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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 © 2014 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).*

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

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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.