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Early shift from ranibizumab to aflibercept for resistant pigment epitelial detachment in classical choroidal neovascularization

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阿柏西普治疗雷珠单抗效果不佳的 CNV 伴难治性色素上皮脱离的疗效

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摘要

目的:评估雷珠单抗反应欠佳患者治疗早期转为阿柏西普治疗疗效。

方法:该研究包括 38 例湿性年龄相关性黄斑变性(W-AMD)患者。18 例反应欠佳患者改用玻璃体内阿柏西普(IVA)每月 3 次疗法,其余 20 例反应欠佳患者持续进行玻璃体内雷珠单抗(IVR)治疗,每月增加 3 次使用。所有改变均行荧光素血管造影术(FA)和光学相干断层扫描成像术(OCT)评估。

结果:患者术前平均视力(VA)和黄斑中心厚度(CMT)分别为 0.84±0.47 logMAR 和 360±84 μm。经过 6 次 IVR 或 3 次 IVR 联合 3 次 IVA 治疗 1mo 后,两组患者视力分别为 1.1±0.14 (P=0.11) logMAR 和 0.48±0.37 (P=0.019) logMAR,黄斑中心厚度分别为 300±79 μm (P=0.002) 和 271±51 μm (P=0.002)。

结论:对于雷珠单抗治疗反应欠佳患者,减少重复性治疗早期转为使用阿柏西普疗法对于视力康复是更好的选择。

关键词:阿柏西普;反应欠佳;难治性;脉络膜新生血管;早期

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Abstract

• AIM: To evaluate the therapeutic effect of aflibercept in patients with suboptimal response to ranibizumab therapy in the early period.

• METHOD: Thirty-eight patients with wet type age related macular degeneration (W-AMD) were involved in this study. Eighteen patients with suboptimal response were shifted to 3 doses monthly intravitreal aflibercept therapy (IVA) and left 20 patients with suboptimal response went on 3 more monthly intravitreal ranibizumab (IVR). All changes were evaluated with fluorescein anigography (FA) and optical coherence tomography (OCT).

• RESULTS: Preoperative mean visual acuity (VA) and central macular thickness (CMT) of patients were 0.84±0.47 logMAR and 360±84 μm, respectively. One month after last IVR and IVA treatments, VA of patients were 1.1±0.34 (P=0.11) logMAR and 0.48±0.37 (P=0.019) logMAR and CMTs were 300±79 μm (P=0.002) and 271±51 μm (P=0.002), respectively.

• CONCLUSION: To eliminate repeated therapy for patients with suboptimal response to ranibizumab therapy, aflibercept might be a good alternative for early visual rehabilitation.

• KEYWORDS: aflibercept; suboptimal response; resistance; choroidal neovascularization; early
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INTRODUCTION

Age related macular degeneration (AMD) is the leading cause of irreversible vision loss in developed countries. So far the most preferred drugs for the treatment of AMD has been ranibizumab (Lucentis; Genentech, South San Francisco, California, USA), bevacizumab and aflibercept (Eylea; Regeneron, Tarrytown, New York, USA). Ranibiziumab is a humanized monoclonal antibody fragment with proven efficacy in the treatment of AMD[1-2]. Vascular endothelial growth factor-A (VEGF-A) is the major protein of pathological angiogenesis and vascular problems in wet AMD. Along with VEGF-A, researchers claim that placental growth factor (PlGF) is augmenting the vascular pathology[3-4]. Ranibizumab is an antigen-binding fragment (Fab) reproduced from bevacizumab, and thus has greater binding ability for VEGF-A relative to that of the parental bevacizumab Fab molecule (Fab-12)[5]. Aflibercept is a

novel vascular endothelial growth factor (VEGF) inhibitor, binding all isoforms of the VEGF-A and PlGF. Aflibercept has got more affinity to VEGF isomers than both bevacizumab and ranibizumab and it has been proved *in vitro* conditions[6]. The aim of this study is to evaluate the secondary therapeutic effect of aflibercept in patients with suboptimal response to ranibizumab therapy for AMD in the early period (after monthly three injecitons).

SUBJECTS AND METHODS

Thirty-eight patients with wet type age related macular degeneration (W-AMD) from Namik Kemal University Department of Ophthalmology between August 2015-March 2016 were involved in this retrospective study. All consequences of procedures were expressed to the patients and informed consent was taken. All the procedure was followed in accordance with the tenets of Declaration of Helsinki. Mean follow up time was 8mo. All of the patients were treated with 3 doses of 0.5 mg intravitreal ranibizumab (IVR) monthly and those who gave suboptimal response were shifted to 3 doses of monthly aflibercept. Suboptimal response was accepted as macular thickness over 300 μm and/or early treatment for diabetic retinopathy study (ETDRS) chart visual gain 3 letters or less at the end of the three doses IVR. Eighteen patients with suboptimal responsive were shifted to 3 doses monthly intravitreal aflibercept (IVA) 2 mg therapy and left 20 patients went on 3 more monthly 0.5 mg IVR therapy. Patients were called monthly and at all visits subjects underwent best corrected ETDRS visual acuity (VA) and comprehensive ophthalmic examination including applanation tonometry, slit-lamp evaluation and dilated binocular indirect ophthalmoscopy. Fluorescein angiography (FA) was performed at enrollment, month 4 and month 8. Optical coherence tomography (OCT) (Cirrus HD-OCT, Carl Zeiss Ophthalmic System Inc, Zeiss-Humphrey, Dublin, California, USA) was performed at each visit.

Statistical Analysis Independent-sample *t*-test, paired sample *t*-test, Mann Whitney *U* and Wilcoxon test were used to measure the differerences between groups. *P*-values lower than 0.05 was accepted as statistically significant.

RESULTS

The mean patient age was 69.4±8.5 (50-85) for intravitreal ranibizumab (IVR) group and 71.7±8.5 (54-84) for intravitreal aflibercept (IVA) group. Twelve female and twenty six male patients were involveld in the study. Only the patients who completed their monthly visits were included and mean follow up time was 8mo for both groups. Basic characteristics are shown in Table 1.

Visual Outcomes Initially, mean early treatment for diabetic retinopathy study (ETDRS) chart visual acuity (VA) was 0.84±0.47 logMAR. After receiving 3 doses of intravitreal ranibizumab patients gained 3 or less letters. After 3 doses of IVR, 18 eyes were shifted to IVA and 20 eyes went on getting 3 more IVR treatment. Right after the first doses of injections VA of patients increased 5 letters in 5 eyes of IVR

Table 1 Patient characteristics

Parameters	IVR group	IVA group
Sex (*n*)		
M	14	12
F	6	6
Injections before (*n*)	none	none
Total injections (*n*)	6 (IVR)	6 (3 IVR+3 IVA)
Mena follow up (mo)	8	8
Age(a)		
Mean ± SD	69.4±8.5	71.7±8.5
Range	50-85	54-84

CMT: Central macular thickness; IVR: Intravitreal ranibizumab; IVA: Intravitreal aflibercept.

Table 2 Visual acuity (logMAR) for 38 eyes with classical choroidal neovascularization, which have suboptimal response to 3 doses of IVR treatment, before and after switching to IVA and unswitched IVR groups

Eye (*n*)	VA at shift to IVA (after 3X IVR)	VA(after 3X IVA)	VA before IVR (before any injections)	VA(after 6X IVR)
1	0.20	0.10	0.50	0.70
2	0.20	0.0	1.60	1.60
3	1.60	0.90	1.30	1.30
4	1.30	1.00	0.50	1.00
5	1.30	1.30	1.30	1.30
6	0.50	0.35	1.30	1.30
7	0.30	0.35	0.70	0.50
8	0.70	0.40	1.40	1.30
9	0.40	0.20	0.70	1.60
10	0.30	0.40	1.30	1.30
11	0.30	0.40	0.50	0.70
12	1.30	1.30	1.60	1.60
13	0.50	0.35	1.30	1.30
14	0.30	0.35	0.50	1.00
15	0.70	0.40	1.30	1.30
16	0.40	0.20	1.30	1.30
17	0.30	0.40	0.70	0.50
18	0.30	0.40	1.40	1.30
19			0.70	1.60
20			1.30	1.30

VA: Visual acuity; IVA: Intravitreal aflibercept; IVR: Intravitreal ranibizumab.

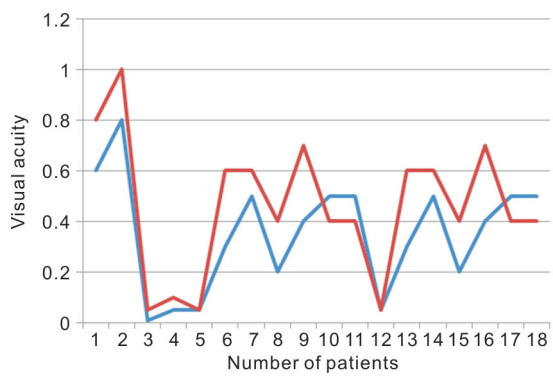

Figure 1 Visual acuity increment after 3X aflibercept for patients with suboptimal response to 3 monthly ranibizumab injections Blue line shows the visual acuity of aflibercept group before injections(After 3 monthly consecutive ranibizumab injections for naive patients); Red line shows the visual acuity gain in aflibercept group after 3 consecutive aflibercept injections for patients with suboptimal response to 3X ranibizumab injections.

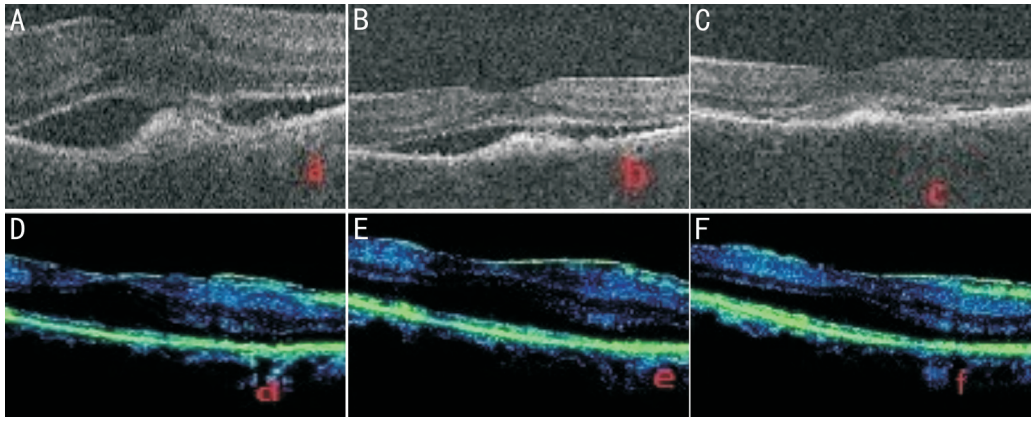

Figure 2 Preoperative and postoperative OCT findings of aflibercept and ranibizumab groups A: Before shift to intravitreal aflibercept (after 3X ranibizumab injections); B: After first aflibercept injection (first month control); C: After 3 aflibercept injection (last control); D: Before injections; E: After 3 ranibizumab injections (3mo control); F: After 6 ranibizumab injections (last control).

Table 3 Treatment results of IVR and IVA groups before and after injections

Parameters	Visual acuity (logMar)					OCT				
	IVR group		IVA group		*P*	IVR group		IVA group		*P*
	mean±s.d	Median	mean±s.d	Median		mean±s.d	Median	mean±s.d	Median	
Before	1.1±0.4	1.3	0.6±0.5	0.4	0.001[a]	372.9±53.7	364.0	345.5±109.2	318.0	0.061[a]
After	1.2±0.3	1.3	0.5±0.4	0.4	0.000[a]	300.0±79.3	288.0	270.9±51.2	272.5	0.074[a]
Difference	0.1±0.3	0.0	−0.1±0.2	−0.2	0.099[a]	−72.9±83.4	−67.0	−74.6±101.3	−52.0	0.725[a]
In-group *P*	0.111[b]		0.019[b]			0.002[b]		0.002[b]		

[a]Mann-Whitney *u*- test; [b]Wilcoxon test; OCT: Optical coherens tomography (Central macular thickness); logMAR: Logarithm of the minimal angle of resolution; IVA: Intravitreal aflibercept; IVR: Intravitreal ranibizumab.

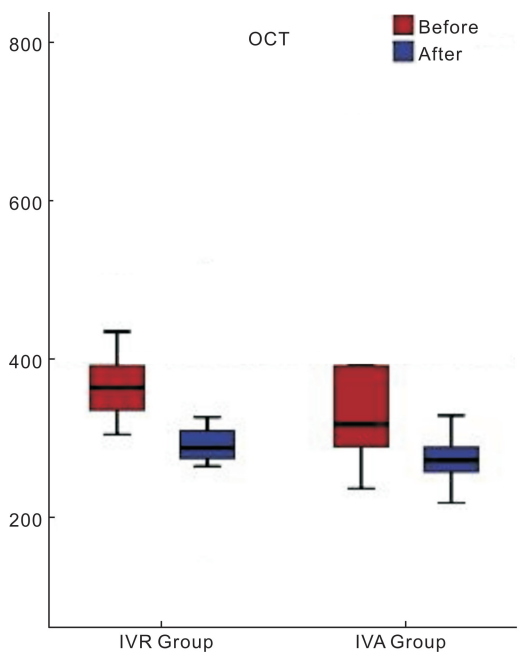

Figure 3 Macular thickness changes in both groups IVR group: Before and after 6X intravitreal ranibizumab injections; IVA group: Before and after 3X aflibercept injections for suboptimal responsers to 3X IVR.

group. After 6 doses of IVR treatment VA gains of patients were: 4 eyes (20%) lost ≥3 letters or more, 8 eyes (40%) remained stable and 8 eyes (40%) gained ≥3 letters or more. After 3 doses of IVA, VAs of patients were like: 5 eyes (27%) lost 3 ETDRS letters or less, 11 eyes (61%) improved ≥3 letters or more and 2 eyes (11%) remained same. No patient lost 15 letters or more. Final VA of IVR and IVA groups were 1.1±0.34 logMAR (*P*=0.11) and 0.48±0.37 logMAR (*P*=0.009), respectively. Table 2 shows VA of groups and figure 1 shows VA gain in IVA group.

Anomical Outcomes Initially mean central macular thickness (CMT) was 372.9±53.7 μm (range 237-736 μm). Before shift to aflibercept mean CMT was 345.5±109 μm (range 243-697μm). After three doses of IVR treatment 14 patients had subfoveal pigment epithelial detachment and 24 patients had subretinal fluid. Eighteen patients were switched to IVA and 20 patients kept on IVR therapy. After switching to IVA treatment, even after the first dose, 12 (66%) of 18 patients had near complete resolution (Figure 2).

Final CMT of IVR and IVA groups were 300±79μm (*P*=0.002) and 271±51μm (*P*=0.002), respectively. Table 3 shows VA and CMT changes of patients and Figure 3 shows CMT changes in IVA group.

Both groups had significant fluid resolution. Two-third of fluid resolution in IVA group was right after the first dose of injection while IVR group had a slower improvement.

Systemic Complications IVR group had no systemic complications but in IVA group one patient had asthma attack twice at the night of the injections.

DISCUSSION

In this comparative restrospective study, we evaluated the visual and anatomical treatment response of patients with

refractory wet-acquired macular degeneration (W-AMD) after switching to aflibercept therapy in the early period. There are many studies that reported anatomical improvement after switching to aflibercept treatment[7-8]. But most of them has got a dissociation between anatomical and visual results. Patients who have recalcitrant intraretinal and/or subretinal fluid are exposed to a long term treatment with the hope of resolution but possibly the longstanding retinal exudation results in poor visual acuity.

The term resistant (unresponsive) is still controversial. Some studies report shift to aflibercept after 34.4 anti-vascular endothelial growth factor (VEGF) injections and some report switches after mean 20.4 anti-VEGF injections[8-9]. But like these studies most of the studies report an excellent anatomical improvement but poorer visual rehabilitation[10-12]. However, some recent studies reported visual improvement after switching to intravitreal aflibercept (IVA) in patients with neovascular ag acquired macular degeneration (AMD) and persistent intraretinal/subretinal fluid despite three consecutive ranibizumab injections[13-14].

Wykoff *et al*[15] in Turf trial demonstrated +0.2 ETDRS letter gain after 3 dose aflibercept 2.0 mg injections in patients with suboptimal response to previous anti-VEGF injections (mean 42 prior injection). Similar to the results mentioned above they reported anatomical improvement in all parameters but could just maintained the visual acuity.

In light of this, Brown *et al*[16-17] reported in the Save trial using ranibizumab 2.0 mg (fourfold dose of FDA approval) in the treatment of patients with neovascular AMD with suboptimal response to monthly 0.5 mg ranibizumab. They declared a +3.3 letter gain after 3 monthly injections of 2.0 mg ranibizumab in 86 participants. But one year results revealed the need to monthly injections of ranibizumab 2.0 mg to maintain the visual gains. Then Genentech conducted the Harbour study and 2.0 mg ranibizumab demonstrated no clinical advantage over the 0.5 mg ranibizumab in recalcitrant eyes and they stopped 2.0 mg ranibizumab trials[18].

Consistent with Harbour study, in this study patients who didn't switch to 2 mg IVA treatment did also respond to the treatment with ranibizumab 0.5 mg treatment (especially after 6th injection) and there was a significant fluid resolution ($P=0.01$). But VA gain was not accompanying with the anatomical results ($P=0.11$). Unlike other studies in our study, patients who were switched to aflibercept treatment had great visual improvement with 3 or more early treatment for diabetic retinopathy study (ETDRS) letters in 61% of patients ($P=0.009$). We think that the most possible reason of this much visual improvement is early shift to IVA. Because a recent study investigating the factors influencing treatment response in AMD that reported in 115 eyes with treatment-naive neovascular AMD the most important reason of functional improvement is baseline VA[19]. One another reason might be the result of strong affinity of aflibercept to all isomers of VEGF-A and plasental growth factor (PlGF) than both ranibizumab and bevacizumab[18]. PlGF only binds to VEGFR1 and this coupling might be reducing the local inflammation on retinal tissues because neutrophils, monocytes and macrophages are the other cell types expressing VEGFR1. Latest studies revealed that PlGF deficiency also has got a great role in retinopathy of prematurity as a proangiogenic precursor on retinal endothelial cells[20-22]. Other than neovascularization local and systemic increase in inflammatory biomarkers indicate that chronic inflammation is one of the major problems in age related macular degeneration[23]. This study demonstrates that aflibercept treatment may be valuable in recalcitrant W-AMD eyes, improving VA in the early period. The effect of IVA is evident right after the first injection. Although proceeding with ranibizumab treatment decrease retinal exudation in patients refractory to 3 load dose ranibizumab 0.5 mg treatment, visual improvement doesn't seem to be related with only fluid resolution. Still we need prospective studies with larger subjects and with more proofs about systemic side effects of IVA.

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