

Brief report

Intravitreal injection of ziv-aflibercept in the treatment of choroidal and retinal vascular diseases

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Abstract

Purpose: To investigate the short-term outcomes after intravitreal injection of ziv-aflibercept in the treatment of choroidal and retinal vascular diseases.

Methods: Thirty-four eyes of 29 patients with age-related macular degeneration (AMD), diabetic retinopathy, and retinal vein occlusion (RVO) received a single dose intravitreal injection of 0.05 ml ziv-aflibercept (1.25 mg). Visual acuity, spectral domain optical coherence tomography (SD-OCT) activity, and possible side effects were assessed before and at 1 week and 1 month after the intervention.

Results: At 1 month after treatment, mean central macular thickness (CMT) significantly decreased from 531.09 μm to 339.5 μm ($P < 0.001$), and no signs of side effects were observed in any subject. All patients responded to treatment in terms of reduction in CMT. The improvement in visual acuity was statistically non-significant.

Conclusion: Our findings suggest that a single dose intravitreal injection of ziv-aflibercept may have acceptable relative safety and efficacy in the treatment of patients with intraocular vascular disease.

The trial was registered in the Iranian Registry of Clinical Trials (IRCT2015081723651N1).

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Keywords: Ziv-aflibercept; Age-related macular degeneration; Diabetic retinopathy; Anti-vascular endothelial growth factor; Retinal vein occlusion

Introduction

Nowadays, many anti-vascular endothelial growth factor (anti-VEGF) agents are used as the first line in the treatment of intraocular vascular diseases.¹ Until recently, the choice of drugs was limited to bevacizumab (Avastin) and ranibizumab

(Lucentis), the former being more popular on account of its lower cost.^{2,3} Aflibercept (Eylea) is a new addition to the group, which may offer better efficiency and a longer effect.⁴

Ziv-aflibercept, an anti-VEGF anticancer drug, has the same structure and exerts the same function as aflibercept, but the latter undergoes a different purification process and contains different buffer solutions that are less irritating when injected intravitreally and has a lower osmolarity.⁵ However, from a commercial perspective, ziv-aflibercept is a much cheaper recombinant fusion protein. Mansour et al⁴ have used evidence from in vitro and in vivo studies^{6,7} to address certain concerns in relation to safety in its intraocular use such as osmolality differences and the risk of inducing changes to

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retinal morphology. Regarding the little available information on the safety and efficacy of ziv-aflibercept in patients with intraocular vascular diseases, we performed this study.

Methods

In this prospective interventional case series, patients with age-related macular degeneration (AMD), diabetic macular edema (DME), or retinal vein occlusion (RVO) who had no sign of eye infection and no history of myocardial infarction or cerebrovascular accident were included in this study.

The Ethics Committee of Tehran University of Medical Sciences approved this study; it adhered to the tenets of the Declaration of Helsinki, and a written informed consent was obtained from all participants.

First, 0.05 ml of aqueous humor was extracted through the limbus area with a 29 gauge needle. Then 0.05 ml (1.25 mg)

of Ziv-aflibercept (Zaltrap, Sanofi and Regeneron Pharmaceuticals, Inc.) was injected into the intravitreal space through the pars plana using a 31 gauge needle.

In addition to intraocular pressure (IOP) monitoring and an ophthalmic exam, the patients were observed for signs of any progression in lens opacity, intraocular inflammation, and change in retinal structure using the spectral domain optical coherence tomography (SD-OCT) before, 1 week, and 1 month after the injections. In this study, “efficacy” referred to reduction in central macular thickness (CMT). Statistical analysis was performed using paired-test or McNemar’s test.

Results

Thirty-four eyes of 29 consecutive patients with a mean age 66.6 ± 11.0 years were enrolled. Five diabetic patients received ziv-aflibercept injections bilaterally. The diagnosis

Table 1
Patient demographics and baseline characteristics.

Characteristic	AMD	RVO	DME
N (full set analysis):	8 eyes in 8 patients	6 eyes in 6 patients	20 eyes in 15 patients
Age (Mean ± SD)	77.4 ± 3.1	66.0 ± 11.7	63.3 ± 10.6
Gender: n (%)			
Male	4 (50.0%)	3 (50.0%)	7 (46.7%)
Female	4 (50.0%)	3 (50.0%)	8 (53.3%)
Prior therapies, n (%)			
Laser therapy: n (%)	1 (12.5%)	1 (16.7%)	13 (65.0%)
Avastin injection: n (%)	6 (75.0%)	1 (16.7%)	16 (80.0%)
Average number of treatments prior to study entry	Mean ± SD: 7.17 ± 3.3 Range: 4–13 injections	6 times	Mean ± SD: 3.7 ± 2.6 Range: 1–12 injections
Time since last injection prior to study enrollment	Median (IQR): 2.0 months (2.25 months) Range: 1–4 months	4 months ago	Median (IQR): 4.5 months (7 months) Range: 1–42 months

N: number, AMD: Age-related macular degeneration, DME: Diabetic macular edema RVO: Retinal vein occlusion, SD: Standard deviation, IQR: Inter quartile range.

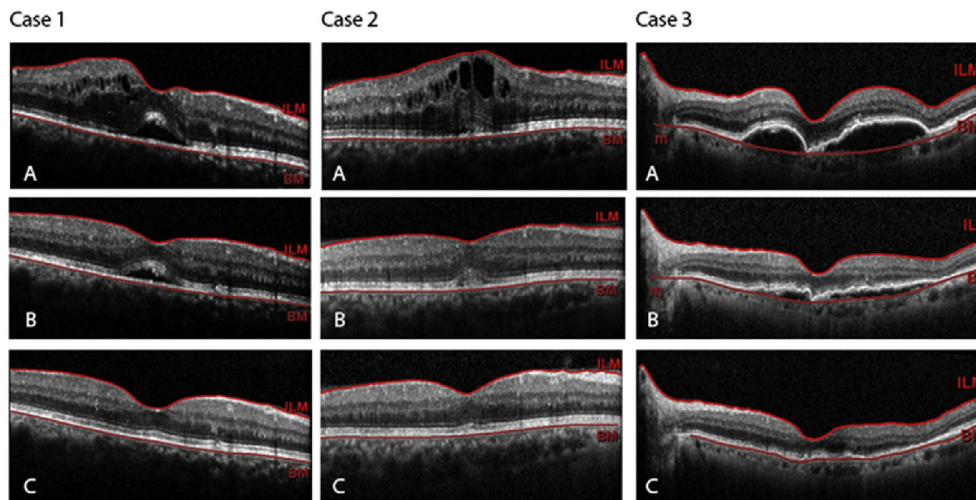


Fig. 1. Spectral domain optical coherence tomography (SD-OCT) scans of 3 eyes (Case 1: DME, Case 2: RVO and Case 3: AMD), which underwent intravitreal ziv-aflibercept, at baseline (A), 1 week (B) and at 1-month (C) follow-up, showing disappearance of subretinal fluid (Case 1), intraretinal fluid (Case 1 and Case 2), CME (Case 2), and PED (Case 3). DME: Diabetic macular edema; RVO: Retinal vein occlusion; AMD: Age-related macular degeneration; CME: Cystoid Macular Edema; PED: Pigment epithelial detachment.

Table 2
Efficacy and safety of ziv-aflibercept injection in eyes with age-related macular degeneration (AMD).

Diagnosis	Variables	Baseline	1 week after injection	1 month after injection	P Value
AMD (n = 8)	CMT (Mean (SD))	511.1 (220.1)	355.9 (162.5)	342.8 (162.8)	0.02
	PED (Mean (SD)), N = 5	269.8 (84.3)	199.4 (75.1)	184.2 (82.2)	0.10
	CDVA in logMAR (Mean (SD))	0.83 (0.50)	0.74 (0.39)	0.73 (0.34)	0.12
	IOP (Mean (SD))	14.4 (2.0)	14.1 (2.2)	15.0 (1.4)	0.28
	CME: n (%)	3 (37.5%)	1 (12.5%)	0 (0.0%)	–
	Sub retinal fluid: n (%)	5 (62.5%)	2 (25.0%)	1 (12.5%)	–
	Intra retinal fluid: n (%)	5 (62.5%)	4 (50.0%)	1 (12.5%)	–
RVO (n = 6)	CMT (Mean (SD))	607.0 (163.5)	325.5 (99.3)	272.3 (60.6)	0.007
	CDVA in logMAR (Mean (SD))	0.86 (0.65)	0.83 (0.68)	0.80 (0.63)	0.76
	IOP (Mean (SD))	14.7 (2.0)	14.6 (1.5)	14.7 (1.9)	1.00
	CME: n (%)	5 (83.3%)	1 (16.6%)	0 (0.0%)	–
	Sub retinal fluid: n (%)	4 (66.7%)	4 (66.7%)	1 (16.6%)	–
	Intra retinal fluid: n (%)	6 (100.0%)	6 (100.0%)	5 (83.3%)	–
DME (n = 20)	CMT (Mean (SD))	521.4 (174.2)	386.5 (154.4)	358.6 (127.6)	<0.001
	CDVA in logMAR (Mean (SD))	0.68 (0.51)	0.62 (0.47)	0.60 (0.49)	0.26
	IOP (Mean (SD))	15.3 (1.4)	14.8 (1.3)	14.7 (1.7)	0.32
	CME: n (%)	13 (65.0%)	7 (35.0%)	5 (25.0%)	–
	Sub retinal fluid: n (%)	10 (50.0%)	8 (40.0%)	5 (25.0%)	–
	Intra retinal fluid: n (%)	20 (100.0%)	20 (100.0%)	18 (90.0%)	–

AMD: Age-related macular degeneration, DME: Diabetic macular edema RVO: Retinal vein occlusion, CMT: Central macular thickness, PED: Pigment epithelial detachment, CDVA: Corrected distance visual acuity, IOP: Intraocular Pressure, CME: cystoid macular edema, SD: Standard deviation.

was DME in 20 eyes (58.8%), AMD in 8 (23.5%), and RVO in 6 eyes (17.7%). The baseline characteristics of 3 diagnostic groups are presented in Table 1.

At 1 month after the intervention, the overall mean corrected distance visual acuity (CDVA) had improved compared to baseline, although the change was not statistically significant (0.75 ± 0.51 vs. 0.68 ± 0.48 logMAR; $P = 0.09$). Mean IOP was unchanged (14.88 ± 1.65 vs. 14.76 ± 1.54 mm Hg, $P = 0.72$). Mean CMT improved from 531.09 ± 185.7 μ m (range, 230–948 μ m) to 339.5 ± 129.1 μ m (range, 153–695 μ m) ($P < 0.001$). The rate of cystoid macular edema (CME) decreased from 61.8% (n = 21) to 14.7% (n = 5) ($P < 0.001$). Subretinal fluid was observed in 19 cases (55.9%) at baseline which reduced to 6 cases (17.6%). CMT decreased in all cases, but visual acuity did not improve in 8 patients (Fig. 1).

No signs of inflammation or new cataract formation were observed, and none of the patients developed infection, retinal detachment, or any other post-injection complication. Table 2 presents these results in the 3 groups of patients with DME, AMD, and RVO.

Discussion

At 1 month after injection, mean CMT and the rate of CME had significantly declined compared to baseline, which is in accordance with previous case studies.^{4,8–14} Avastin is currently the most cost-effective therapy for the management of choroidal and retinal vascular diseases.⁴ In this study, although all ziv-aflibercept injections were prepared from a multi-dose vial, no case of intraocular infection was observed. The possibility to use a multi-dose vial for several patients, in addition to administering an 8-cycle rather than a 12-cycle regimen in the first year contribute to better cost-effectiveness of ziv-aflibercept compared to Avastin.⁴

Additionally, at 1 month after injection, there was no case of serious side effects. Following in vitro and in vivo studies which established that the intraocular application of the ziv-aflibercept was devoid of toxic effects on the retinal pigment epithelium cells,^{6,7,14,15} the first report concerning the intraocular use of ziv-aflibercept in humans was published by Rafael et al in 2015.¹⁴ Their study was conducted on a patient with exudative AMD receiving intravitreal injection of ziv-aflibercept (0.07 ml, 25 mg/ml, total 1.75 mg) and no side effects or ocular toxicity was observed after a one-month follow-up. The latter studies also noted the relative safety of ziv-aflibercept after intravitreal administration for intraocular vascular disease.^{4,8,13,16} However, complications may occur with frequent use and higher doses (up to 2 mg) of the drug.

The limitations of this study include the small sample size, the diverse diagnoses, and lack of a control group. Also, the possible adverse effect of the drug on electrophysiologic testing was not evaluated. Studies with longer follow-up of cases receiving multiple doses are needed to assess the risk of intraocular inflammation and other side effects.

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