Intravitreal Aflibercept Injection for Macular Edema Due to Central Retinal Vein Occlusion

Two-Year Results from the COPERNICUS Study

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Purpose: To evaluate the efficacy and safety of intravitreal aflibercept injection (IAI) for the treatment of macular edema secondary to central retinal vein occlusion (CRVO).

Design: Randomized, double-masked, phase 3 trial.

Participants: A total of 188 patients with macular edema secondary to CRVO.

Methods: Patients received IAI 2 mg (IAI 2Q4) (n = 114) or sham injections (n = 74) every 4 weeks up to week 24. During weeks 24 to 52, patients from both arms were evaluated monthly and received IAI as needed, or pro re nata (PRN) (IAI 2Q4 + PRN and sham + IAI PRN). During weeks 52 to 100, patients were evaluated at least quarterly and received IAI PRN.

Main Outcome Measures: The primary efficacy end point was the proportion of patients who gained ≥15 letters in best-corrected visual acuity (BCVA) from baseline to week 24. This study reports week 100 results.

Results: The proportion of patients gaining ≥15 letters was 56.1% versus 12.3% ($P<0.001$) at week 24, 55.3% versus 30.1% ($P<0.001$) at week 52, and 49.1% versus 23.3% ($P<0.001$) at week 100 in the IAI 2Q4 + PRN and sham + IAI PRN groups, respectively. The mean change from baseline BCVA was also significantly higher in the IAI 2Q4 + PRN group compared with the sham + IAI PRN group at week 24 (+17.3 vs. −4.0 letters; $P<0.001$), week 52 (+16.2 vs. +3.8 letters; $P<0.001$), and week 100 (+13.0 vs. +1.5 letters; $P<0.0001$). The mean reduction from baseline in central retinal thickness was 457.2 versus 144.8 μm ($P<0.001$) at week 24, 413.0 versus 381.8 μm at week 52 ($P = 0.546$), and 390.0 versus 343.3 μm at week 100 ($P = 0.366$) in the IAI 2Q4 + PRN and sham + IAI PRN groups, respectively. The mean number (standard deviation) of PRN injections in the IAI 2Q4 + PRN and sham + IAI PRN groups was 2.7±1.7 versus 3.9±2.0 during weeks 24 to 52 and 3.3±2.1 versus 2.9±2.0 during weeks 52 to 100, respectively. The most frequent ocular serious adverse event from baseline to week 100 was vitreous hemorrhage (0.9% vs. 6.8% in the IAI 2Q4 + PRN and sham + IAI PRN groups, respectively).

Conclusions: The visual and anatomic improvements after fixed dosing through week 24 and PRN dosing with monthly monitoring from weeks 24 to 52 were diminished after continued PRN dosing, with a reduced monitoring frequency from weeks 52 to 100. *Ophthalmology 2014;■:1–7 © 2014 by the American Academy of Ophthalmology.*

**Group members are listed online in Appendix 1 (available at www.aaojournal.org).*

Macular edema is the most common cause of decreased vision in patients with central retinal vein occlusion (CRVO).[1,2] Despite some reduction in macular edema, grid laser photocoagulation provides no visual benefit in patients with macular edema secondary to CRVO.[3] In contrast, treatment with intravitreal corticosteroid injections or implants has met with some clinical success.[4–6] Clarification of the central role of vascular endothelial growth factor (VEGF) in the pathophysiology of vascular permeability led to the use of anti-VEGF therapies for treatment of macular edema.[7–9] More recently, clinical trials have demonstrated the efficacy of intravitreal anti-VEGF agents for treatment of macular edema secondary to CRVO.[10–13]

Intravitreal aflibercept (known in the scientific literature as VEGF Trap-Eye; Regeneron Pharmaceuticals, Inc., Tarrytown, NY; and Bayer HealthCare Pharmaceuticals, Berlin, Germany) is a fusion protein comprising key domains of human VEGF receptors 1 and 2 with immunoglobulin-G Fc.[14] Intravitreal aflibercept binds multiple isoforms of human VEGF-A and placental growth factor with high affinity and has demonstrated efficacy for the treatment of wet age-related macular degeneration and diabetic macular edema.[15,16] Two parallel trials, the COPERNICUS and GALILEO studies, evaluated the efficacy and safety of intravitreal aflibercept injection (IAI) for the treatment of macular edema secondary to CRVO.[10–12] The primary efficacy end point of the COPERNICUS study was at week 24, and the results for weeks 24 and 52 were reported.[10,11] We present the 100-week results of the COPERNICUS study.

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Methods

Study Design

The COPERNICUS study was a 2-year, phase 3, randomized, double-masked clinical trial conducted across 61 sites in the United States, Canada, Colombia, India, and Israel (see Appendix 1 for a list of study investigators). The respective institutional review boards/ethics committees approved the protocol, which was carried out in compliance with ethical guidelines of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act. All participants provided written informed consent before the initiation of the study-specific procedures. The study was registered with ClinicalTrials.gov (identifier no. NCT00943072). Data for this report were collected between July 2009 and April 2012.

The design and eligibility criteria for the COPERNICUS study have been reported previously.[10,11] Only 1 eye from each patient was included in the study. Patients with macular edema secondary to CRVO who had a central retinal thickness (CRT) of ≥250 μm and a best-corrected visual acuity (BCVA) of 20/40 to 20/320 (73 to 24 letters) were randomly assigned in a 3:2 ratio to receive IAI 2 mg (IAI 2Q4) or sham injections every 4 weeks up to week 24. From week 24 to 52, all patients were evaluated monthly and received IAI on an as-needed, or pro re nata (PRN), basis if they had a >50 μm increase in CRT compared with the lowest previous measurement, new or persistent cystic retinal changes or subretinal fluid, persistent diffuse edema >250 μm in the central subfield, loss of ≥5 letters from the best prior measurement in conjunction with any increase in CRT, or an increase of ≥5 letters in BCVA from the most recent visit (suggesting a patient may not have reached maximal response yet). If none of the re-treatment criteria were met, patients received a sham injection. From week 52 to 100, patients from both study arms were evaluated at least quarterly and received IAI PRN according to the same re-treatment criteria. Patients could be evaluated and dosed as frequently as every 4 weeks if deemed necessary by the investigators. Masking was not performed during weeks 52 to 100. All patients were eligible to receive panretinal laser photocoagulation at any time during the study if they progressed to clinically significant ocular neovascularization.

Study End Point Assessments

The primary efficacy end point was the proportion of patients who gained ≥15 letters in BCVA from baseline to week 24. We report the 100-week results of the COPERNICUS study. Efficacy end points at week 100 were all exploratory and included the proportion of patients who gained ≥15 letters in BCVA; change from baseline in the mean BCVA and CRT; proportion of patients progressing to neovascularization of the anterior segment, optic disc, or elsewhere in the fundus; and change from baseline in the mean National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) total score.

The efficacy and safety end points were assessed as described previously.[10,11] The BCVA and CRT were assessed every 4 weeks from baseline to week 52, and every 12 weeks from week 52 to 100. Fundus photography and fluorescein angiography were performed at screening and weeks 12, 24, 36, 52, and 100. Vision-related quality of life was assessed at baseline and weeks 24, 52, and 100 using the NEI VFQ-25, which was administered by site personnel before intravitreal injections.

Statistical Analyses

The full analysis set included all randomized patients who received any study medication and had a baseline BCVA assessment and at least 1 BCVA assessment after baseline. Proportions were analyzed using a 2-sided Cochran–Mantel–Haenszel test. Continuous variables were analyzed with an analysis of covariance, with treatment group, region, and baseline BCVA as fixed factors and the respective baseline variable as a covariate. In the analysis of the proportion of patients who gained ≥15 letters, patients who discontinued before week 24 and had fewer than 5 injections were considered nonresponders; otherwise, missing values were imputed using the last-observation-carried-forward method. In the analysis of the proportion of patients with no retinal fluid, observed values were used. For all other efficacy end points, missing data were imputed using the last-observation-carried-forward method. Time to first injection was analyzed using Kaplan–Meier methodology. Safety was analyzed in the safety analysis set, which included all randomized patients who received any study treatment. Ocular and nonocular treatment-emergent serious adverse events (SAEs) from week 52 to 100 were analyzed among week 24 completers within the safety analysis set.

Results

Patient Disposition, Demographics, and Baseline Characteristics

A total of 115 patients were randomized to receive IAI, and 74 patients were randomized to receive sham. With the exception of 1 patient in the IAI group, all randomized patients were treated in the study and included in the safety analysis set (n = 114 for the IAI group and n = 74 for the sham group). As reported previously, 1 sham patient was excluded from the full analysis set (n = 114 for the IAI group and n = 73 for the sham group) because of the lack of a postbaseline BCVA assessment.[10] The percentages of patients completing the study in the IAI 2Q4 + PRN and sham + IAI PRN groups were 95.7% versus 81.1% at week 24, 93.0% versus 77.0% at week 52, and 88.7% versus 67.6% at week 100, respectively. Major reasons for discontinuation before week 100 in the IAI 2Q4 + PRN group were adverse events (3.5%), consent withdrawal (4.3%), loss to follow-up (1.7%), and protocol deviation (0.9%). No patient in the IAI 2Q4 + PRN group discontinued because of treatment failure. Major reasons for discontinuation before week 100 in the sham + IAI PRN group were adverse events (5.4%), lack of efficacy (5.4%), loss to follow-up (6.8%), death (5.4%), withdrawal of consent (4.1%), and protocol deviations (2.7%).

Demographic and baseline characteristics of patients were similar in both treatment groups.[10,11] Overall, 56.1% of patients in the IAI group and 71.2% of sham patients had CRVO for less than 2 months. Most patients were judged to have <10 disc areas of capillary nonperfusion at baseline (67.5% in the IAI group and 68.5% in the sham group) and a baseline BCVA of ≥35 letters (>20/200; 75.4% in the IAI group and 75.3% in the sham group).

Efficacy

The proportion of patients who gained ≥15 letters was significantly higher in the IAI 2Q4 + PRN group compared with the sham + IAI PRN group at week 24 (56.1% vs. 12.3%; $P<0.001$), week 52 (55.3% vs. 30.1%; $P<0.001$), and week 100 (49.1% vs. 23.3%; $P<0.001$) (Fig 1A). The mean change from baseline BCVA was also significantly higher in the IAI 2Q4 + PRN group compared with the sham + IAI PRN group at week 24 (+17.3 vs. −4.0 letters; $P<0.001$), week 52 (+16.2 vs. +3.8 letters; $P<0.001$), and week 100 (+13.0 vs. +1.5 letters; $P<0.0001$) (Fig 1B).

The mean reduction from baseline in CRT was 457.2 versus 144.8 μm at week 24 ($P<0.001$), 413.0 versus 381.8 μm at week 52, and 390.0 versus 343.3 μm at week 100 in the IAI 2Q4 + PRN and