Jpn J Ophthalmol (2015) 59:261–265
DOI 10.1007/s10384-015-0387-z

THE OFFICIAL INTERNATIONAL JOURNAL OF THE JAPANESE OPHTHALMOLOGICAL SOCIETY

CLINICAL INVESTIGATION

Intravitreal aflibercept for ranibizumab-resistant exudative age-related macular degeneration with choroidal vascular hyperpermeability

Yoko Nomura[1] · **Yasuo Yanagi**[1]

Received: 7 November 2014 / Accepted: 10 April 2015 / Published online: 16 May 2015

Abstract
Purpose To investigate anatomical responses and visual changes in cases of exudative age-related macular degeneration (AMD) with choroidal vascular hyperpermeability (CVH) that responded poorly to multiple ranibizumab injections and were treated with intravitreal aflibercept.
Design Retrospective comparative study.
Participants Twenty-five consecutive patients attending the outpatient clinic of the University of Tokyo Hospital who showed an insufficient response to multiple intravitreal ranibizumab injections and were switched to intravitreal aflibercept injections between March and June 2013. All patients were treated with intravitreal aflibercept in a treat-and-extend regimen and followed up for at least 12 months.
Methods Presence or absence of CVH was determined by indocyanine green angiography. Changes of best-corrected visual acuity (BCVA) and central retinal thickness (CRT) at 12 months were compared between the CVH (+) AMD and CVH (−) AMD eyes.
Results The improvement in logMAR BCVA at 12 months was larger in the CVH (−) AMD eyes than in the CVH (+) AMD eyes (−0.18 vs −0.026; $P = 0.0089$, *t*-test). The changes in CRT did not differ significantly between the groups (−122 ± 101 μm in the CVH (−) AMD eyes and −159 ± 118 μm in the CVH (+) AMD eyes; $P = 0.44$, *t*-test). The proportion of the eyes without intraretinal or subretinal fluid or hemorrhage was 88 % in the CVH (−) AMD and 67 % in the CVH (+) AMD ($P = 0.21$, *t*-test).
Conclusions Compared with AMD without CVH, AMD with CVH showed poorer visual gain resulting from intravitreal aflibercept treatment.

Keywords Age-related macular degeneration · Choroidal vascular hyperpermeability · Aflibercept

Introduction

Choroidal vascular hyperpermeability (CVH), detected as multifocal choroidal hyperfluorescence by indocyanine green angiography (ICGA), was first demonstrated in central serous chorioretinopathy (CSC) [1–5], and was also reported two decades ago in eyes with polypoidal choroidal vasculopathy (PCV) [6]. More recently, PCV with CVH has been investigated [7–10]. Some investigators demonstrate that CVH is associated with inferior outcomes after intravitreal anti-vascular endothelial growth factor (VEGF) treatment (ranibizumab or bevacizumab) for PCV [9, 10], and it is now generally accepted that CVH plays a pivotal role in PCV. However, CVH is not unique to CSC or PCV, but is also associated with typical AMD (tAMD). One study [11] reports that in eyes with choroidal neovascularization (CNV) accompanied by CVH, type 1 CNV was more frequent than previously thought, while type 2 CNV and polypoidal lesions were sometimes observed. These studies led us to hypothesize that exudative AMD eyes with CVH may have different characteristics [12] and

Electronic supplementary material The online version of this article (doi:10.1007/s10384-015-0387-z) contains supplementary material, which is available to authorized users.

✉ Yasuo Yanagi
yanagi-tky@umin.org; yanagi-tky@umin.ac.jp

[1] Department of Ophthalmology, Graduate School of Medicine and Faculty of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

respond differently to those without CVH, regardless of whether it is tAMD or PCV.

There are no studies that have investigated the effects of CVH on treatment outcomes of exudative AMD using aflibercept for 12 months. Thus, to clarify the treatment outcomes of patients with exudative AMD with CVH, we conducted a retrospective study focusing on the treatment outcomes of intravitreal aflibercept treatment for patients that responded poorly to conventional anti-VEGF therapy (i.e., ranibizumab). We used a treat-and-extend protocol with a maximal treatment interval of 8 weeks.

Methods

Subjects

Subjects were consecutive patients who started intravitreal aflibercept treatment between March and June 2013 and were followed up for at least 12 months after the first aflibercept treatment at the outpatient macular clinic of the University of Tokyo Hospital. Only those patients whose best-corrected visual acuity (BCVA) data and spectral domain optical coherence tomography (SD-OCT) images were available at baseline and at 3, 6 and 12 months after the initial treatment were included. After excluding eyes with a previous history of laser photocoagulation, verteporfin photodynamic therapy, or vitrectomy, or with any other pathologic conditions, such as diabetic retinopathy, 25 subjects were included. All subjects had a history of insufficient response to multiple intravitreal ranibizumab injections. The decision as to whether to change from ranibizumab to aflibercept was made at the discretion of the attending doctor and the reasons for switching the treatment were investigated retrospectively. All data were collected as part of clinical examinations and retrospectively reviewed. OCT examinations were performed at some time between 9 am and 5 pm. Institutional review board approval was obtained from the University of Tokyo.

Choroidal vascular hyperpermeability

Similar to previous reports [8–11], CVH was defined as the presence within the choroid of multifocal areas of hyperfluorescence with blurred margins identified in the late phase of ICGA. Two independent investigators judged cases in a blinded manner. In cases where their judgment differed, they re-examined the images together to reach a consensus.

Aflibercept treatment

Aflibercept (2 mg/0.05 ml; Eylea®, Regeneron, NY, USA) was injected into the vitreous cavity in a standard manner. After three intravitreal injections of aflibercept were administered at months 0, 1, and 2, additional injections were administered as a modified treat-and-extend regimen [13, 14]; the patients were treated monthly until no signs of macular hemorrhage and no intraretinal or subretinal fluid were observed on SD-OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany). Then the treatment interval was lengthened by 2 weeks to a maximum of 8 weeks if no signs of recurrent exudation were noted on OCT for the second consecutive time. The follow-up period was shortened by 2 weeks if any signs of exudation or new macula hemorrhage were evident.

Treatment outcomes

Treatment outcomes were analyzed in a similar method to the one we employed previously [15]. Best-corrected visual acuity (BCVA) was measured using a Landolt C chart at baseline, 3, 6 and 12 months. BCVA scores were converted to the logarithm of the minimum angle of resolution (logMAR) values for statistical analysis. Central retinal thickness (CRT) was defined as the retinal thickness from the inner limiting membrane to the surface of the retinal pigment epithelium (RPE) of the central points in the horizontal scanning lines. Choroidal thickness was defined as the distance between Bruch's membrane and the chorioscleral border. CRT and choroidal thickness were measured using electronic calipers in the SD-OCT at baseline, 3, 6 and 12 months after the initial treatment. Changes in BCVA, CRT, and choroidal thickness and the number of intravitreal aflibercept injections in 12 months were examined. The proportion of the eyes with exudative findings on SD-OCT at 12 months was also investigated.

Statistical analysis

Statistical analysis was performed using JMP software version 10.0 (SAS Institute, Cary, NC, USA). Categorical data were assessed using the chi-square test, and continuous variables were compared using Student's *t*-test. A P value <0.05 was considered significant. Regression analysis was performed to determine the association between the changes of BCVA and baseline BCVA. The associations between the changes of BCVA and baseline characteristic factors, such as baseline BCVA and the presence or absence of hyperpermeability were examined by multiple regression analysis.

Results

Patient characteristics are summarized in Table 1. CVH was observed in nine eyes. One patient with CVH (+) AMD and one patient with CVH (−) AMD had a history of

Table 1 Patient characteristics

	CVH (−) AMD	CVH (+) AMD	*P* value
Patients, *n*	16	9	
Male, *n* (%)	9 (56.3)	7 (77.8)	0.28†
Age, years	73.6 ± 6.5	77.1 ± 9.2	0.34*
PCV, *n* (%)	9 (56.3)	8 (88.9)	0.093†
Baseline logMAR BCVA	0.32 ± 0.26	0.21 ± 0.23	0.31*

Data presented as mean ± standard deviation unless otherwise indicated

CVH choroidal vascular hyperpermeability, *AMD* age-related macular degeneration, *PCV* polypoidal choroidal vasculopathy, *BCVA* best-corrected visual acuity

* Student *t*-test, † Chi-square test

CSC. Sex, age, and baseline BCVA did not differ significantly between the CVH (+) AMD and CVH (−) AMD eyes (Table 1). The ratio of PCV tended to be higher in the CVH (+) AMD than in CVH (−) AMD eyes. The mean number of previous ranibizumab treatments was 9.0 in the CVH (−) AMD and 7.7 in the CVH (+) AMD ($P = 0.34$, *t*-test) (Supplemental Table). The reason for switching to aflibercept is shown in the Supplemental Table.

The mean changes in BCVA after the initial ranibizumab treatments are shown in Fig. 1. In the CVH (−) AMD, the mean BCVA was 0.32 logMAR at baseline and significantly improved to 0.17, logMAR at 3 months ($P < 0.0001$); to 0.14 logMAR at 6 months ($P < 0.0001$); and to 0.14 logMAR at 12 months ($P < 0.0001$). In the CVH (+) AMD, the mean BCVA was 0.21 logMAR and did not improve at any follow-up period; i.e., it was 0.13 logMAR at 3 months ($P = 0.13$); 0.13 logMAR at 6 months ($P = 0.10$); and 0.19 logMAR at 12 months ($P = 0.53$). The change in logMAR BCVA at 12 months in the CVH (−) AMD eyes (−0.18) was larger than that in the CVH (+) AMD eyes (−0.026, $P = 0.0089$). Regression analysis revealed that a better baseline BCVA is associated with poor VA change ($r = -0.45$, $P = 0.025$). Multiple regression analysis was performed, with the baseline BCVA and the presence or absence of CVH as variables, to exclude the possibility that the slightly better baseline BCVA in the CVH (−) AMD eyes, rather than CVH itself, was associated with the change in BCVA. Results showed that the presence of CVH was associated with less improvement in BCVA ($P = 0.016$, $\beta = -0.45$) independent of baseline BCVA ($P = 0.047$, $\beta = -0.36$). On the other hand, the subtype of AMD (i.e., tAMD or PCV) was not associated with the change in BCVA at 12 months ($P = 0.82$). The mean number of intravitreal aflibercept injections was 9.4 in the CVH (+) AMD eyes and 9.0 in the CVH (−) AMD eyes, showing no statistical difference ($P = 0.60$, *t*-test).

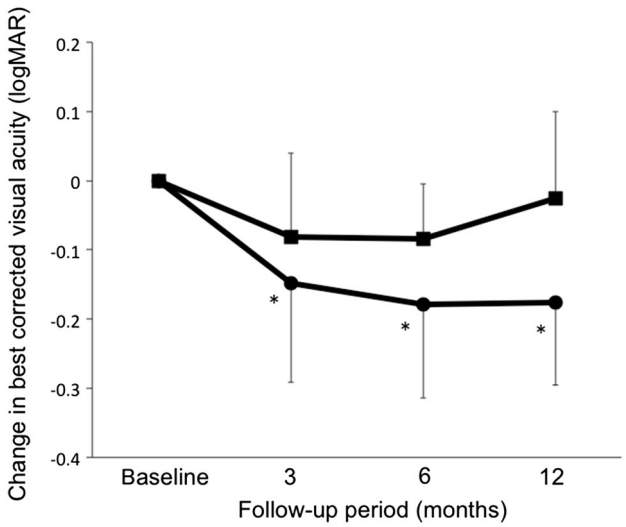

Fig. 1 Mean changes in BCVA (logMAR) after initial aflibercept treatment. In the CVH (−) group (*black circles*), mean BCVA was significantly improved at 3, 6, and 12 months. In the CVH (+) group (*black squares*), mean BCVA (logMAR) did not improve at any follow-up point. Significant improvement in BCVA compared to baseline is denoted by an *asterisk*. *Bar* indicates standard deviation. *BCVA* best-corrected visual acuity, *logMAR* logarithm of minimum angle of resolution, *CVH* choroidal vascular hyperpermeability

The mean changes in CRT after the initial ranibizumab treatment are shown in Fig. 2. In the CVH (−) AMD, the mean CRT was 283 μm at baseline and had significantly decreased to 175 μm at 3 months ($P = 0.0014$), to 157 μm at 6 months ($P \leq 0.0002$), and to 161 μm at 12 months ($P < 0.0002$). In the CVH (+) AMD, the mean CRT was 316 μm at baseline and had decreased to 164 μm at 3 months ($P = 0.0029$), 156 μm at 6 months ($P = 0.0042$), and 157 μm at 12 months. ($P = 0.0037$). The change in CRT at 12 months did not differ between the groups (−122 ± 101 μm in the CVH (−) AMD eyes and −159 ± 118 μm in the CVH (+) AMD eyes; $P = 0.44$, *t*-test). The mean changes in choroidal thickness after the initial ranibizumab treatment are shown in Fig. 3. The mean baseline choroidal thickness in the CVH (+) AMD eyes (300 μm) was significantly thicker than in the CVH (−) AMD eyes (205 μm, $P = 0.032$). The changes in

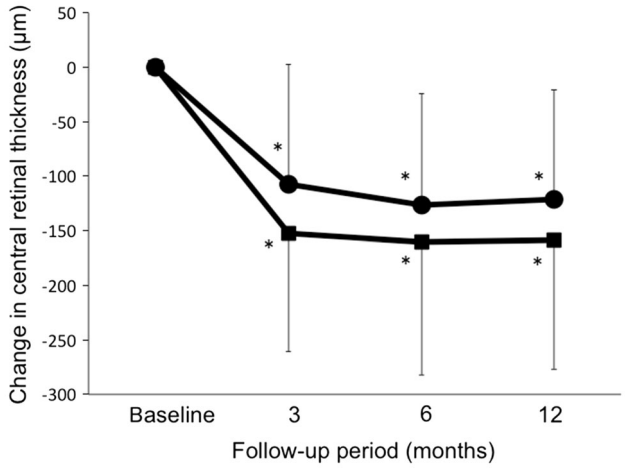

Fig. 2 Mean changes in CRT after initial aflibercept treatment. In both the CVH (−) group (*black circles*) and CVH (+) group (*black squares*), mean CRT significantly decreased at 3, 6, and 12 months. Significant improvement in CRT compared to baseline is denoted by an *asterisk*. *Bar* indicates standard deviation. *CRT* central retinal thickness, *CVH* choroidal vascular hyperpermeability

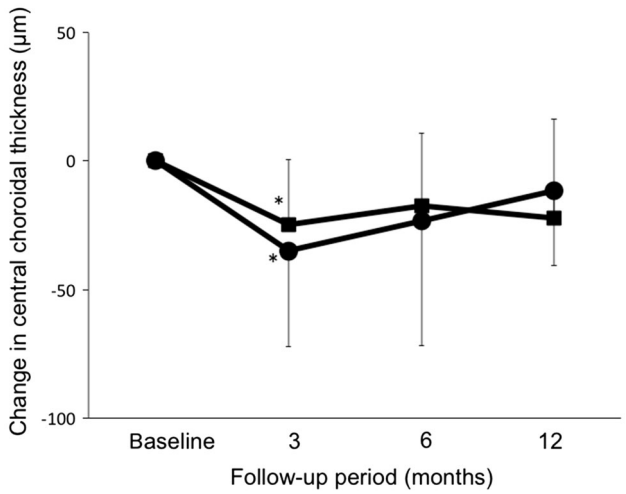

Fig. 3 Mean changes in central choroidal thickness after initial aflibercept treatment. In both the CVH (−) group (*black circles*) and CVH (+) group (*black squares*), mean central choroidal thickness significantly decreased at 3 months. Significant improvement in central choroidal thickness compared to baseline is denoted by an *asterisk*. *Bar* indicates standard deviation. *CVH* choroidal vascular hyperpermeability

choroidal thickness were -12 ± 29 μm in the CVH (−) AMD eyes and -22 ± 39 μm in the CVH (+) AMD eyes, with no statistically significant differences between the two groups ($P = 0.48$). The proportion of the eyes without intraretinal or subretinal fluid or hemorrhage at 12 months was 88 % in the CVH (−) AMD and 67 % in the CVH (+) AMD ($P = 0.21$, *t*-test).

Discussion

In the present study, the CVH (+) AMD eyes showed poor visual improvement following the intravitreal aflibercept injections compared with the CVH (−) AMD eyes. In a previous study on PCV [10], CVH was associated with poor outcomes after intravitreal anti-VEGF treatment (bevacizumab or ranibizumab) at 12 months.

To the best of our knowledge, no studies have examined the association between CVH and the treatment outcomes of intravitreal aflibercept for 12 months. Several studies demonstrate favorable anatomical outcomes of aflibercept for exudative AMD patients that responded poorly to ranibizumab [16–20]. However, most studies demonstrate limited visual gain after switching to aflibercept [18–20]. The present findings are consistent with previous results [10] and extend them to cover aflibercept treatment. Of particular note is that multiple regression analysis showed that hyperpermeability, but not the subtype of AMD, was associated with the changes in BCVA. Intriguingly, the choroidal thickness at 12 months in the CVH (+) AMD eyes did not decrease from the baseline, despite continuous aflibercept injections, whereas the exudative changes regressed in both the CVH (−) AMD and CVH (+) AMD eyes. In PCV, CVH was related to persistent retinal fluid levels 1 month after the third ranibizumab injection [9]. In that previous study, 57 subjects were all treatment-naïve PCV patients who received ranibizumab injections, so we cannot simply compare these results with ours. In the present study, discrepancy was observed between functional and anatomical improvements. Despite the anatomical improvement not being clear, a plausible explanation for the lack in functional improvements may be that the functional impairment in the retinal and RPE cells at baseline was more severe in the CVH (+) AMD eyes than in the CVH (−) AMD eyes, limiting visual recovery. The patients in this study showed poor anatomical responses to previous intravitreal ranibizumab injections and 80 % of these patients showed no exudative findings at 12 months after initial aflibercept injection. Despite the anatomical improvements, the eyes with CVH showed poorer visual gains compared to the eyes without CVH. Further investigations are needed to clarify this mechanism(s).

There are several limitations to the present study. First, the study is a retrospective design and not based on a pre-established protocol. Second, all patients were from a single institution and the number of subjects was moderately small. Further prospective studies are needed to confirm the effect of CVH to the outcome of intravitreal aflibercept treatment.

In conclusion, the present study demonstrated that AMD with CVH shows poorer visual gain by intravitreal

aflibercept treatment. AMD with CVH may have a different pathology from conventional AMD and should be distinguished accordingly.

Conflicts of interest Y. Nomura, None; Y. Yanagi, None.

References

1. Piccolino FC, Borgia L. Central serous chorioretinopathy and indocyanine green angiography. Retina. 1994;14:231–42.
2. Prunte C, Flammer J. Choroidal capillary and venous congestion in central serous chorioretinopathy. Am J Ophthalmol. 1996;121:26–34.
3. Spaide RF, Campeas L, Haas A, Yannuzzi LA, Fisher YL, Guyer DR, et al. Central serous chorioretinopathy in younger and older adults. Ophthalmology. 1996;103:2070–9.
4. Lafaut BA, Salati C, Priem H, De Laey JJ. Indocyanine green angiography is of value for the diagnosis of chronic central serous chorioretinopathy in elderly patients. Graefe's Arch Clin Exp Ophthalmol. 1998;236:513–21.
5. Tsujikawa A, Ojima Y, Yamashiro K, Ooto S, Tamura H, Nakagawa S. Punctate hyperfluorescent spots associated with central serous chorioretinopathy as seen on indocyanine green angiography. Retina. 2010;30:801–9.
6. Spaide RF, Yannuzzi LA, Slakter JS, Sorenson J, Orlach DA. Indocyanine green videoangiography of idiopathic polypoidal choroidal vasculopathy. Retina. 1995;15:100–10.
7. Sasahara M, Tsujikawa A, Musashi K, Gotoh N, Otani A, Mandai M, et al. Polypoidal choroidal vasculopathy with choroidal vascular hyperpermeability. Am J Ophthalmol. 2006;142:601–7.
8. Jirarattanasopa P, Ooto S, Nakata I, Tsujikawa A, Yamashiro K, Oishi A, et al. Choroidal thickness, vascular hyperpermeability, and complement factor H in age-related macular degeneration and polypoidal choroidal vasculopathy. Invest Ophthalmol Vis Sci. 2012;53:3663–72.
9. Koizumi H, Yamagishi T, Yamazaki T, Kinoshita S. Relationship between clinical characteristics of polypoidal choroidal vasculopathy and choroidal vascular hyperpermeability. Am J Ophthalmol. 2013;155:305–13.
10. Cho HJ, Kim HS, Jang YS, Han JI, Lew YJ, Lee TG, et al. Effects of choroidal vascular hyperpermeability on anti-vascular endothelial growth factor treatment for polypoidal choroidal vasculopathy. Am J Ophthalmol. 2013;156:1192–200.
11. Miyake M, Tsujikawa A, Yamashiro K, Ooto S, Oishi A, Tamura H, et al. Choroidal neovascularization in eyes with choroidal vascular hyperpermeability. Invest Ophthalmol Vis Sci. 2014;55:3223–30.
12. Nomura Y, Takahashi H, Tan X, Obata R, Yanagi Y. Widespread choroidal thickening and abnormal midperipheral fundus autofluorescence characterize exudative age-related macular degeneration with choroidal vascular hyperpermeability. Clin Ophthalmol. 2015;9:297–304.
13. Abedi F, Wickremasinghe S, Islam AF, Inglis KM, Guymer RH. Anti-VEGF treatment in neovascular age-related macular degeneration: a treat-and-extend protocol over 2 years. Retina. 2014;34:1531–8.
14. Gupta OP, Shienbaum G, Patel AH, Fecarotta C, Kaiser RS, Regillo CD. A treat and extend regimen using ranibizumab for neovascular age-related macular degeneration clinical and economic impact. Ophthalmology. 2010;117:2134–40.
15. Nomura Y, Takahashi H, Tan X, Fujimura S, Obata R, Yanagi Y. Effects of vitreomacular adhesion on ranibizumab treatment in Japanese patients with age-related macular degeneration. Jpn J Ophthalmol. 2014;58:443–7.
16. Chang AA, Li H, Broadhead GK, Hong T, Schlub TE, Wijeyakumar W, et al. Intravitreal aflibercept for treatment-resistant neovascular age-related macular degeneration. Ophthalmology. 2014;121:188–92.
17. Kumar N, Marsiglia M, Mrejen S, Fung AT, Slakter J, Sorenson J, et al. Visual and anatomical outcomes of intravitreal aflibercept in eyes with persistent subfoveal fluid despite previous treatments with ranibizumab in patients with neovascular age-related macular degeneration. Retina. 2013;33:1605–12.
18. Bakall B, Folk JC, Boldt HC, Sohn EH, Stone EM, Russell SR, et al. Aflibercept therapy for exudative age-related macular degeneration resistant to bevacizumab and ranibizumab. Am J Ophthalmol. 2013;156:15–22.
19. Heussen FM, Shao Q, Ouyang Y, Joussen AM, Muller B. Clinical outcomes after switching treatment from intravitreal ranibizumab to aflibercept in neovascular age-related macular degeneration. Graefe's Arch Clin Exp Ophthalmol. 2014;252:909–15.
20. Cho H, Shah CP, Weber M, Heier JS. Aflibercept for exudative AMD with persistent fluid on ranibizumab and/or bevacizumab. Br J Ophthalmol. 2013;97:1032–5.