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Subfoveal Choroidal Thickness during Aflibercept Therapy for Neovascular Age-Related Macular Degeneration

Twelve-Month Results

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Purpose: To investigate changes in subfoveal choroidal thickness after intravitreal aflibercept injections (IAIs) for neovascular age-related macular degeneration (AMD) at 12 months.

Design: Retrospective, consecutive, interventional case series.

Participants: One hundred forty-four patients with treatment-naïve neovascular AMD examined at 3 university hospitals.

Methods: After a loading phase of 3 monthly 2.0-mg IAIs, the patients were injected bimonthly with additional rescue injections performed for worsening. Subfoveal choroidal thickness in IAI-treated eyes was evaluated using enhanced depth imaging optical coherence tomography (OCT) or swept-source OCT.

Main Outcome Measures: Changes in subfoveal choroidal thickness over a 12-month period.

Results: Of the 144 treated eyes, 58 (40.3%) had typical neovascular AMD and 86 (59.7%) had polypoidal choroidal vasculopathy (PCV). The mean subfoveal choroidal thickness of treated eyes decreased from 268.1±101.3 μm at baseline to 233.0±99.7 μm at 3 months and remained unchanged at 232.4±99.6 μm at 12 months (percentage decrease, 13.3% at 12 months compared with baseline; $P < 0.0001$), although there was some fluctuation in between treatments. This decrease in subfoveal choroidal thickness was associated significantly with gain in visual acuity for PCV eyes ($P = 0.0087$; $R = 0.28$), but not for eyes with typical neovascular AMD ($P = 0.17$; $R = 0.18$). Eyes without persistent or recurrent retinal fluid after the loading phase showed greater decrease in subfoveal choroidal thickness compared with those with persistent or recurrent retinal fluid, in both typical neovascular AMD ($P = 0.042$) and PCV ($P = 0.038$) eyes.

Conclusions: Subfoveal choroidal thickness decreased over 12 months with IAI therapy in eyes with neovascular AMD. Changes in subfoveal choroidal thickness after IAIs seem to be related to visual and anatomic outcomes. *Ophthalmology 2016;123:617-624 © 2016 by the American Academy of Ophthalmology.*

Neovascular age-related macular degeneration (AMD) is one of the leading causes of significant visual loss in developed countries.[1] To date, many lines of therapies have been attempted to inhibit the exudation caused by choroidal neovascularization (CNV). Currently, intravitreal injection of anti−vascular endothelial growth factor (VEGF) agents is the most widely used therapy to suppress CNV in AMD.

Ranibizumab (Lucentis; Genentech, Inc, South San Francisco, CA) is a humanized anti-VEGF antibody fragment designed selectively to bind all forms of biologically active VEGF-A.[2,3] Ranibizumab has been shown to produce significant improvement of vision in AMD patients, with low risks of serious systemic and ocular adverse events.[4–9] Aflibercept (Eylea; Regeneron Pharmaceuticals, Tarrytown, NY; and Bayer AG, Leverkusen, Germany) is a relatively new anti-VEGF drug. The drug is a soluble decoy receptor fusion protein consisting of the binding domains of VEGF receptors 1 and 2 fused to the Fc portion of human immunoglobulin G-1, allowing for binding to all isoforms of VEGF-A, VEGF-B, and placental growth factor.[10,11] In the VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD 1 and 2 trials, intravitreal aflibercept injections (IAIs) dosed monthly or every 2 months after 3 initial monthly doses showed noninferior efficacy and safety when compared with monthly intravitreal ranibizumab injections.[12]

Previous reports demonstrated that anti-VEGF agents have a pharmacologic effect not only on CNV, but also on the underlying choroid, as visualized by optical coherence tomography (OCT).[13,14] In eyes with neovascular AMD treated with 3 monthly injections of 0.5 mg ranibizumab followed by as-needed retreatment through 12 months, we previously reported that the mean subfoveal choroidal

http://dx.doi.org/10.1016/j.ophtha.2015.10.039
ISSN 0161-6420/15

thickness was significantly decreased at 12 months compared with baseline.[14] However, other investigators did not find any significant changes in subfoveal choroidal thickness,[15,16] and therefore, there seem to be conflicting data on whether choroidal thickness changes with ranibizumab therapy in eyes with neovascular AMD.

Recently, we reported that choroidal thickness decreased after 3 monthly 2.0-mg IAIs in eyes with neovascular AMD, not only at the foveal center, but also across the entire macula.[13] Interestingly, this decrease in subfoveal choroidal thickness was much greater than that reported for 3 monthly intravitreal ranibizumab injections.[13–16] In the current study, we aimed to corroborate those short-term findings by examining changes in subfoveal choroidal thickness over 12 months of IAI therapy in eyes with neovascular AMD. We also evaluated the relationships between baseline and change in subfoveal choroidal thickness with 12-month anatomic and visual outcomes on IAI therapy.

Methods

This study was a retrospective, interventional case series involving 144 patients with treatment-naïve neovascular AMD who were examined initially at the Macula Services of Tokyo Women's Medical University, Fukushima Medical University, or Kyorin University School of Medicine between December 1, 2012, and October 31, 2013. During the period, a total of 172 patients with treatment-naïve AMD were scheduled to receive 3 consecutive monthly IAIs followed by bimonthly IAI injections over 1 year. Of the 172 patients, 15 were lost to follow-up, 5 elected to continue IAI therapy based on the treat-and-extend regimen,[9] 2 elected to continue IAI therapy based on the pro re nata (as-needed) regimen,[8] 1 was converted to ranibizumab therapy, 1 was converted to pegaptanib therapy, 1 did not receive IAI at 2 months or thereafter because of the development of retinal pigment epithelium (RPE) tear, and 1 did not receive IAI at 2 months or thereafter because of the development of vitreous hemorrhage requiring pars plana vitrectomy. Two eyes with retinal angiomatous proliferation[17] who completed the 12-month follow-up at 1 institution were not included in this study because different treatment protocols combined with photodynamic therapy (PDT) with verteporfin were used for patients with retinal angiomatous proliferation at the other 2 institutions. Of the 144 patients included in the analyses, 95 patients also were included in our previous study regarding the changes in the choroidal thickness after 3 monthly IAIs.[13] When patients received IAI therapy bilaterally during the 12-month period, only the eye treated first was included in the study. Diagnosis of subtype of neovascular AMD, either typical neovascular AMD or PCV, was made by trained retina specialists (H.K., M.K., A.Y.) based on funduscopic and angiographic findings. Typical neovascular AMD was characterized by exudative changes resulting from the presence of CNV as confirmed by fluorescein angiography and indocyanine green angiography (ICGA). The diagnosis of PCV was based on the ICGA finding of polypoidal structures present at the border of a branching choroidal vascular network.[18] The orange-red protrusions under the RPE were directly observed biomicroscopically in many eyes, corresponding to the polypoidal lesions detected with ICGA. The exclusion criteria were any of the following: (1) non-AMD macular disorders, such as angioid streaks; (2) a spherical equivalent of −6 diopters or less, chorioretinal atrophic changes secondary to pathologic myopia, or both; (3) a history of intraocular surgery within 6 months; (4) a history of pars plana vitrectomy; and (5) systemic contraindications for IAIs.

At baseline, all 144 patients underwent comprehensive ophthalmic examination including decimal best-corrected visual acuity (BCVA) testing with Landolt C charts, dilated funduscopy, color fundus photography, fluorescein angiography and ICGA using a confocal scanning laser ophthalmoscopy (HRA-2; Heidelberg Engineering, Inc, Heidelberg, Germany), and OCT. At each monthly visit over the 12-month period, all patients underwent BCVA testing, dilated funduscopy, color fundus photography, and OCT. All 144 patients were administered a 2.0-mg IAI monthly for 3 months during a loading phase: at baseline, 1 month, and 2 months. Thereafter, patients received IAIs bimonthly: at 4, 6, 8, and 10 months. Between the fixed bimonthly treatments, eyes were given rescue injections if any of the following were observed: (1) worsening of subretinal fluid, intraretinal fluid, or both by OCT; (2) new macular hemorrhage; (3) expanding pigment epithelial detachment; or (4) decreased visual acuity more than the equivalent of 10 Early Treatment Diabetic Retinopathy Study letters in the presence of retinal fluid on OCT.

Subfoveal choroidal thickness was measured with either swept-source OCT (DRI-OCT; Topcon, Tokyo, Japan) at Tokyo Women's Medical University or enhanced depth imaging OCT (Heidelberg Spectralis; Heidelberg Engineering Inc, Heidelberg, Germany) at Fukushima Medical University and Kyorin University. A high intersystem correlation between the 2 OCT devices was reported previously,[19] and the same OCT machine was used for all visits for each patient. With swept-source OCT, 12-mm horizontal and vertical line scans through the foveal center were obtained, and up to 96 B-scan images were averaged to reduce the speckle noise. With enhanced depth imaging OCT, 9-mm horizontal and vertical scans through the foveal center were obtained using a method reported previously.[20] All images for enhanced depth imaging OCT were obtained using an eye-tracking system, and 100 scans were averaged. Subfoveal choroidal thickness was defined as the distance between the hyperreflective line corresponding to Bruch's membrane beneath the RPE and the inner surface of the sclera at the foveal center and was measured manually using the OCT's caliper function. All OCT measurements were performed by 2 independent well-trained retina specialists (H.K., M.K., A.Y., M.S., I.M., A.A.O.) at each institution who were masked to all patient information including treatment status. The average of the values measured by the 2 investigators was used for analysis. A macula was judged to be dry when there was complete resolution of subretinal and intraretinal fluid on OCT.

The primary outcome was change in subfoveal choroidal thickness in IAI-treated eyes over 12 months. The percentage decrease in subfoveal choroidal thickness at each time point compared with that at baseline then was calculated. When no change in subfoveal choroidal thickness was observed, the percentage decrease was 0%. In addition, to see if choroidal thickness was associated with clinical outcomes, we performed correlation analyses on the following 4 subjects: subfoveal choroidal thickness at baseline and BCVA, decrease in subfoveal choroidal thickness and BCVA, subfoveal choroidal thickness at baseline and persistence or recurrence of retinal fluid, and decrease in subfoveal choroidal thickness and persistence or recurrence of retinal fluid.

Data were analyzed with frequency and descriptive statistics. Mean values were compared by paired and unpaired t tests. Before analyses, BCVA was converted to logarithm of the minimum angle of resolution units. Correlation analyses were performed by use of the Pearson correlation test. Data were expressed as the mean ± standard deviation, and a P value less than 0.05 was considered to be significant. All tests were 2 sided. Statistical analyses were performed using SPSS software version 18.0 (SPSS, Inc, Chicago,