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Treat-and-Extend Regimen with Aflibercept for Neovascular Age-Related Macular Degeneration

Efficacy and Macular Atrophy Development

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Purpose: To evaluate the effects of intravitreal injection of aflibercept using a treat-and-extend dosing regimen on treatment-naïve neovascular age-related macular degeneration (AMD) and the development of macular atrophy.

Design: Retrospective, interventional case series.

Participants: Eyes (n = 137) with treatment-naïve neovascular AMD, including 18 eyes with typical AMD with classic choroidal neovascularization (CNV), 44 eyes with typical AMD with occult CNV, 58 eyes with polypoidal choroidal vasculopathy, and 17 eyes with retinal angiomatous proliferation (RAP).

Methods: Clinical records of eyes with neovascular AMD that underwent 3 consecutive monthly intravitreal injections of aflibercept followed by a treat-and-extend dosing regimen were reviewed, and the corresponding imaging studies were analyzed.

Main Outcome Measures: Changes in best-corrected visual acuity (BCVA), central macular thickness (CMT), central choroidal thickness (CCT), and the extent of macular atrophy in the macular area during a 2-year follow-up period.

Results: In all subtypes after 1 and 2 years, CMT and CCT were reduced significantly, whereas macular atrophy showed significant enlargement. At baseline, the extent of macular atrophy was greater in RAP than other subtypes; after 2 years, the macular atrophy enlargement was also greatest in RAP and correlated negatively with CCT ($rs = -0.72$; $P < 0.01$). Best-corrected visual acuity showed significant improvement after 1 and 2 years in all subtypes other than RAP. In RAP, BCVA was improved significantly after 1 year, but the magnitude of this improvement lost statistical significance after 2 years.

Conclusions: Treat-and-extend with intravitreal aflibercept may be effective for improving BCVA and ameliorating exudative changes in neovascular AMD. However in RAP, choroidal thinning during the treatment regimen may accelerate enlargement of macular atrophy, thereby diminishing the improvement in BCVA after 2 years. *Ophthalmology Retina 2017;■:1–7 © 2017 by the American Academy of Ophthalmology*

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Age-related macular degeneration (AMD), the leading cause of adult blindness in developed countries,[1] is classified into 2 major forms: dry AMD (also called nonneovascular AMD) and wet AMD (also called neovascular AMD).[2] Although effective treatments are lacking for dry AMD, wet AMD has been treated by many methods. In the past decade, intravitreal anti–vascular endothelial growth factor (VEGF) therapy has become a major treatment strategy. Of the main anti-VEGF agents used to treat wet AMD, ranibizumab and aflibercept have regulatory approval for ophthalmic use, whereas bevacizumab is used off label. Although all of these agents exert antiangiogenic effects by inhibiting VEGF-A, aflibercept additionally inhibits VEGF-B and placental growth factor.[3–5] There are several intravitreal anti-VEGF regimens, and ophthalmologists increasingly have chosen proactive treat-and-extend regimens in recent years.[6,7]

Macular atrophy is a critical factor related to visual acuity in patients with AMD.[8,9] Macular atrophy is detected as hypofluorescent areas on fundus autofluorescence (FAF), and atrophy at the fovea leads to severe vision loss.[8,9] The enlargement of macular atrophy secondary to intravitreal anti-VEGF therapy has been reported.[10,11] Although it is important to resolve the exudative changes in AMD, the development of macular atrophy during anti-VEGF therapy also warrants attention. It is known that choroidal thinning may occur under anti-VEGF therapy,[12,13] and recent studies indicate that the choroidal thinning may be associated with the development of macular atrophy.[11,14]

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Neovascular AMD is divided into 3 subtypes: typical AMD (tAMD), polypoidal choroidal vasculopathy (PCV), and retinal angiomatous proliferation (RAP).[15] Typical AMD is divided further into tAMD with type 1 and type 2 choroidal neovascularization (CNV) according to Gass classification.[16] Type 1 CNV occurs under the retinal pigment epithelium (RPE), which often shows occult CNV on fluorescein angiography (FA). Type 2 CNV occurs over the RPE, which often shows classic CNV on FA. Recently, it has been suggested that the optimal treatment strategy may depend on AMD subtype.[11,17]

In the current study, we investigated the 2-year efficacy of aflibercept treat-and-extend for all neovascular AMD subtypes and associated development of macular atrophy.

Methods

This study was performed under approval of the institutional review board of Gunma University School of Medicine and complied with the guidelines of the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study. We retrospectively studied 137 eyes of 135 patients (98 eyes of 97 men; 39 eyes of 38 women) with previously untreated neovascular AMD. The patients started the regimen between November 2013 through October 2014, then continued it for 2 years using a treat-and-extend regimen with aflibercept at Gunma University Hospital. The average patient age was 73.1 years (range, 45−90 years). All patients underwent a complete ophthalmic examination, including slit-lamp biomicroscopy with a noncontact fundus lens (SuperField lens; Volk Optical, Inc, Mentor, OH), color fundus photography and FAF (Canon CX-1; Canon, Tokyo, Japan), near infrared reflectance, FA, indocyanine green angiography (Spectralis HRA + OCT; Heidelberg Engineering, Heidelberg, Germany), and swept-source OCT with 8 mm of axial resolution (DRI OCT-1; Topcon Corp, Tokyo, Japan) or spectral-domain OCT with 5 mm of axial resolution (Cirrus OCT; Zeiss Meditec, Inc, Dublin, CA). The diagnostic criteria of neovascular AMD subtypes were based on those of previous reports.[15,16] The diagnoses of reticular pseudodrusen were based on combined color fundus photography and near infrared reflectance according to previous reports.[18,19]

All eyes were treated solely by intravitreal injection of aflibercept (2 mg/0.05 ml) using a treat-and-extend dosing regimen according to previous reports.[6,11] Briefly, the strategy consists of loading and maintenance phases. In the loading phase, patients receive 3 monthly injections of aflibercept. In the maintenance phase, the interval of injections is extended by 2 weeks if there is no exudative change, whereas the interval is shortened by 2 weeks if any exudative change is seen. These assessments are conducted at all visits. The scheduled treatment interval was extended to a maximum of 12 weeks in the current study.

Best-corrected visual acuity (BCVA), central macular thickness (CMT), and central choroidal thickness (CCT) were examined at every visit. Best-corrected visual acuity was determined with a manifest refraction and recorded as decimal values and converted to logarithm of the minimum angle of resolution units. Central macular thickness and CCT were measured on B-scan OCT images using the computer-based caliper measurement tool in the OCT system. Central macular thickness was defined as the distance between the internal limiting membrane and the RPE at the fovea. Central macular thickness included any CNV, subretinal fluid, and intraretinal cysts. Central choroidal thickness was defined as the distance between Bruch's membrane and the margin of the choroid and sclera under the fovea. The area of macular atrophy was measured on the FAF image before the initial intravitreal injection of aflibercept, then 1 and 2 years after initial treatment, by a modified method reported previously.[9,11] Briefly, the well-demarcated hypoautofluorescent areas with greatest linear dimension of 0.25 mm or more in the macular area, defined by the Early Treatment Diabetic Retinopathy Study grid with a 6000-μm diameter, was measured manually by ImageJ software (developed by Wayne Rasband, National Institutes of Health, Bethesda, MD; available at https://imagej.nih.gov/ij/; Supplemental Fig 1, available at www.ophthalmologyretina.org). The hypoautofluorescent area resulting from hemorrhage and peripapillary atrophy were excluded from the measurement. Any patient with cataract obscuring the FAF images, RPE tear at baseline, newly developed RPE tear during treatment, or massive subretinal hematoma of 3 disc diameters or more was excluded from the measurement of macular atrophy area. In FAF imaging using a flash fundus camera−based system, the hypoautofluorescence in the fovea resulting from macular pigment is mild, thereby not obscuring the area of macular atrophy. The total number of injections in the first and second year was counted for all patients. The data for CMT, CCT, and macular atrophy area were recorded independently by 2 examiners (H.M., K.M.) masked to the patients' information, and if the measurement difference exceeded 15% of the mean of the 2 values, there was open adjudication with the senior author (M.M.).

In statistical analysis, the paired Student t test or Wilcoxon signed-rank test was used to compare the differences between BCVA, CMT, CCT, or macular atrophy area at baseline and other time points. The Mann−Whitney U test was used to compare unpaired values of CCT. The Spearman rank correlation coefficient was calculated to study the association between CCT and the area of macular atrophy. The Kruskal−Wallis and Steel−Dwass tests were used to evaluate differences in incidence of reticular pseudodrusen, number of intravitreal injections, and area of macular atrophy among the subtypes of wet AMD. The data analyses were performed using Excel 2016 (Microsoft Corp, Redmond, WA) with add-in software Statce14.[20] $P < 0.05$ was considered significant.

Results

A total of 137 eyes of 135 patients with neovascular AMD were classified into 4 subtypes: 18 eyes of 18 patients with tAMD with classic (type II) CNV (11 eyes of 11 men, 7 eyes of 7 women; average age, 75.7 years), 44 eyes of 44 patients with tAMD with occult (type I) CNV (37 eyes of 37 men, 7 eyes of 7 women; average age, 71.5 years), 58 eyes of 58 patients with PCV (45 eyes of 45 men, 13 eyes of 13 women; average age, 72.4 years), and 17 eyes of 16 patients with RAP (5 eyes of 5 men, 12 eyes of 11 women; average age, 77.2 years). Reticular pseudodrusen were observed in 5 eyes (27.7%) with tAMD with classic CNV, in 3 eyes (6.8%) with tAMD with occult CNV, in 1 eye (1.7%) with PCV, and in 13 eyes (76.5%) with RAP. The incidence of reticular pseudodrusen was significantly higher in RAP than in other AMD subtypes (vs. AMD classic CNV, $P < 0.05$; vs. AMD occult CNV, $P < 0.01$; vs. PCV, $P < 0.01$).

Best-corrected visual acuity (average ± standard error) measurements at baseline, after 1 year, and after 2 years were 0.63±0.08, 0.44±0.09 ($P < 0.05$), and 0.45±0.09 ($P < 0.01$) in tAMD with classic CNV; 0.26±0.05, 0.12±0.04 ($P < 0.001$), and 0.14±0.06 ($P < 0.001$) in tAMD with occult CNV; 0.27±0.04, 0.11±0.04 ($P < 0.001$), and 0.14±0.04 ($P < 0.001$) in PCV; and 0.57±0.08, 0.28±0.07 ($P < 0.01$), and 0.37±0.08 ($P = 0.21$) in RAP, respectively. Best-corrected visual acuity improved significantly after 1 and 2 years in tAMD with classic CNV, tAMD with occult CNV, and PCV. In RAP, BCVA improved significantly after 1 year compared with baseline, but lost significance after 2 years (Fig 1).

Central macular thickness (average ± standard error) measurements at baseline, after 1 year, and after 2 years were 428±42