Int J Clin Exp Med 2015;8(7):11572-11578
www.ijcem.com /ISSN:1940-5901/IJCEM0009557

Case Report

Intravitreal ranibizumab therapy for retinal arterial macroaneurysm

Muhammet Kazim Erol[1], Berna Dogan[1], Deniz Turgut Coban[1], Devrim Toslak[1], Ayse Cengiz[1], Deniz Ozel[2]

[1]Department of Antalya Training and Research Hospital, Eye Clinic, Antalya, Turkey; [2]Department of Biostatistics and Medical Informatics of Akdeniz University Medical Faculty, Antalya, Turkey

Received April 24, 2015; Accepted June 22, 2015; Epub July 15, 2015; Published July 30, 2015

Abstract: Aim: To evaluate the anatomic and functional results of intravitreal ranibizumab injection for treatment of symptomatic retinal arterial macroaneurysm (RAM). Materials and Methods: A series of seven patients (seven eyes) who had been diagnosed with symptomatic RAM were assessed by comprehensive ophthalmologic examination, fluorescein angiography (FA), optical coherence tomography (OCT), and indocyanine green angiography (ICGA). All patients were treated by intravitreal ranibizumab injection within one week of diagnosis and retreated upon evidence of persistent serous detachment or hemorrhage involving the macula on OCT. Anatomical recovery was examined by FA, OCT, and ICGA. Best-corrected visual acuity (BCVA) and central macular thickness (CMT) were evaluated using the Snellen chart and optical coherence tomography, respectively, at baseline; at 1, 3, and 6 months; and at the final visit. The BCVA and CMT values at baseline and the final visit were compared using the Wilcoxon signed rank test and determination of logarithm of the minimal angle of resolution (logMAR) of BCVA value. Results: Over a mean follow-up period of 10.86 ± 5.4 months, significant visual and anatomical recovery was observed, with visual acuity improving by three or more lines in all seven patients. The mean logMAR of BCVA improved from 1.09 ± 0.60 to 0.16 ± 0.16 (p = 0.018) and mean CMT decreased from 427.5 ± 132.4 μm to 208.7 ± 23.1 μm (P = 0.018). No complications were observed with intravitreal ranibizumab injection. Conclusion: İntravitreal ranibizumab is an effective therapy for symptomatic RAM, improving BCVA and decreasing CMT.

Keywords: Anti-vascular endothelial growth factor, best-corrected visual acuity, central macular thickness, ranibizumab, retinal arterial macroaneurysm

Introduction

Retinal arterial macroaneurysm (RAM) is an acquired, localized, fusiform, or saccular dilation of retinal arterial branches that occurs in the macular or postequatorial regions [1, 2]. RAM most commonly develops in hypertensive women aged between 50 and 80 years [3]. RAM usually occurs in the first three orders of the arterial tree, where the perfusion pressure is high and the thin stretched arterial sac is relatively easily perforated [4], and frequently occurs at arteriovenous crossings. At the point where the arterial and venous walls are in contact, the adventitial layer is absent, providing the arterial wall with less structural support and increasing the risk of aneurysm formation at this point [1]. Histologic study of the macroaneurysm is necessary to confirm true aneurysm formation as characterized by vessel wall thickening, change in hyaline, and elastotic degeneration [5]. Histopathologically, aging of arterioles is characterized by arterial dilatation with variable degrees of artery wall hyalinization and surrounding retinal exudate or hemorrhage. Visual acuity usually deteriorates due to associated retinal edema; exudation; serous retinal detachment; and subretinal, retinal, and preretinal hemorrhage [3] The treatment of symptomatic RAM is controversial [6]. Although current treatment options rarely improve visual acuity, early diagnosis and treatment are indicated when macular edema or hemorrhage involves the fovea [7]. One current treatment option is intravitreal injection of anti-vascular endothelial growth factor (VEGF) drugs. Although anti-VEGF drugs have been shown to prevent the formation of abnormal blood vessels and counteract VEGF-induced vascular permeability [8], little research has examined

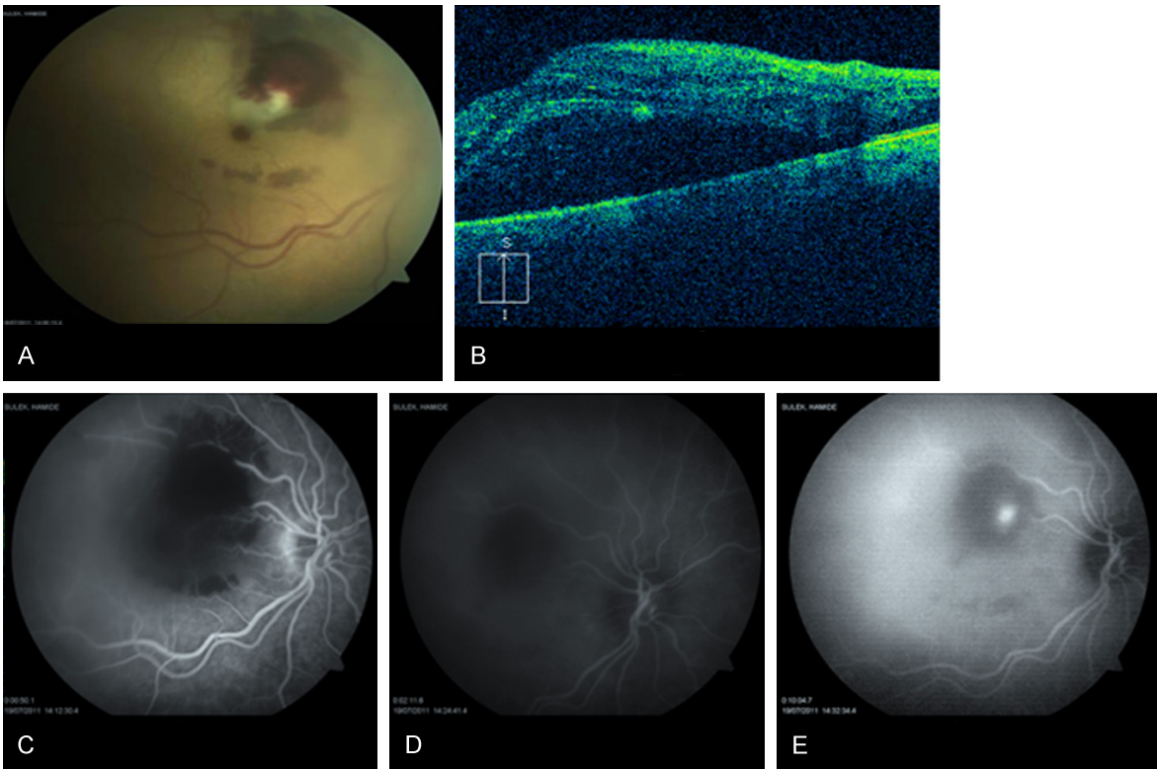

Figure 1. Images from the right eye of a 68-year old woman with symptomatic retinal arterial macroaneurysm (Case 1). A. Fundus photography shows retinal arterial macroaneurysm. B. Optical coherence tomography demonstrates presence of subretinal fluid and retinal edema. Central macular thickness OD is 582 μm. Best-corrected visual acuity was assessed by counting fingers. C. Fluorescein angiography image. D. Early-stage indocyanine green angiography image. E. Indocyanine green angiography image showing focal hyperfluorescence attributable to superotemporal macroaneurysm.

their efficacy in the treatment of symptomatic RAM. To help fill this research gap, this study examined the anatomic and functional results of intravitreal ranibizumab injection for treatment of symptomatic RAM in a series of patients.

Materials and methods

The study included a series of seven patients (seven eyes) with symptomatic RAM who had been diagnosed with RAM subsequent to examination at Antalya Training and Research Hospital, Turkey between June 2011 and October 2014. Informed consent was obtained from the patients in accordance with the tenets of the Declaration of Helsinki. Diagnosis of RAM had been based on the results of fundus examination, fluorescein angiography (FA), and indocyanine green angiography (ICGA). The inclusion criteria were the presence of symptomatic RAM as characterized by exudative and/or hemorrhagic manifestation involving the fovea (including subretinal/intraretinal fluid and/or hemorrhage), vision loss, and confirmation of RAM by FA and ICGA. The exclusion criteria were previous treatment for RAM and diagnosis of any other disease able to affect visual acuity. All patients underwent a comprehensive ophthalmologic examination, including refraction and measurement of best-corrected visual acuity (BCVA), indirect ophthalmoscopy, slit-lamp biomicroscopy, FA, ICGA, and optical coherence tomography (OCT; Cirrus HD OCT, Carl Zeiss Meditec, Dublin, CA, USA). The location of the macroaneurysm and associated serous retinal detachment or hemorrhage was recorded (**Figure 1**).

The primary outcome measure was BCVA at baseline; at 1, 3, and 6 months; and at the final visit. The secondary outcome measure was central macular thickness (CMT) at baseline; at 1, 3, and 6 months; and at the final visit. Patients were examined on the first postoperative day; at 1 week; at 1, 3, 6 months; and at

Table 1. Characteristics of seven patients with retinal arterial macroaneurysm

Case	Age	Sex	Fovea	Treatment	Medical History	Baseline BCVA	Final BCVA	Baseline CMT	Final CMT	Follow-up Period (mo)
1	68	F	PRH, SRH, SRD	IVR#2	HT	CF	20/40	582	163	10
2	72	M	PRH, SRD	IVR#2	HT	20/200	20/20	466	220	19
3	64	F	PRH, IRH, SRD	IVR#2	HT, DM	CF	20/32	575	230	6
4	78	M	PRH, SRH, SRD	IVR#2	HT	20/400	20/50	278	223	8
5	75	F	IRH, SRD	IVR #2	HT	20/200	20/20	488	194	6
6	79	F	IRH, SRD	IVR#2	HT	20/63	20/32	284	211	18
7	71	M	SRD, PRH	IVR#2	HT	20/32	20/20	320	220	9

BCVA: best-corrected visual acuity; CF: counting fingers; IVR: intravitreal ranibizumab injection; PRH: preretinal hemorrhage; IRH: intraretinal hemorrhage; SRH: subretinal hemorrhage; SRD: serous retinal detachment; CMT: central macular thickness; HT: hypertension; DM: diabetes mellitus.

the final visit. BCVA was measured using the Snellen chart at baseline and at the final visit after intravitreal ranibizumab injection treatment. For statistical analysis, all measurements were transposed into the logarithm of the minimal angle of resolution (logMAR) of BCVA. CMT was measured by optical coherence tomography.

Treatment for all patients consisted of intravitreal injection ranibizumab (Lucentis 0.5 mg/0.05 ml; Novartis, Basel, Switzerland) initiated within one week of diagnosis. After the first injection, patients were retreated upon evidence of persistent serous detachment or hemorrhage involving the macula on OCT. The BCVA and CMT values at baseline and the final visit were compared using the Wilcoxon signed rank test. SPSS software version 13.0 (SPSS Inc, Chicago, Illinois, USA) was used for all analyses. A *P* value of less than 0.05 was considered statistically significant.

Results

(**Table 1**) summarizes the characteristics of the seven patients and their treatment results. The mean age was 72.7 ± 5.3 years (range, 64-79 years) and the mean follow-up period was 10.8 ± 5.3 months (range, 6-19 months). All patients had a history hypertension and all seven eyes showed various hemorrhagic complications, of which most showed a combination of preretinal, subretinal, intraretinal hemorrhage and serous detachment. At baseline the mean logMAR of BCVA was 1.09 ± 0.60 (Snellen equivalent: 20/245) and the mean CMT was 427.5 ± 132.4 μm. At the final visit the mean logMAR of BCVA was 0.16 ± 0.16 (Snellen equivalent: 20/29; P = 0.018) and the mean CMT was 208.7 ± 23.1 μm (P = 0.018). Significant anatomical recovery, as confirmed by fluorescein angiography, OCT, and FA showing complete closure of the macroaneurysm (**Figures 2**, **3**), was observed in all patients. Rapid and significant improvement in visual acuity, as measured by improvement by three or more lines, was also observed in all patients. Both BCVA and CMT were found to have significantly improved at the final visit (Wilcoxon signed rank test $P < 0.05$ for all variables); (**Table 2**). No complications, such as endophthalmitis, traumatic lens injury, or retinal detachment, were observed with intravitreal ranibizumab injection.

Discussion

As RAM has been associated with sudden loss of vision secondary to abrupt bleeding due to rupture of the aneurysm [7], determining the best means of its treatment is imperative. However, the treatment of symptomatic RAM is controversial. Among the recommendations provided to date, Vander et al. suggested the following: (1) patients with good vision and no macular involvement should be observed; (2) patients with decreased vision due to intraretinal, preretinal, or vitreous hemorrhage should be observed over several months for spontaneous resolution before treatment is provided; and (3) patients with macular involvement (edema, exudates, or submacular hemorrhage) should be treated immediately [9]. Of the two current treatment options, observation and laser photocoagulation, the findings regarding the latter have been mixed. Whereas a previous study reported that laser photocoagulation for

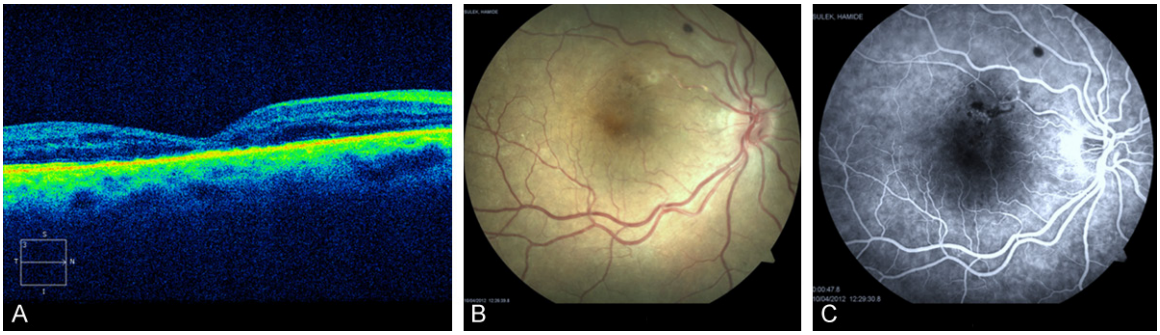

Figure 2. Images from the right eye of 68-year old woman with symptomatic retinal arterial macroaneurysm treated with intravitreal ranibizumab injections (Case 1). A. Optical coherence tomography at the last follow-up visit 10 months following two injections demonstrating stable, normal fovea. Central macular thickness OD is 163 µm. Best-corrected visual recovery recovered to 20/40. B. Fundus photography 10 months following two intravitreal ranibizumab injections showing resolution of the retinal hemorrhages and edema. C. Fluorescein angiography showing angiographic closure of the macroaneurysm.

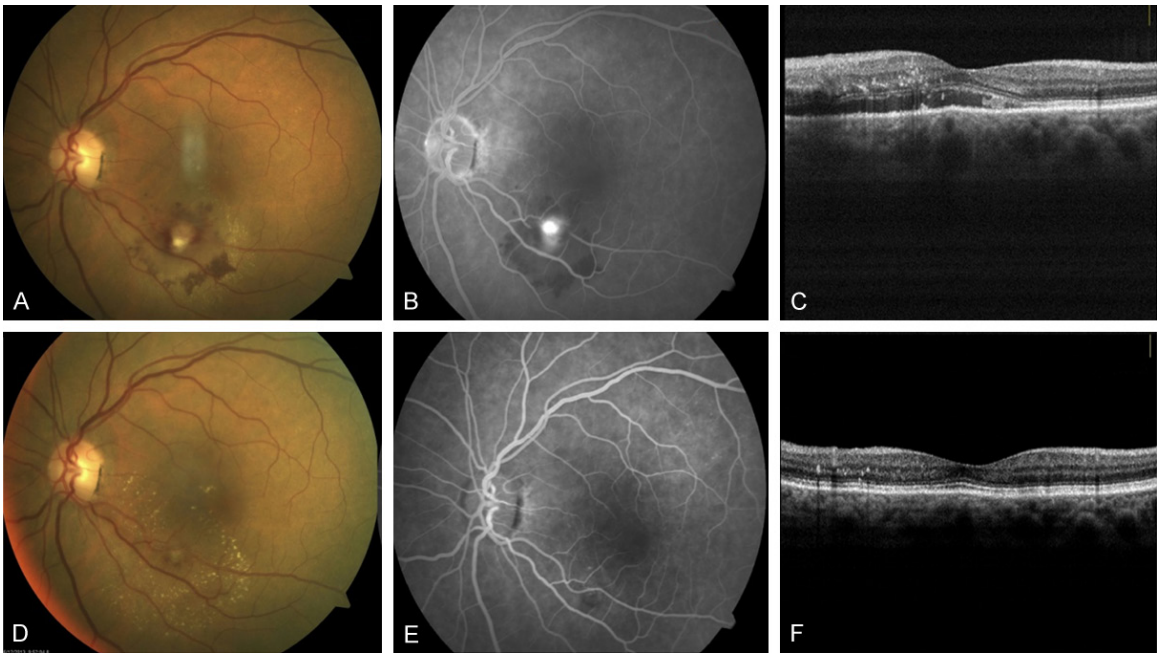

Figure 3. Images from the left eye of a 75-year old woman with symptomatic retinal arterial macroaneurysm (Case 5). A. Fundus photography shows retinal arterial macroaneurysm. B. Fluorescein angiography showing focal hyperfluorescence attributable to retinal arterial macroaneurysm. C. Optical coherence tomography demonstrates presence of subretinal fluid and retinal edema. Central macular thickness OS is 488 µm. Best-corrected visual acuity is 20/200. D. Fundus photography performed at the last follow-up visit six months following two intravitreal ranibizumab injections showing resolution of the retinal hemorrhages and edema. E. Angiographic closure of macroaneurysm. F. Optical coherence tomography performed at the last follow-up visit six months following two intravitreal ranibizumab injections demonstrating stable, normal fovea. Central macular thickness OS is µm 194 µm. Best-corrected visual acuity recovered to 20/20.

RAM does not improve visual acuity [6], recent studies have shown that it does improve visual acuity [10, 11]. However, laser photocoagulation is associated with many complications, including enlargement of the laser scar, choroidal neovascularization, and subretinal fibrosis.

VEGF stimulates endothelial production of nitric oxide, a vasodilator, and has been associated with activation of coagulation cascades. As anti-VEGF drugs reduce nitric oxide, leading to vasoconstriction, they reduce macular edema [12]. Intravitreal injection of VEGF inhibitors,

Table 2. Baseline and final best-corrected visual acuity and central macular thickness in patients with symptomatic retinal arterial macroaneurysm

	Baseline	Final	P (Wilcoxon signed rank test)
Mean ± SD logMAR of BCVA	1.09 ± 0.60	0.16 ± 0.16	0.018
Mean ± SD CMT (μm)	427.5 ± 132.4	208.7 ± 23.1	0.018

BCVA: best -corrected visual acuity; CMT: central macular thickness; logMAR: logarithm of minimal angle of resolution.

such as ranibizumab or bevacizumab, is more recent therapeutic alternative that has been found effective for the treatment of neovascular age-related macular degeneration [13], macular edema due to diabetes [14], and vein occlusion [15]. VEGF inhibition in these pathologies results in reduced vascular permeability and central macular thickness [16], leading to visual improvement, and may facilitate clearing of the various retinal hemorrhages [17]. In accordance with these findings, intravitreal injection of anti-VEGF drugs has been considered a treatment option for RAM. Pichi et al [18] found that intravitreal injection of bevacizumab is an effective therapy for complex RAM, leading to rapid improvement in BCVA and central retinal thickness. In addition, Cho et al. [16] reported that intravitreal bevacizumab injection likely hastens resolution of macular edema and hemorrhage secondary to RAM. In one study, intravitreal injection of ranibizumab in one RAM patient resulted in closure of the macroaneurysm, leading to resolution of the associated macular edema and visual improvement [19]. In all these studies, rapid and almost complete resolution of the hemorrhage and significant visual recovery were observed.

The visual symptoms can be caused by macular edema, and multilevel retinal hemorrhage. Final BCVA strongly depends on the location of the hemorrhage. As subretinal hemorrhage rapidly causes damage to the overlying retina [20] and subretinal blood can be toxic, subretinal hemorrhage is the most damaging to retinal tissue, especially in the macular area. The outer retinal toxicity associated with subretinal hemorrhage is presumably caused by three factors: a mechanical barrier effect that prevents metabolic exchange between the retinal pigment epithelium and outer retina, iron-related toxicity, and fibrin-mediated retinal damage [21]. Irreversible damage to photoreceptor and retinal pigmented epithelial cells can occur after two weeks, which can lead to permanent loss of central vision [20]. Rapid and correct diagnosis is thus very important in subretinal hemorrhage due to the risk of retinal toxicity [21]. Patients with vitreous hemorrhage or premacular hemorrhage have a better visual prognosis than those with macular edema, intraretinal hemorrhage, or submacular hemorrhage [22].

Among the seven cases examined here, the two cases (Cases 1 and 4) characterized by subretinal and preretinal hemorrhage experienced rapid visual and anatomic rehabilitation after intravitreal ranibizumab injection had been initiated within one week of diagnosis at the hospital. Regarding their visual rehabilitation, the BCVA of Cases 1 and 4 recovered to 20/40 and 20/50, respectively. They thus experienced greater visual improvement than had three RAM patients with preretinal and subretinal hemorrhage who had been treated by Asık et al. [11] with frequency doubled Nd: YAG laser (LightLas 532), whose BCVA recovered to 20/200. While the results obtained with intravitreal ranibizumab injection appear to be better than that obtained after laser therapy, direct comparison between these results is not possible because of variation among the basal BCVA of the patients included in the studies.

Several case reports, in addition to the current study, have obtained encouraging results regarding intravitreal anti-VEGF treatment for RAM [23, 24]. Their results indicate that intravitreal ranibizumab therapy may resolve the RAM, leading to resolution of the associated macular edema, and consequently visual improvement. Regarding the mechanism by which they improve vision and anatomy, anti-VEGF drugs might actively close the involved pathologically permeabilized retinal artery and normalize the vessel wall formation by localized inhibition of VEGF. In the seven-patient case series examined here, significant visual and anatomical recovery was observed, as evidenced by recovery of serous detachment, res-

olution of macular edema within two months, and visual acuity improvement by three or more lines in all seven cases. In accordance with these findings, the mean logMAR of BCVA improved from 1.09 ± 0.60 (Snellen equivalent: 20/245) to 0.16 ± 0.16 (Snellen equivalent: 20/29; p = 0.018) and the mean CMT decreased from 427.5 ± 132.4 μm to 208.7 ± 23.1 μm. The observed beneficial effects of intravitreal ranibizumab therapy for treatment of RAM reported here warrant further investigation. Future prospective randomized studies are necessary for to identify the precise effects of anti-VEGF treatment as a treatment for symptomatic RAM.

Disclosure of conflict of interest

None.

Adress correspondence to: Dr. Berna Dogan, Antalya Training and Research Hospital, Eye Clinic, Antalya, Turkey. Tel: +90 532 583 71 70; E-mail: bernadoga3@hotmail.com

References

[1] Lavin MJ, Marsh RJ, Peart S, Rehman A. Retinal arterial macroaneurysms: a retrospective study of 40 patients. Br J Ophthalmol 1987; 71: 817-825.

[2] Lewis RA, Norton EW, Gass JD. Acquired arterial macroaneurysm of the retina. Br J Ophthalmol 1976; 60: 21-30.

[3] Rabb MF, Gagliano DA, Teske MP. Retinal arterial macroaneurysms. Surv Ophthalmol 1988; 33: 73-96.

[4] Abdel-Khalek MN, Richardson J. Retinal macroaneurysm: natural history and guidelines for treatment. Br J Ophthalmol 1986; 70: 2-11.

[5] Fitche C, Streeten BW, Freedman AH. A histopathologic study of retinal arterial aneurysms. Am J Ophthalmol 1987; 85: 509-518.

[6] Brown DM, Sobol WM, Folk JC, Weingeist TA. Retinal arteriolar macroaneurysms: long-term visual outcome. Br J Ophthalmol 1994; 78: 534-538.

[7] Moosavi RA, Fong KC, Chopdar A. Retinal artery macroaneurysm: clinical and fluorescein angiographic features in 34 patients. Eye 2006; 20: 1011-1020.

[8] Chanana B, Azad RV. Intravitreal bevacizumab for macular edema secondary to retinal macroaneurysm. Eye 2009; 23: 493-494.

[9] Vander JF, Duker JS, Jaeger EA. Miscellaneous diseases of the fundus. In: Tasman W, Jaeger E editors. Duane's Clinical Ophthalmology. Revised ed. Vol 3. Philadelphia: Lippincott-Raven; 1997. pp. 8-10.

[10] Parodi MB, Iacono P, Ravalico G, Bandello F. Subthreshold laser treatment for retinal arterial macroaneurysm. Br J Ophthalmol 2011; 95: 534-538.

[11] Asık N, Coskun E, Koytak IA, Erol MK, Ozerturk Y. Treatment of ruptured retinal artery macroaneurysms with frequency doubled Nd: YAG laser. Turkiye Klinikleri J Ophthalmol 2009; 18: 230-235.

[12] Campochiaro PA, Hafız G, Shah SM. Ranibizumab for macular edema due to retinal vein occlusions: implication of VEGF as a critical stimulator. Mol Ther 2008; 16: 791-799.

[13] Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, Kim RY, Marina Study Group. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006; 355: 1419-1431.

[14] Chun DW, Heier JS, Topping TM, Duker JS, Bankert JM. A pilot study of multiple intravitreal injections of ranibizumab in patients with center-involving clinically significant diabetic macular edema. Ophthalmology 2006; 113: 1702-1712.

[15] Pieramici DF, Rabena M, Castellarin AA. Ranibizumab for the treatment of macular edema associated with perfused central retinal vein occlusions. Ophthalmology 2008; 115: 47-54.

[16] Cho HJ, Rhee TK, Kim HS, Han JI, Lee DW, Cho SW, Kim JW. Intravitreal bevacizumab for symptomatic retinal arterial macroaneurysm. Am J Ophthalmol 2013; 155: 898-904.

[17] Verheul HM, Pinedo HM. Possible molecular mechanisms involved in the toxicity of angiogenesis inhibition. Nat Rev Cancer 2007; 7: 475-485.

[18] Pichi F, Morara M, Torrazza C, Manzi G, Alkabes M, Balducci N, Vitale L, Lembo A, Ciardella AP, Nucci P. Intravitreal bevacizumab for macular complications from retinal arterial macroaneurysms. Am J Ophthalmol 2013; 155: 287-294.

[19] Wenkstern AR, Petersen H. Intravitreal ranibizumab in retinal macroaneurysm. Graefes Arch Clin Exp Ophthalmol 2010; 248: 1667-1670.

[20] Toth CA, Morse LS, Hjelmeland LM. Fibrin direct early retinal damage after experimental subretinal hemorrhage. Arch Ophthalmol 1991; 109: 723-729.

[21] Townsend-Pico WA, Meyers SM, Lewis H. Indocyanine green angiography in the diagnosis of retinal arterial macroaneurysms associated with submacular and preretinal hemorrhages: a case series. Am J Ophthalmol 2000; 129: 33-37.

[22] Tonotsuka T, Imai M, Saito K. Visual prognosis for symptomatic retinal arterial macroaneurysm. Jpn J Ophthalmol 2003; 47: 498-502.
[23] Javey G, Moshfeghi AN, Moshfeghi AA. Management of ruptured retinal arterial macroaneurysm with intravitreal bevacizumab. Ophthalmic Surg Lasers Imaging 2010; 41: 1-5.
[24] Tsakpinis D, Nasr MB, Tranos P, Giannopoulos T, Symeonidis C, Dimitrakos SA, Konstas AG. The use of bevacizumab in a multilevel retinal hemorrhage secondary to retinal macroaneurysm: a 39-month follow-up case report. Clin Ophthalmol 2011; 5: 1475-14