Taiwan Journal of Ophthalmology 5 (2015) 128–131

Contents lists available at ScienceDirect

Taiwan Journal of Ophthalmology

journal homepage: www.e-tjo.com

Brief communication

Rescue effects of intravitreal aflibercept in the treatment of neovascular age-related macular degeneration

Ning-Yi Hsia [a], Chun-Ju Lin [a, b, *], Jane-Ming Lin [a, b, c], Wen-Lu Chen [a, b, c], Peng-Tai Tien [a], Yi-Hao Ho [a], Chung-Yuan Kuo [a], Yi-Yu Tsai [a, b]

[a] Department of Ophthalmology, China Medical University Hospital, Taichung, Taiwan
[b] School of Medicine, China Medical University, Taichung, Taiwan
[c] School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan

ARTICLE INFO

Article history:
Received 23 December 2014
Received in revised form
19 May 2015
Accepted 20 May 2015
Available online 15 July 2015

Keywords:
aflibercept
bevacizumab
neovascular age-related macular degeneration
posterior subtenon triamcinolone
ranibizumab

ABSTRACT

We report the rescue results of intravitreal aflibercept in patients with treatment-resistant neovascular age-related macular degeneration (AMD). We retrospectively analyzed eyes with neovascular AMD resistant to posterior subtenon triamcinolone, intravitreal ranibizumab, and/or bevacizumab treatment in a tertiary medical center in middle Taiwan between December 2013 and October 2014. We then switched treatment to 2.0 mg aflibercept. The main outcome included changes in best-corrected visual acuity and central foveal thickness measured by optical coherence tomography during monthly follow-up. There were 204 patients with neovascular AMD, and the percentage of refractory cases was 1.96% (4 of 204 cases). Our study included five eyes of four patients that were resistant to multiple treatments and subsequently switched to aflibercept. The mean age was 71.25 ± 11.09 years (range 57–83 years). Treatments were on average 6.6 times previously. Upon switching to aflibercept treatment, the average central foveal thickness on optical coherence tomography was 505.6 ± 270.86 μm (range 150–815 μm). After aflibercept treatment, the average central foveal thickness was 192 ± 51.76 μm (range 149–274 μm). All patients showed anatomic improvement, and 80% of the eyes (4 of 5 eyes) had improved best-corrected visual acuity and 20% of the eyes (1 of 5 eyes) had stable visual acuity. Patients tolerated the treatment well without serious adverse events. This short-term study showed that intravitreal aflibercept was effective and safe in treatment-resistant neovascular AMD cases. However, analysis of more cases and long-term follow-ups are mandatory.

Copyright © 2015, The Ophthalmologic Society of Taiwan. Published by Elsevier Taiwan LLC. All rights reserved.

1. Introduction

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in developed countries and accounts for 8.7% of blindness worldwide. The age-specific prevalence of late AMD in Asian populations is comparable with that reported in Caucasian populations.[1,2] Prominent advances in antiangiogenesis therapy have revolutionized the management of neovascular AMD. The current standard therapy includes posterior subtenon triamcinolone and intravitreal administration of monoclonal antibody-based therapies directed against vascular endothelial growth factor (VEGF). The two most widely used drugs are ranibizumab (Lucentis; Genentech Inc., South San Francisco, CA, USA), a recombinant VEGF-specific antibody fragment, and bevacizumab (Avastin; Genentech Inc.), a monoclonal VEGF-specific antibody. Several studies revealed that patients with AMD had favorable visual and anatomic responses to ranibizumab, bevacizumab, and/or triamcinolone.[1–14] However, there were still reports of patients who had a good initial response to ranibizumab or bevacizumab, but became resistant with decreased response over time to further intravitreal injections. Although the mechanism of this resistance is not yet clear, tachyphylaxis may be the reason.[3–6]

Aflibercept (EYLEA; Regeneron Pharmaceuticals, Inc., Tarrytown, New York, NY, USA, and Bayer Healthcare Pharmaceuticals, Berlin, Germany), a recombinant fusion protein that binds to

Conflicts of interest: None of the authors have any conflicts of interest related to this manuscript.

* Corresponding author. Department of Ophthalmology, China Medical University Hospital, 2 Yuh-Der Road, Taichung City 40447, Taiwan.
E-mail address: doctoraga@gmail.com (C.-J. Lin).

http://dx.doi.org/10.1016/j.tjo.2015.05.001
2211-5056/Copyright © 2015, The Ophthalmologic Society of Taiwan. Published by Elsevier Taiwan LLC. All rights reserved.

members of the VEGF family, was approved by the United States Food and Drug Administration for the treatment of exudative AMD in November 2011 and by the Taiwan Food and Drug Administration in June 2013. The Vascular Endothelial Growth Factor Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration (VIEW) studies proved the safety and efficacy of the treatment.[7] Aflibercept binds to all VEGF-A and VEGF-B isoforms, as well as to placenta growth factor, and has a greater binding affinity for VEGF molecules than for either ranibizumab or bevacizumab.[8,9] Cheng and Chan[10] also reported a local case of neovascular AMD, in which a rapid response to intravitreal aflibercept was observed after development of tachyphylaxis to bevacizumab and/or ranibizumab. Therefore, we conducted this retrospective study, and discovered favorable anatomic and functional outcomes in patients with previously treatment-resistant AMD in a tertiary medical center in central Taiwan.

2. Methods

We conducted a retrospective, noncomparative, consecutive, interventional case series study. We retrospectively analyzed the eyes of patients with neovascular AMD that were resistant to posterior subtenon triamcinolone, intravitreal ranibizumab, or bevacizumab treatment, and then switched to aflibercept treatment between December 2013 and October 2014. Informed oral and written consents were obtained from all patients. The inclusion criteria are as follows: (1) eyes with the diagnosis of neovascular AMD [the presentation of drusen and choroidal neovascularization, confirmed by fluorescein angiography and optical coherence tomography (OCT), and having passed the peer review of Taiwan National Health Insurance for ranibizumab]; (2) having previously been injected with posterior subtenon triamcinolone, intravitreal bevacizumab, and/or ranibizumab, and followed by increasing or persistent subretinal fluid or retinal edema on OCT; and (3) the fluid having to be refractory to at least three monthly injections prior to the first aflibercept injection. The criteria for treatment with aflibercept were the same as the retreatment criteria for bevacizumab or ranibizumab regarding the presence of intraretinal or subretinal fluid. We recorded general data, including data on patient age, race, sex, laterality, medical history, BCVA, intraocular pressure, and results of external ocular and slit-lamp examinations. Each patient had a thorough bilateral fundus examination with indirect ophthalmoscopy, fundus photographs, fluorescein angiography, and spectral-domain OCT (Cirrus HD-OCT; Carl Zeiss Meditec, Inc., Dublin, CA, USA) scans. All patients received at least one intravitreal aflibercept injection (2.0 mg/0.05 mL) under topical anesthesia as rescue treatment. Prior to the intravitreal injection, the pupils were dilated with 1% tropicamide (Mydriacyl; Alcon Co., Belgium, USA), and the topical antibiotic levofloxacin (Cravit; Santen Pharmaceutical Co., Osaka, Japan) was applied before the intravitreal injections. Topical anesthesia with 0.5% proparacain hydrochloride (Alcaine; Alcon Pharmaceuticals, Belgium) was given at 2-minute intervals prior to the surgery. Each eye was prepared in a sterile manner using 5% povidone/iodine. Aflibercept (2 mg/0.05 mL) was injected intravitreally via the pars plana (3.5 mm away from the limbus). Levofloxacin eyedrops were given four times daily for 1 week. Information on the methods of initial management and number of subsequent treatments was collected. The final anatomic outcome, final BCVA, and complications were reviewed, and changes in vision and retinal status were recorded. The main outcome measures included changes in BCVA and central foveal thickness (CFT), measured by spectral-domain OCT scan during monthly follow-up. All cases were followed up for more than 2 months. We analyzed data including patient age, fundus findings and follow-up period.

3. Results

In our hospital, 204 patients with neovascular AMD were treated between December 2013 and October 2014. Among them, only five eyes of four cases were refractory to posterior subtenon triamcinolone, intravitreal bevacizumab, and/or ranibizumab treatment. The percentage of the refractory cases is 1.96%. Our study analyzed a total of five eyes from four patients resistant to multiple treatments with posterior subtenon triamcinolone, intravitreal bevacizumab, and/or ranibizumab, who were subsequently switched to a minimum of one injection of aflibercept (Table 1). The patients included five men and one woman. The mean age was 71.25 ± 11.09 years (range 57–83 years). The percentage of our refractory AMD cases is 1.96% (4 of 204 cases). They were all responsive to aflibercept for rescue therapy (100%). The patients had received an average of 6.6 (range 3–10) previous posterior subtenon triamcinolone, intravitreal ranibizumab, and/or bevacizumab injections. Upon switching to aflibercept treatment, the average CFT on OCT was 505.6 ± 270.86 μm (range 150–815 μm). After switching to aflibercept, the patients were treated and followed up monthly. Each eye received an average of 3.8 aflibercept injections (range 1–7). We followed up with these patients for 2–11 months. After intravitreal aflibercept treatment, the average CFT measured by OCT was 192 ± 51.76 μm (range 149–274 μm). Compared with the visit before the first injection of aflibercept, there was a significant average decrease (by 313.6 μm) in CFT. All eyes showed anatomic improvement after switching to aflibercept treatment. The baseline and changes in OCT scans for all five eyes before and after intravitreal aflibercept treatment are illustrated in Fig. 1. The results showed that 80% of the eyes (4 of 5 eyes) had improved BCVA, and 20% of the eyes (1 of 5 eyes) had stabilization of visual acuity. Patients tolerated the treatment well without serious adverse events, such as endophthalmitis, noninfectious endophthalmitis, vitreous hemorrhage, retinal tear, retinal detachment, or sustained elevations in pressure.

4. Discussion

This retrospective interventional case series in a tertiary medical center in central Taiwan studied the treatment response of eyes with neovascular AMD that developed resistance to treatments with posterior subtenon triamcinolone, intravitreal bevacizumab, and/or ranibizumab, and were subsequently switched to a minimum of one injection of aflibercept. We administered triamcinolone by posterior subtenon instead of intravitreal injection due to the concerns of the complications of cataract and increased intraocular pressure. In this study, the refractory cases were a minority. Of a total of 204 cases, only four were refractory to posterior subtenon triamcinolone, intravitreal bevacizumab, and/or ranibizumab. The percentage of the refractory cases is 1.96%, and there were no related studies that mentioned about this ratio.

As shown by several current reports,[8–12] our study demonstrated anatomic and visual improvement after switching to aflibercept in cases with persistent macular edema despite prior anti-VEGF treatments. The protocol of intravitreal aflibercept treatment in the recent studies was mostly three monthly loading doses followed by bimonthly injections. As our patients had to pay ~40,000 NT dollars for one aflibercept injection at that time, we treated the four of five eyes with three monthly loading doses followed by prn injections when recurrent macular edema occurred.

Our study revealed two main explanations for the improvement: the pharmacodynamics of aflibercept and the possible tachyphylaxis to prior treatment with ranibizumab or bevacizumab. First, aflibercept binds to all isoforms of VEGF-A, VEGF-B, and PlGF, with a significantly higher binding affinity for VEGF than

Table 1
Summary of basic demographics, CFT, and best-corrected visual acuity of five eyes of four patients with rescue aflibercept treatment of neovascular age-related macular degeneration.

Case	Age/sex	Eye	Pre-Tx BCVA	Pre-Tx CFT (μm)	PSTK	IVB	IVR	Pre-IVA BCVA	Pre-IVA CFT (μm)	Interval (mo)[a]	IVA	Final BCVA	Final CFT (μm)	Follow-up (mo)
1	69/F	OD (1)	0.01	476	3	3	2	0.01	670	1	7	0.1	274	11
		OS (2)	0.2	217	0	0	5	0.05	150	1	3	0.6	146	11
2	83/M	OD (3)	CF at 15 cm	664	1	0	6	CF at 10 cm	583	1	1	0.05	194	2
3	76/M	OD (4)	0.2	710	0	4	6	0.1	815	13	3	0.2	149	6
4	57/M	OS (5)	0.01	313	0	0	3	0.01	310	1	5	0.09	197	3

BCVA = best-corrected visual acuity; CF = counting fingers; CFT = central foveal thickness; F = female; HM = hand movement; IVA = intravitreal aflibercept; IVB = intravitreal bevacizumab; IVR = intravitreal ranibizumab; M = male; No. = number; OD = right eye; OS = left eye; PSTK = posterior subtenon kenacort; Tx = treatment.
[a] Interval represents the time between the last treatment of PSTK, IVB, or IVR and before the IVA and follow up the time between the last IVA treatment and the final outpatient visit.

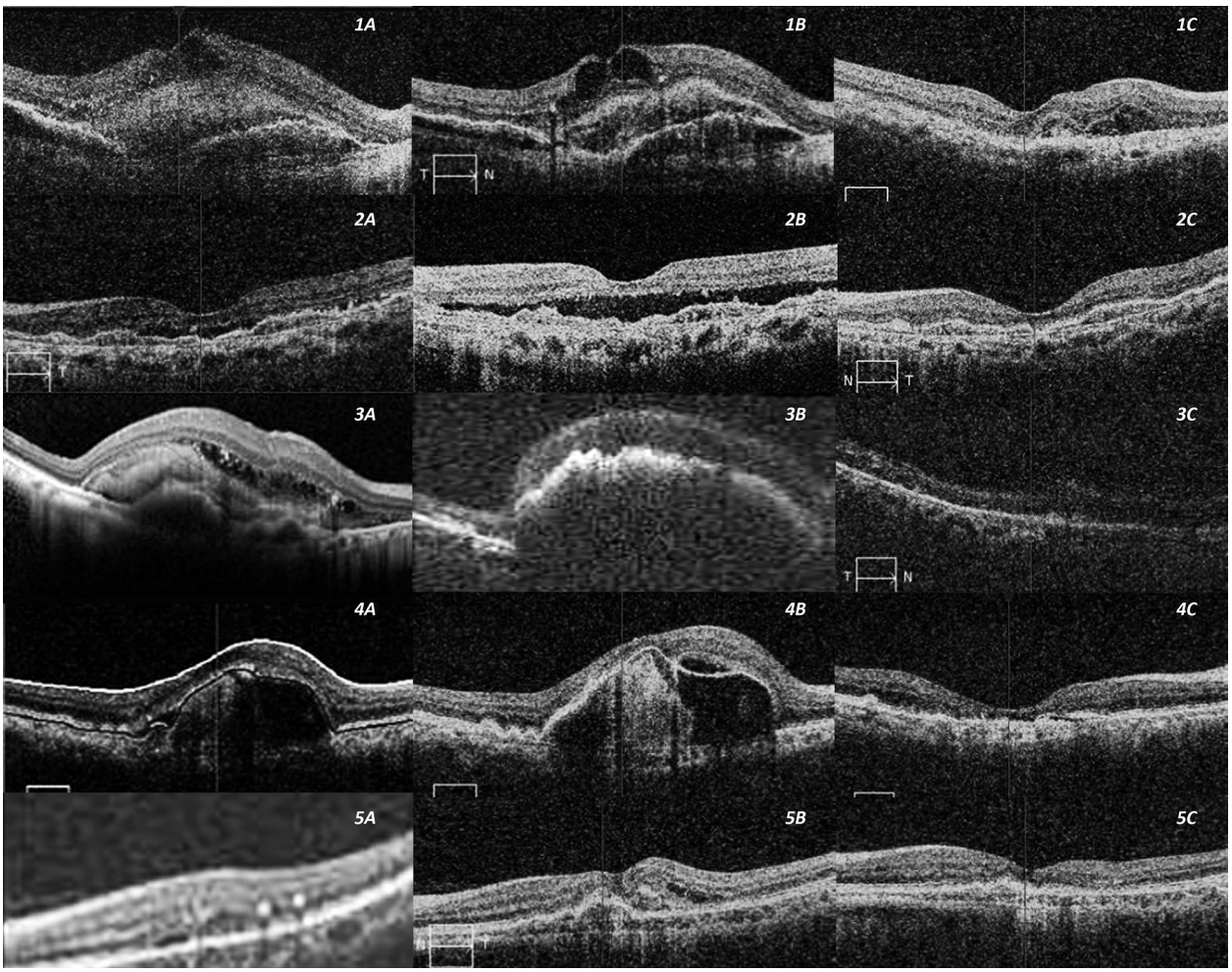

Fig. 1. OCT scans in five eyes: (A) baseline OCT scans; (B) OCT scans before intravitreal aflibercept treatment; and (C) OCT scans after intravitreal aflibercept treatment. OCT = optical coherence tomography.

for both ranibizumab and bevacizumab. In addition, mathematical models predict that a single intravitreal injection of aflibercept 2.0 mg lasts between 48 days and 83 days (compared with 30 days for ranibizumab). Aflibercept thus may neutralize VEGF more effectively.[8] Second, tachyphylaxis, an acute decrease in theresponse to a drug after its initial dose or a series of small doses administered, might be another possible mechanism for the observed effect after switching to aflibercept.[3–6]

In our study, all eyes showed anatomic improvement after switching to aflibercept treatment. Compared with the visit before the first injection of aflibercept, there was a significant average decrease in CFT by 313.6 μm. The study showed that 80% of eyes had improved BCVA and 20% had stabilized visual acuity after switching to aflibercept. The disproportion between anatomic improvement and functional outcome could be attributed to chronic photoreceptor degeneration and loss of photoreceptors, which might have limited the visual potential.[9] During at least 2 months of treatment, a generally favorable safety profile was observed for intravitreal aflibercept, and currently no eyes developed significant ocular safety events such as endophthalmitis, noninfectious endophthalmitis, vitreous hemorrhage, retinal tear, retinal detachment, or sustained elevations in intraocular pressure.

Limitations of our study include the small sample size, uncontrolled retrospective design of the study, the use of Snellen visual acuity and nonstandard treatment protocols, and a lack of consistent performance of fluorescein and indocyanine angiography prior to switching to aflibercept. Nevertheless, this short-term study in a tertiary medical center in central Taiwan showed that intravitreal aflibercept treatment was effective and safe in eyes of neovascular AMD that were resistant to triamcinolone, ranibizumab, and/or bevacizumab. Treatment with aflibercept can be considered an alternative rescue treatment in eyes with neovascular AMD that do not respond to other anti-VEGF treatments. Further follow-up is required to determine the long-term efficacy of aflibercept treatment in these treatment-resistant neovascular lesions.

Funding/support

No financial support was received for this submission.

References

1. Wong WL, Su X, Li X, et al. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health*. 2014;2:e106–e116.
2. Kawasaki R, Yasuda M, Song SJ, et al. The prevalence of age-related macular degeneration in Asians: a systematic review and meta-analysis. *Ophthalmology*. 2010;117:921–927.
3. Binder S. Loss of reactivity in intravitreal anti-VEGF therapy: tachyphylaxis or tolerance? *Br J Ophthalmol*. 2012;96:1–2.
4. Eghøj MS, Sørensen TL. Tachyphylaxis during treatment of exudative age-related macular degeneration with ranibizumab. *Br J Ophthalmol*. 2012;96:21–23.
5. Forooghian F, Cukras C, Meyerle CB, Chew EY, Wong WT. Tachyphylaxis after intravitreal bevacizumab for exudative age-related macular degeneration. *Retina*. 2009;29:723–731.
6. Schaal S, Kaplan HJ, Tezel TH. Is there tachyphylaxis to intravitreal antivascular endothelial growth factor pharmacotherapy in age-related macular degeneration? *Ophthalmology*. 2008;115:2199–2205.
7. Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. *Ophthalmology*. 2014;121:193–201.
8. Kumar N, Marsiglia M, Mrejen S, 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;33:1605–1612.
9. Cho H, Shah CP, Weber M, Heier JS. Aflibercept for exudative AMD with persistent fluid on ranibizumab and/or bevacizumab. *Br J Ophthalmol*. 2013;97:1032–1035.
10. Cheng CK, Chan TY. Rapid response to intravitreal aflibercept in neovascular age-related macular degeneration after development of tachyphylaxis to bevacizumab and ranibizumab. *Taiwan J Ophthalmol*. 2014;4:40–44.
11. Bakall B, Folk JC, Boldt HC, et al. Aflibercept therapy for exudative age-related macular degeneration resistant to bevacizumab and ranibizumab. *Am J Ophthalmol*. 2013;156:15–22.
12. Chang AA, Li H, Broadhead GK, et al. Intravitreal aflibercept for treatment-resistant neovascular age-related macular degeneration. *Ophthalmology*. 2014;121:188–192.
13. Katome T, Naito T, Nagasawa T, Shiota H. Efficacy of combined photodynamic therapy and sub-Tenon's capsule injection of triamcinolone acetonide for age-related macular degeneration. *J Med Investig*. 2009;56:116–119.
14. Hatta Y, Ishikawa K, Nishihara H, Ozawa S, Ito Y, Terasaki H. Effect of photodynamic therapy alone or combined with posterior subtenon triamcinolone acetonide or intravitreal bevacizumab on choroidal hypofluorescence by indocyanine green angiography. *Retina*. 2010;30:495–502.