M, 2.0-mg PRN, and 2.0-mg Q1M groups, respectively. At month 12, the proportions of eyes losing fewer than 15 letters were 100.0%, 96.55%, 96.15%, and 100.0%, respectively (Fig 3).

Improvements in BCVA with conbercept treatment were associated with a decrease in CRT measured with OCT imaging.

Table 2. Best-Corrected Visual Acuity Outcomes at Months 3 and 12

Time Point	0.5-mg Group			2.0-mg Group		
Month 3						
BCVA (letters)		58.39±17.30			59.46±16.13	
Change from BSL (letters)		8.97±13.08			10.43±10.65	
Month 12	As Needed (n = 26)	Monthly (n = 29)	Total (n = 55)	As Needed (n = 26)	Monthly (n = 30)	Total (n = 56)
BCVA (letters)	60.88±17.42	60.10±17.52	59.92±18.82	60.04±18.54	64.30±16.37	62.64±17.12
Change from BSL (letters)	14.31±17.07	9.31±10.98	10.49±15.99	12.42±16.39	15.43±14.70	13.61±14.97

BCVA = best-corrected visual acuity; BSL = baseline.
Data are mean ± standard deviation.

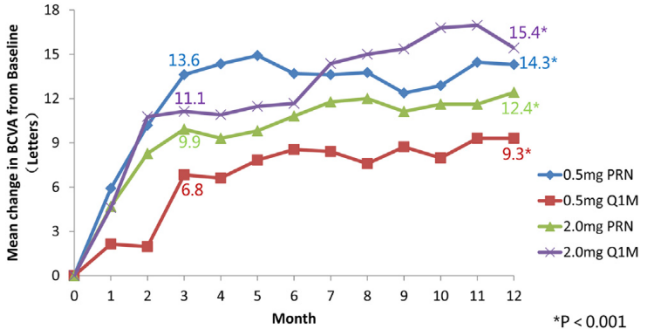

Figure 2. The mean change in best-corrected visual acuity (BCVA) from baseline over time in patients in the 4 dosing regimen treatment groups through 12 months. PRN = pro re nata (as needed); Q1M = monthly.

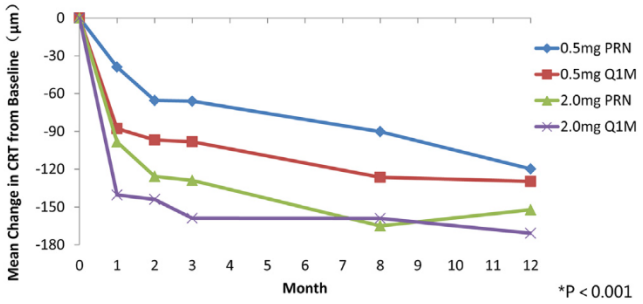

Figure 4. The mean change in central retinal thickness (CRT) from baseline over time using the 4 dosing regimens through 12 months. The CRT reduced rapidly during the first 3-month loading phase and then continued to decrease through month 12. PRN = pro re nata (as needed); Q1M = monthly.

The CRT decrease observed at month 3 continued to decrease through month 12. By month 12, the mean CRT measurements had decreased by 116.0±194.84 μm (0.5-mg PRN; $P = 0.0056$), 131.6±180.42 μm (0.5-mg Q1M; $P = 0.0005$), 157.8±183.98 μm (2.0-mg PRN; $P = 0.0003$), and 168.7±185.47 μm (2.0-mg Q1M; $P<0.0001$) for each group, respectively (Fig 4; Table 3).

The reductions of leakage area, CNV area, and lesion size on FA compared with baseline were statistically significant (Fig 5). All types of neovascular AMD (classic, occult, and predominantly classic lesions) were included in the study, and after 12 months of treatment, there were no significant differences between the 4 dosing groups with respect to changes in the lesions ($P>0.05$).

Over the maintenance phase, the mean numbers of conbercept injections at 12 months were 4.73 (0.5-mg PRN group), 8.34 (0.5-mg Q1M group), 4.88 (2.0-mg PRN group), and 8.57 (2.0-mg Q1M group). The 0.5-mg PRN group had 3.6 fewer injections than the 0.5-mg Q1M group, and the 2.0-mg PRN group had 3.7 fewer injections than the 2.0-mg Q1M group. The study results confirmed that the PRN groups received significantly fewer injections than the Q1M groups ($P<0.05$). The difference in the number of injections and the difference in the improvement of BCVA between both PRN groups were not statistically significant ($P>0.05$).

Safety

Intravitreal conbercept was well tolerated. The most common ocular AEs that occurred were associated with intravitreal injections such as transient increased intraocular pressure, vitreous floaters, cataract, conjunctival hemorrhage, and corneal

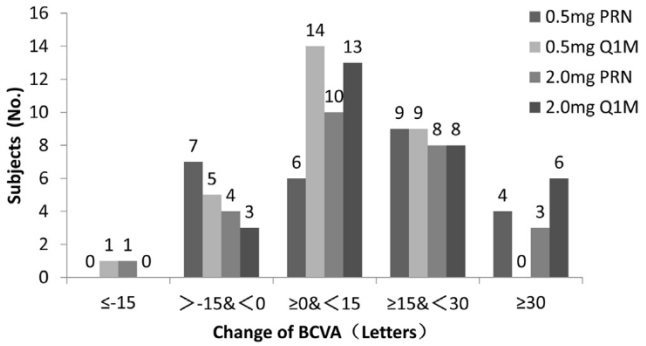

Figure 3. The number of patients with change in best-corrected visual acuity (BCVA) from baseline at month 12 in the 4 dosing regimens. PRN = pro re nata (as needed); Q1M = monthly.

inflammation. Most AEs were reported as mild or moderate and disappeared with or without treatment. During the entire study period, 39 patients (66.1%) in the 0.5-mg group reported AEs, which included 4 (6.78%) related to the study drug, 11 (18.64%) associated with intravitreal injections, and 7 (11.86%) SAEs; 45 patients (73.77%) in the 2.0-mg group reported AEs, which included 4 (6.56%) related to the study drug, 17 (27.87%) associated with intravitreal injection, and 3 (4.92%) SAEs.

During the maintenance phase, the incidence rates of ocular AEs in the study eyes were 23.1%, 20.7%, 27.0%, and 30.0% for the 0.5-mg PRN, 0.5-mg Q1M, 2.0-mg PRN, and 2.0-mg Q1M groups, respectively. The group with the highest exposure, the 2.0-mg Q1M group, also had the highest rate of AEs. However, because of the limited sample size, this phase 2 study was not powered adequately to assess the significance of these differences in AEs among the treatment groups. The SAEs affecting study eyes were uncommon in all treatment groups. One patient in the 0.5-mg PRN group received cataract extraction and intraocular lens implantation using phacoemulsification because of cataract progression with reduction in BCVA (compared with baseline) during the study. The patient recovered well after surgery and did not exit the study. One patient in the 2.0-mg Q1M group was hospitalized after the last injection because of pain in the study eye, a decrease of 7 letters in BCVA (decreased by 65 letters compared with baseline), foreign body sensation, and vitreous opacity. This patient underwent a tap for presumed endophthalmitis, and although the bacterial culture results were negative, this patient was diagnosed clinically with infectious endophthalmitis and received antibiotic therapy. After the antibiotic therapy, the symptoms of inflammation dissipated, with a concomitant gradual improvement in BCVA. By the last study visit, the BCVA was restored to 70 letters, and the cornea and lens were clear. The investigators judged that both SAEs might have been related to treatment. In addition, 2 patients experienced visual acuity decreases of more than 30 letters (compared with the last assessment of BCVA before the most recent treatment). One case occurred in the nonstudy eye. The other one occurred in the study eye during the loading phase with the 0.5-mg dose, and the investigator thought it was in the patient's best interest to exit the study.

No systematic (nonocular) AE was judged by the investigators to be related to the study drug or to the study procedure. No events described by the Antiplatelet Trialists' Collaboration occurred during the study. There were no cardiovascular or cerebrovascular events such as heart failure, stroke, or arterial thrombosis. There were no apparent allergic reactions, and there were no deaths during the study period. All SAEs, the frequent study drug–related AEs, and the study procedure–related AEs are summarized in Table 4.

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