Evaluation of the Effect of Intravitreal Ranibizumab Injection on Cardiac Ischemic Parameters and Vascular Endothelial Function

İntravitreal Ranibizumab Enjeksiyonunun Kardiak İskemik Parametreler ve Vasküler Endotelyal Fonksiyon Üzerine Etkilerinin İncelenmesi

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ABSTRACT

Purpose: To evaluate the effect of intravitreal ranibizumab injection on cardiac ischemic parameters and vascular endothelial function.

Methods: This observational, prospective case series included 30 patients with age-related macular degeneration (ARMD), 24 patients with diabetic macular edema (DME) and 30 control cases. All participants received intravitreal injections of 0.5 mg ranibizumab in ARMD and DME groups, but control groups participants were not given intravitreal injections. Cardiac ischemic parameters including total creatinine kinase, creatinine kinase-MB and endothelial function measured with flow-mediated dilatation of the brachial artery with two-dimensional and Doppler ultrasonography were evaluated before and 1day and 1 month after the injection.

Results: Mean age of the ARMD patients was 67.80±5.67, DME was 65.42±7.12, control group was 67.33±5.70 (p:0.431). LDH, AST and ALT values were found lower at 30th day after injection in DME group. Myoglobin values were found lower at post-injection period in ARMD group. Ranibizumab is observed to have affected LDH, AST, ALT and miyoglobin. Despite the statistically significant FMD values in ARMD and DME groups, percentage FMD values showed no statistically significant differences.

Conclusions: Besides its antianjiogenic action, ranibizumab was shown to display distinct effects on endothelial cells in in-vitro studies. On the contrary, we did not observe any significant change in vascular endothelial function. Furthermore, knowledge of the effect of ranibizumab on cardiovascular system was generally recruited from the retrospective studies. So our prospective study confirms that intravitreal injections of ranibizumab were not associated with significant risks of myocardial ischemia.

Key words: Ranibizumab, Cardiac Ischemia, Vascular Endothelial Function.

ÖZ

Amaç: İntravitreal Ranibizumab enjeksiyonunun kardiak iskemik parametreler ve vasküler endotelyal fonksiyon üzerine etkilerinin değerlendirilmesi

Gereç-Yöntem: Gözlemsel, prospektif olgu serisi olan bu çalışmaya yaşa bağlı makula dejenerasansı (YBMD) olan 30 hasta, diyabetik maküler ödemi (DMÖ) olan 30 hasta ve 30 sağlıklı kontrol olgusu dahil edilmiştir. YBMD ve DMÖ olan bütün hastalara 0.5 mg ranibizumab intravitreal olarak uygulanmıştır. Kontrol grubundaki katılımcılara ise intravitreal enjeksiyon yapılmamıştır. Enjeksiyon öncesi ve enjeksiyondan sonraki 1. gün ve 1. ayda; total kreatin kinaz, kreatin kinaz –MB'yi de içeren kardiak iskemik parametreler istenmiş ve endotelyal fonksiyon, akım aracılı dilatasyon ölçüm metodu ile 2 boyutlu ve Doppler ultrasonografi aracılığıyla brakial arterden bakılmıştır.

Sonuçlar: Ortalama yaş, YBMD grubunda 67.80±5.67, DMÖ grubunda 65.42±7.12 ve kontrol grubunda 67.33±5.70 'dır (p:0.431). LDH, AST ve ALT değerleri enjeksiyon sonrası 30. günde DMÖ grubunda daha düşük bulunmuştur. Myoglobin değerleri YBMD gru-

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bunda enjeksiyon sonrasında daha düşük tespit edilmiştir. Ranibizumab'ın LDH, AST, ALT ve miyoglobine etkisi olduğu görülmüştür. FMD değerleri YBMD ve DMÖ grubunda istatistiksel olarak anlamlı düzeyde farklı iken, FMD yüzdelik değerlerde gruplar arası fark saptanmamıştır.

Tartışma: Antianjiojenik özelliği olan ranibizumabın invitro çalışmalarda endotel hücrelerini de etkilediği görülmüştür. Öte yandan, biz çalışmamızda vasküler endotelyal fonksiyonda herhangi bir farklılık saptamadık. Ek olarak ranibizumabın kardiovasküler sistemi etkilediği önceki çalışmalarda ortaya konmuş olsa da biz prospektif bu çalışmada ranibizumabın miyokard iskemisi ile anlamlı ölçüde ilişkisi olmadığını gösterdik.

Anahtar Kelimeler: Ranibizumab, kardiak iskemi, vasküler endotelyal fonksiyon

INTRODUCTION

VEGF was first isolated in 1983 as a factor to increase vascular permeability. It plays a role in pathological angiogenesis and embryonic vasculogenesis. VEGF levels rise in response to hypoxia and angiogenic response that occurs with low oxygen pressure. There are five forms of VEGF: A,B,C,D, and E. Placental growth factor (PIGF) is also considered as a member of VEGF family. Among subtypes of VEGF, VEGF-A is the most important one, playing a significant role in the formation of pathological angiogenesis in neoplastic, inflammatory, and vascular eye diseases. Excessive release of VEGF-A can be observed in lung, breast, bladder, and kidney cancers and in many tumors such as glioblastoma multiforme. In different studies, VEGFs have been shown to play important roles in the pathogenesis of neovascular eye diseases. Increased VEGF expression has been shown in surgically removed choroidal neovascular membranes of the patients having wet age-related macular degeneration. Excessive release of VEGF-A has been observed in eyes with subretinal neovascularization, diabetic retinopathy, central retinal vein occlusion, iris neovascularization, retinal detachment, and retinopathy of prematurity. Relationship between pathological ocular neovascularization and increased VEGF-A level has led testing anti-VEGF therapies, and successful results were achieved.[1-3]

Ranibizumab (LucentisR_; NovartisPharma AG, Basel, Switzerland and Genentech, Inc., South San Francisco, CA, USA) was approved by the FDA in 2006 for use in wet macular degeneration.[4] Subsequently, the FDA approved its use also for diabetic macular edema, branch and central retinal vein occlusions. Ranibizumab has been approved in our country since 2008 and has been widely used for aforementioned diseases.[5-9]

The efficacy of intravitreal Ranibizumab treatment has been recognized for many retinal diseases today, while many topical and systemic side effects related to the treatment have been reported in several studies. Systemic side effects due to intravitreal use of AntiVEGF drugs include arterial thromboembolic events (ATEs), venous thrombosis, hypertension, nonocular hemorrhage, gastrointestinal disorders, and death.[10-12]

However, in these studies, only the incidence of side effects has been reported. Laboratory measurements such as cardiac enzymes and endothelial function have not been compared between the control group and anti-VEGF-A-treated group. The aim of this study was to compare the effects of intravitreal application of ranibizumab, which is an anti-VEGF-A agent, on biochemical parameters and endothelium in patients with wet age-related macular degeneration and diabetic macular edema by means of laboratory measurements.

METHODS

This study was conducted in the Ophthalmology and Cardiology clinics of our hospital, in accordance with the Declaration of Helsinki, and after obtaining oral and written consents of the patients. This observational, prospective case series included a total of 30 patients with age-related macular degeneration(ARMD), 24 patients with diabetic macular edema(DME), who were injected Ranibizumab intravitreally and 30 control cases, who were not given intravitreal injections but whose blood samples were taken and FMD test were done at three time points.

To diminish any confounders that might influence endothelial function, patients with previous coronary arterial disease, previous cerebrovascular or peripheral vascular disease, hypertension, renal failure, liver dysfunction, hyperlipidemia, chronic systemic disease including auto-immune diseases, smoking history and patients using anti-hyperlipidemic drugs, those with glaucoma or intraocular inflammatory disease and those underwent ocular surgery or ocular injection were excluded. Sixteen diabetic patients have used only oral antidiabetic agents, 6 diabetic patients have used oral antidiabetic agents with insulin treatment and 2 diabetic patients have used only insulin treatment. The ARMD patients did not use any medications.

Systemic eye examination and routine biochemical tests were ordered for all patients included in the study prior to injection of ranibizumab. Blood pressures and pulse rates of the patients were also recorded. Cardiological examination was performed by an experienced cardiologist and also endothelial function was measured by ultrasound. Endothelial function was assessed by FMD (flow-mediated dilatation) method.

According to this method, diastolic diameter of the brachial artery was measured at the antecubital fossa with a high-frequency (7-13 MHz) ultrasound probe, and then to induce ischemia, the cuff of the routinely used blood pressure measuring device was attached to the patient's arm, systolic

blood pressure was increased over 50 mmHg and kept so, as inflated for 5 minutes. At the end of the 5 minute period, the measurement was repeated at antecubital fossa. Percentage change in diameter compared to baseline measurement was assessed as FMD. Then, all patients were given intravitreal injections of 0.5 mg ranibizumab. Routine eye examination, biochemical tests, cardiological examination and endothelial function measurements with Doppler ultrasound were repeated 24 hours and 30 days after injection.

Statistical Analysis

Shapiro-Wilk's test was used to assess the data for normality and Levene's test was used for variance homogeneity. Between group comparisons were performed by using Kruskal-Wallis analysis followed by a Siegel-Castellan multiple comparison test and between time comparisons were done by using Friedman analysis followed by a Bonferroni test of variance. Values are expressed as median(25^{th}-75^{th} percentiles). Values are expressed as median(25th-75th percentiles). Analyses were performed using R 2.15.0 software. $p<0.05$ was considered as statistically significant.

RESULTS

Mean age of the patients was 67.80±5.67 for ARMD, 65.42±7.12 for DME and 67.33±5.70 for control group (p=0.431). ARMD group constituted 14 female and 16 male patients, DME group 12 female and 12 male patients, and finally control group constituted 16 female and 15 male cases (p=0.977). Cardiological examination revealed no difference between pre-injection and post-injection.

In DME group, FMG (Fasting Blood Sugar) and total cholesterol values were found higher, but MCV(mean cell volume) was found lower than the other groups at pre-injection and post- injection period. AST (aspartate aminotransferase), ALT (alanine aminotransferase), LDH (lactate dehydrogenase) values at day 30 were lower than pre-injection values in DME group. FMD and FMD pressure decreased at day 30, however FMD percentage displayed no statistically significant difference in DME group.

The FMD, FMD pressure, BUN (blood urea nitrogen) , total cholesterol values were found higher and the FMD percentage values were found lower at pre-injection period in ARMD group. In ARMD group, the Myoglobin values were found to decrease, but the FMD and the FMD pressure were found to increase in timeline. However FMD percentage displayed no statistically significant difference in ARMD group as DME group in timeline. Other biochemical measurements displayed no statistically significant differences. The pre-injection and post-injection FMD percentage values did not differ statistically (Table 1). Differences determined in FMG, ALT, total CK and FMD measurements were only statistically significant, but not clinically relevant. Pre-treatment and post-treatment values were very close to each other at all the measurements.

DISCUSSION

Ranibizumab is a humanised monoclonal antibody fragment, that is a Fab fragment, produced in Escherichia coli cells by recombinant DNA technology. It binds to all isoforms of VEGF-A (e.g. VEGF110, VEGF121 and VEGF165) with a high affinity and prevents binding of the VEGF-A to endothelial surface receptors VEGFR-1 and VEGFR-2. Thus, it reduces endothelial cell proliferation, vascular permeability and angiogenesis.[1-3]

Besides ranibizumab, bevacizumab and pegabtanib sodium are intravitreal anti-VEGF drugs possessing similar mechanism of action. When we consider these Anti-VEGF drugs as a group, adverse effects can be generalized in the group, as well. As an example to systemic use of Anti-VEGF drugs, bevacizumab, which is an Anti-VEGF agent and used intravenously for colorectal cancer agent, shows serious systemic side effects such as arterial thromboembolism, gastrointestinal perforation, hemorrhage, hypertensive crises, and nephrotic syndrome, as reported in various publications. However, these patients were receiving concurrent chemotherapy.[13-15] Other studies using this therapy intravenously for ocular disease in a healthier population have not reported nearly the same risks.[16-17] Many studies have been conducted to examine whether these side effects associated with the systemic use of anti-VEGF drugs also occur in intravitreal applications.[18-21]

After intravitreal administrations, very low systemic concentrations (pg/ml) of ranibizumab have been reported, while it was suggested that anti-VEGF-A treatment may cause adverse events associated with the normal growth, repair and regeneration as a result of entering to the circulatory system.[22]

Thus, according to the Antiplatelet Trialists' Collaboration (APTC) (1994) classification, the incidence of hypertension and thromboembolic events and its relationship with systemic inhibition of VEGF-A should be investigated in research studies. In the MARINA study, 12 and 24 months data showed similar incidence rates of hypertension and arterial thromboembolic events compared to the control group. Accordingly, the incidence of the main arterial thromboembolic events such as myocardial infarction and ischemic or hemorrhagic stroke, was found to be compatible with the AMD patients in general populations in several studies.[4, 23-27] In our country, ranibizumab have reported as a safety treatment with no systematic complications in many studies.[28-35] On the other hand, some studies suggested compared with placebo, systemic thrombotic events also occurred more often in all anti-VEGF treatments.[36-37] Several studies have shown higher rates of these adverse effects in using bevacizumab compared to ranibizumab, although other studies have indicated no significant differences in terms of systemic side effect profile of these two drugs.[12, 38-42] These studies reporting no significant differences for side

Table 1:

Variables	Control			ARMD			DME		
	Basal	1	30	Basal	1	30	Basal	1	30
FBG	95.5(84.0-108.0) A,a	93.5(86.0-106.0) A,a	98.0(86.0-106.0) A,a	88.0(83.0-103.0) A,a	123.0(107.0-139.0) B,a	105.0(89.0-109.0) A,a	337.5(157.3-382.0) A,b	225.5(158.5-355.8) A,b	237.0(175.3-346.0) A,b
BUN	16.0(14.0-16.0) A,a	15.0(14.0-16.0) A,a	15.0(13.0-16.0) A,a	18.0(16.0-21.0) A,b	19.0(16.0-21.0) A,b	18.0(14.0-20.0) A,b	16.0(13.3-20.8) A,ab	16.5(14.3-22.3) A,ab	17.5(14.0-21.0) A,ab
Creatinine	0.8(0.7-0.9) A,a	0.8(0.6-0.9) A,a	0.8(0.7-0.9) A,a	0.9(0.6-1.1) A,a	0.9(0.8-1.1) A,a	0.9(0.7-1.0) A,a	0.7(0.6-0.9) A,a	0.8(0.6-0.9) A,a	0.7(0.6-0.8) A,a
AST	20.0(17.0-27.0) A,a	20.5(18.0-26.0) A,a	20.0(18.0-26.0) A,a	21.0(20.0-24.0) A,a	22.0(19.0-25.0) A,a	23.0(19.0-25.0) A,a	20.5(19.0-23.5) A,a	20.0(17.3-24.3) AB,a	18.5(16.0-21.0) B,a
ALT	16.0(13.0-17.0) A,a	15.5(13.0-18.0) A,a	15.5(13.0-17.0) A,a	17.0(15.0-20.0) A,ab	17.0(14.0-18.0) A,a	16.0(14.0-19.0) A,a	20.5(17.3-32.8) A,b	20.0(16.3-29.0) AB,a	18.0(12.5-28.5) B,a
GGT	18.0(15.0-26.0) A,a	19.0(14.0-28.0) B,a	20.5(16.0-30.0) C,a	26.0(19.0-43.0) A,a	25.0(22.0-40.0) A,a	25.0(20.0-38.0) A,a	24.5(20.3-54.0) A,a	22.0(17.8-61.8) A,a	24.0(22.0-52.0) A,a
Totalcholesterol	191.0(178.0-196.0) A,a	190.0(180.0-198.0) AB,a	190.0(178.0-200.0) B,a	201.0(188.0-225.0) A,b	205.0(193.0-229.0) A,b	208.0(180.0-227.0) A,b	202.5(199.5-222.3) A,b	212.5(206.8-217.5) A,b	204.5(182.8-227.8) A,b
LDL	110.0(106.0-123.0) A,a	112.0(104.0-120.0) A,a	112.0(104.0-124.0) A,a	114.0(103.0-145.0) A,a	124.0(109.0-147.0) A,a	118.0(104.0-147.0) A,a	120.0(111.5-138.8) A,a	128.0(115.3-138.0) A,a	123.0(64.5-143.5) A,a
HDL	56.5(42.0-63.0) A,a	54.5(42.0-61.0) B,a	51.0(39.0-55.0) C,a	48.0(40.0-55.0) A,a	48.0(40.0-53.0) A,a	46.0(41.0-51.0) A,a	54.5(38.5-62.3) A,a	53.5(39.0-60.8) A,a	47.5(37.3-54.8) B,a
Triglyceride	142.5(115.0-170.0) A,a	152.5(126.0-180.0) A,a	143.5(130.0-170.0) A,a	158.0(140.0-183.0) A,a	172.0(125.0-184.0) A,a	160.0(129.0-226.0) A,a	165.0(89.5-253.5) A,a	162.5(112.8-287.8) A,a	150.5(119.5-213.8) A,a
LDH	178.0(171.0-201.0) A,a	180.5(176.0-198.0) A,a	184.0(176.0-206.0) A,a	212.0(181.0-241.0) A,ab	224.0(189.0-237.0) A,b	219.0(167.0-275.0) A,a	225.5(192.3-269.3) A,b	212.5(180.3-241.0) B,ab	183.0(169.8-224.5) C,a
Total CK	91.5(68.0-106.0) A,a	87.0(66.0-102.0) B,a	85.0(59.0-104.0) B,a	98.0(65.0-160.0) A,a	79.0(56.0-138.0) A,a	87.0(56.0-146.0) A,a	84.0(59.5-135.5) A,a	70.0(48.5-106.0) A,a	83.5(42.5-131.5) A,a
CKMB	14.0(10.0-18.0) A,a	13.0(12.0-18.0) A,a	13.5(12.0-18.0) A,a	14.0(7.0-16.0) A,a	15.0(10.0-17.0) A,a	12.0(9.0-18.0) A,a	14.0(9.3-20.3) A,a	13.0(8.3-16.8) A,a	13.0(9.3-16.5) A,a
Miyoglobin	31.8(21.5-62.6) A,a	28.7(21.0-63.1) A,a	23.6(21.5-55.6) B,a	46.2(29.2-53.3) A,a	39.1(24.9-45.4) B,a	38.5(25.0-46.0) B,a	27.9(21.5-37.2) A,a	28.9(21.0-32.0) A,a	27.5(19.6-36.5) A,a
Hemoglobin	15.0(14.7-15.6) A,a	15.0(14.7-15.6) A,a	15.2(14.7-15.6) B,a	14.7(13.5-15.9) A,a	14.7(14.0-15.8) A,a	14.9(14.0-16.0) A,a	14.8(14.1-15.7) A,a	14.6(13.9-15.2) A,a	14.5(13.5-14.9) A,a
MCV	90.9(89.5-93.6) A,a	91.0(89.0-93.8) A,a	91.0(88.8-93.8) A,a	88.3(86.0-91.4) A,ab	88.4(85.0-91.3) A,ab	87.0(85.0-90.4) A,b	86.8(84.9-89.3) A,b	88.1(84.1-89.2) A,b	85.8(83.4-88.7) A,b
PLT	245.0(205.0-261.0) A,a	230.0(205.0-252.0) A,a	230.0(208.0-255.0) A,a	228.0(178.0-298.0) A,a	236.0(166.0-311.0) A,a	213.0(168.0-320.0) A,a	237.0(212.3-272.0) A,a	236.0(215.5-291.0) A,a	255.5(204.5-291.8) A,a
FMD	43.0(37.0-49.0) A,a	43.5(40.0-49.0) AB,a	44.0(41.0-49.0) B,ab	54.0(42.5-57.5) A,b	55.0(44.0-57.0) B,b	55.0(42.5-57.0) AB,a	41.0(33.3-49.8) A,a	44.0(34.0-46.0) A,a	43.0(33.8-45.0) A,b
FMD Pressure	48.0(43.0-52.0) A,a	48.0(46.0-52.0) AB,a	49.0(47.0-52.0) B,ab	57.0(46.0-61.5) A,b	58.0(46.0-64.0) B,b	58.0(46.5-61.5) AB,a	46.0(36.3-53.5) A,a	47.0(37.8-53.8) A,ab	46.0(37.3-51.3) A,b
FMD (%)	11.0(7.0-13.9) A,a	10.7(6.8-13.9) A,a	9.8(6.8-13.6) A,a	5.0(4.6-8.6) A,b	7.5(6.2-10.2) A,a	6.4(5.4-10.3) A,b	6.8(5.9-8.5) A,ab	8.4(6.3-10.9) A,a	8.3(5.9-11.9) A,ab

Values are expressed as median(25th-75th percentiles). Different upper cases in a row indicates statistically significant differences among times (for instance, in ARMD group, FBG values were found statistically higher in 1 ... than basal and 30 .. values). Different lower cases in a row indicates statistically significant differences among groups (for instance, in basal values, FBG values were found statistically higher in DME group than other groups).

effect occurrence between patients on treatment and control groups were all incidence studies.

Several in vitro studies have confirmed that VEGF-stimulated proliferation of retinal or choroidal endothelial cells is inhibited by ranibizumab or bevacizumab.[43-45] To the best of our knowledge, up to this present study, the studies examining the potential changes in biochemical markers, such as CK, which is determined to be related with cardiovascular events; and ALT, GGT, and cholesterol levels, which are thought to be related with cardiovascular events, following administration of anti-VEGF drugs are not available in the literature. Furthermore, any study evaluating the effects of anti-VEGF drugs on arterial endothelial functions is not available in the literature.

As it is well known, arterial endothelial dysfunction is one of the key early events in atherogenesis, that can lead to structural atherosclerotic changes. Following intra-arterial infusion of pharmacologic substances which are known to increase the release of endothelial nitric oxide, endothelial functions can be determined by measuring vasomotor functions in coronary arteries and in the periphery. These invasive methods are ineligible to be used in the studies dealing with asymptomatic subjects, which can be seen as a disadvantage. Thus, noninvasive tests have been developed to evaluate endothelial function. One of the most common of these invasive tests is an ultrasound-based method, measuring arterial diameter in response to an increase in shear stress, which can induce endothelium-dependent dilatation. Endothelial function assessed by using this method revealed a significant correlation with the invasive testing of coronary endothelial function, as well as a correlation with the severity and extent of coronary atherosclerosis.[46]

In our study, we examined the effects of antiVEGF drugs by using FMD method, both on certain biochemical parameters and also on endothelial function. Especially total CK, GGT and cholesterol levels, which may be associated with cardiovascular diseases, and FMD percentage values did not show any clinically significant differences [47-50]. Statistically significant LDH, AST and ALT values was found in DME group. LDH, AST and ALT values were lower at 30th day after injection in DME group. Myoglobin values were found lower at post-injection period in ARMD group. Ranibizumab could have affected LDH, AST, ALT and myoglobin or it is possible that Ranibizumab may not have any influence on LDH, AST, ALT, and myoglobin. However, this is not a certain factor that increases cardiovascular risk. Because the increase in cardiovascular risk is correlated with the increase in these enzymes, but these enzymes decreased following injection of ranibizumab, in our study. We have hypothesized that the statistical significance determined in LDH, AST, ALT and miyoglobin values can be related with the small number of the study group, and with slight variations detected in the values of a few patients. Despite the statistically significant FMD values, the percentage FMD values showed no statistically significant differences, which is considered as the clinically most important parameter for endothelial function.

As we mentioned previously, ranibizumab was shown to display distinct effects on endothelial cells in in-vitro studies, furthermore, knowledge of the effect of ranibizumab on cardiovascular system was generally recruited from the retrospective studies. Our study suggested that ranibizumab could be a useful treatment agent with no significant change in vascular endothelial function.

CONCLUSION

In summary, this present study is important as being the first prospective case-control study examining biochemical parameters and FMD, which are determined to be related with cardiovascular events, in intravitreal patient group. However, the small number of our patient group is a limitation, and we suggest more valuable results can be achieved in further multicenter studies.

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REFERENCES / KAYNAKLAR

1. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med. 2003; 9: 669-676.
2. Ferrara N. Role of vascular endothelial growth factor in physiologic and pathologic angiogenesis: therapeutic implications. Semin Oncol 2002; 29: 10-14.
3. Yi X, Ogata N, Komada M, Yamamoto C, Takahashi K, Omori K et al. Vascular endothelial growth factor expression in choroidal neovascularization in rats. Graefes Arch Clin Exp Ophthalmol.1997;235:313-319.
4. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY et al; MARINA Study Group. Ranibizumab for Neovascular Age-Related –MacularDegeneration. N Eng J Med.2006; 355: 1419-1431.
5. Massin P, Bandello F, Garweg JG, Hansen LL, Harding SP, Larsen M et al. Safety and efficacy of ranibizumab in diabetic macular edema (RESOLVE study): a 12-month, randomized, controlled, double masked, multicenter phase II study. Diabetes Care. 2010; 33:2399-2405.
6. Nguyen QD, Shah SM, Khwaja AA, Channa R, Hatef E, Do DV, et al. READ-2 StudyGroup. Two-year outcomes of the Ranibizumab for Edema of the macula in Diabetes (READ-2) Study. Ophthalmology .2010;117:2146-2151.
7. Mitchell P, Bandello F, Schmidt-Erfurth U, Lang GE, Massin P, Schlingemann RO et al. The RESTORE Study : Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy for Diabetic Macular Edema. Ophthalmology. 2011;118:615-625.
8. Brown DM, Campochiaro PA, Singh RP, , Li Z, Gray S, Saroj N et al; CRUISE Investigators. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary endpoint results of a phase III study. Ophthalmology 2010;117:1124-1133.

9. Campochiaro PA, Heier JS, Feiner L, Gray S, Saroj N, Rundle AC et al; BRAVO Investigators. Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary endpoint results of a phase III study. Ophthalmology 2010;117:1102–1112.
10. van der Reis MI, La Heij EC, De Jong-Hesse Y, Ringens PJ, Hendrikse F, Schouten JS. A Systematic Review of the Adverse Events Of Intravitreal Anti–Vascular Endothelial Growth Factor Injections. Retina. 2011;31:1449-69.
11. Gunther JB, Altaweel MM. Bevacizumab (Avastin) for the Treatment of Ocular Disease. Surv Ophthalmol. 2009;54: 372-400.
12. Johnson D, Sharma S. Ocular and systemic safety of bevacizumab and ranibizumab in patients with neovascular age-related macular degeneration. Curr Opin Ophthalmol 2013; 24:205–212.
13. Scappaticci FA, Skillings JR, Holden SN, Gerber HP, Miller K, Kabbinavar F et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. J Natl Cancer Inst 2007; 99:1232–1239.
14. Ranpura V, Hapani S, Chuang J, Wu S. Risk of cardiac ischemia and arterial thromboembolic events with the angiogenesis inhibitor bevacizumab in cancer patients: a meta-analysis of randomized controlled trials. Acta Oncol 2010; 49:287–297.
15. Food and Drug Administration. Label Avastin. Genentech.Available at: www.accessdata.fda.gov/drugsatfda_docs/label/
16. Michels S, Rosenfeld PJ, Puliafito CA, Marcus EN, Venkatraman AS. Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration twelve-week results of an uncontrolled open-label clinical study. Ophthalmology. 2005;112:1035-47.
17. Moshfeghi AA, Rosenfeld PJ, Puliafito CA, Michels S, Marcus EN, Lenchus JD et al. Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration: twenty-four-week results of an uncontrolled open-label clinical study. Ophthalmology.2006;113:1-12.
18. Wu L, Martinez-Castellanos MA, Quiroz-Mercado H, Arevalo JF, Berrocal MH, Farah ME et al, Twelve-month safety of intravitreal injections of bevacizumab (Avastin): results of the Pan-American Collaborative Retina Study Group (PACORES). Graefes Arch Clin Exp Ophthalmol 2008;246:81–87.
19. Valmaggia C, Niederberger H, Lang C, Kloos P, Haueter I. The treatment of choroidal neovascularisation with intravitreal injections of bevacizumab (Avastin) [in German]. Klin Monatsbl Augenheilkd 2008;225:380-384.
20. Spaide RF, Laud K, Fine HF, Klancnik JM Jr, Meyerle CB, Yannuzzi LA et al. Intravitreal bevacizumab treatment of choroidal neovascularization secondary to agerelated macular degeneration. Retina 2006;26:383-390.
21. Fong KC, Kirkpatrick N, Mohamed Q, Johnston RL. Intravitreal bevacizumab (Avastin) for neovascular agerelated macular degeneration using a variable frequency regimen in eyes with no previous treatment. Clin Experiment Ophthalmol 2008;36:748–755.
22. Carneiro AM, Costa R, Falcão MS, Barthelmes D, Mendonça LS, Fonseca SL et al. Vascular endothelial growth factor plasma levels before and after treatment of neovascular age-related macular degeneration with bevacizumab or ranibizumab. Acta Ophthalmol. 2012;90:25-30.
23. Brown DM, Michels M, Kaiser PK, Heier JS, Sy JP, Ianchulev T; ANCHOR Study Group. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two years results of the ANCHOR study. Ophthalmology. 2009; 116:57-65.
24. Lalwani GA, Rosenfeld PJ, Fung AE, Dubovy SR, Michels S, Feuer W et al. A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study. Am J Ophthalmol. 2009;148:43-58.
25. Abraham P, Yue H, Wilson L. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER study year 2. Am J Ophthalmol. 2010;150:315-324.
26. Dedania VS, Bakri SJ. Current perspectives on ranibizumab. Clin Ophthalmol. 2015;9:533-542.
27. Shikari H, Silva PS, Sun JK.Complications of intravitreal injections in patients with diabetes. Semin Ophthalmol. 2014; 29:276-289.
28. Kocak N, Kaya M, Barut Selver Ö, Ayhan Z, Kaynak S. Early Results of Ranibizumab Monotherapy in Patients with choroidal neovascularization. Turk J Ophtalmol. 2011; 41: 10-15.
29. Karaca U, Durukan AH, Erdurman FZ, Sobacı G, Bayraktar MZ. Results of Intravitreal Ranibizumab Treatment for Exudative Age-Related Macular Degeneration. Turk J Ophtalmol. 2012; 42: 25-29.
30. Koçak N, Aslankara H, Türüthan D, Kaynak S. Comparison of Ranibizumab and Pegabtanib Sodium Monotherapies in Terms of Rates of Stabilization After the First Three Doses. Turk J Ophtalmol. 2012; 42: 211-215.
31. Aslankara H, Öner FH, Yaman A, Ergin MH, Saatçi AO. Injection in Wet Type Age-Related Macular Degeneration. Ret-Vit 2010;18:134-138.
32. Sengül A, Artunay Ö, Yüzbaşıoğlu E, Rasier R, Senel A, Bahcecioğlu H. Results of Intravitreal Ranibizumab Treatment for Choroidal Neovascularization Secondary to Age-Related Macular Degeneration. Ret-Vit 2010;18:143-148.
33. Eken V, Batıoğlu F, Özmert E. Retina Ven Tıkanıklığına Bağlı Maküla Ödeminin Tedavisinde İntravitreal Ranibizumab (Lucentis®) Enjeksiyonunun Etkinliği. Ret-Vit 2011;19:108-112.
34. Gedik Oğuz Y, Batıoğlu F, Özmert E. The Results of Intravitreal Ranibizumab Injection for Choroidal Neovascularization From Causes Other Than Age-Related Macular Degeneration. Ret-Vit 2011;19:231-236.
35. Dündar H, Altınkaynak H, Kocasaraç C, Hazar L, Yüksel K. Intravitreal Ranibizumab Therapy in Wet Type Macular Degeneration. Turk J Ophtalmol 2014; 44: 356-360.
36. Scott LJ, Chakravarthy U, Reeves BC, Rogers CA. Systemic safety of anti-VEGF drugs: a commentary. Expert Opin Drug Saf. 2015;14:379-88.
37. Schmid MK, Bachmann LM, Fäs L, Kessels AG, Job OM, Thiel MA.Efficacy and adverse events of aflibercept, ranibizumab and bevacizumab in age-related macular degeneration: a trade-off analysis. Br J Ophthalmol. 2015;99:141-146.
38. Curtis LH, Hammill BG, Schulman KA, Cousins SW. Risks of mortality, myocardial infarction, bleeding, and stroke associated with therapies for age-related macular degeneration. Arch Ophthalmol. 2010;128:1273-9.
39. Bressler NM, Boyer DS, Williams DF, Butler S, Francom SF, Brown B et al. Cerebrovascular accidents in patients treated for choroidal neovascularization with ranibizumab in randomized controlled trials. Retina. 2012;32:1821-8.
40. Campbell RJ, Gill SS, Bronskill SE, Paterson JM, Whitehead M, Bell CM. Adverse events with intravitreal injection of vascular endothelial growth factor inhibitors: nested case-control study. BMJ 2012;345:e4203 doi: 10.1136/bmj.e4203.
41. Campbell RJ, Bell CM, Paterson JM, Bronskill SE, Moineddin R, Whitehead M, et al. Stroke rates after introduction of vascular endothelial growth factor inhibitors for macular degeneration: a time series analysis. Ophthalmology. 2012;119:1604-8.

42. Hwang DJ, Kim YW, Woo SJ, Park KH. Comparison of systemic adverse events associated with intravitreal anti-VEGF injection: ranibizumab versusbevacizumab. J Korean Med Sci. 2012;27:1580-5.
43. Deissler H, Deissler H, Lang S, Lang GE. VEGF-induced effects on proliferation, migration and tight junctions are restored by ranibizumab (Lucentis) in microvascular retinal endothelial cells. Br J Ophthalmol 2008;92:839-43.
44. Stewart EA, Samaranayake GJ, Browning AC, Hopkinson A, Amoaku WM. Comparison of choroidal and retinal endothelial cells: characteristics and response to VEGF-isoforms and anti-VEGF treatment. Exp Eye Res 2011;93:761-6.
45. Spitzer MS, Wallenfels-Thilo B, Sierra A, Yoeruek E, Peters S, Henke-Fahle S et al. Antiproliferative and cytotoxic properties of bevacizumab on different ocular cells. Br J Ophthalmol 2006;90:1316-21.
46. Raitakari OT, Celermajer DS. Flow-mediated dilatation. Br J Clin Pharmacol. 2000;50:397-404.
47. Schindhelm RK, Dekker JM, Nijpels G, Bouter LM, Stehouwer CD, Heine RJ, Diamant M. Alanine aminotransferase predicts coronary heart disease events: A 10-year follow-up of the Hoorn Study. Atherosclerosis. 2006; 191: 391–396.
48. Moe KT, Wong P. Current trends in diagnostic biomarkers of acute coronary syndrome. Ann Acad Med Singapore. 2010;39:210-5.
49. Fraser A, Harris R, Sattar N, Ebrahim S, Smith GD, Lawlor DA. Gamma-glutamyltransferase is associated with incident vascular events independently of alcohol intake: analysis of the British Women's Heart and Health Study and Meta-Analysis. Arterioscler Thromb Vasc Biol. 2007;27:2729-2735.
50. Tanaka T, Okamura T. Blood cholesterol level and risk of stroke in community-based or worksite cohort studies: a reviewof Japanese cohort studies in the past 20 years. Keio J Med. 2012;61:79-88.