의학석사 학위논문

Current Smoking is Associated with a Poor Visual Acuity Improvement after Intravitreal Ranibizumab Therapy in Patients with Exudative Age-Related Macular Degeneration

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2013년 1월

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by
Sangmoon Lee

A thesis submitted to the Department of Clinical Medical Science in partial fulfillment of the requirements for the Degree of Master of Science in Clinical Medical Sciences at Seoul National University College of Medicine

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Approved by Thesis Committee:

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학위논문 원문제공 서비스에 대한 동의서

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② 본인의 논문을 디지털화하여 인터넷 등 정보통신망을 통한 논문의 일부 또는 전부의 복제.배포 및 전송 시 무료로 제공하는 것에 동의합니다.

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논문제목: Current Smoking is Associated with a Poor Visual Acuity Improvement after Intravitreal Ranibizumab Therapy in Patients with Exudative Age-Related Macular Degeneration

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ABSTRACT

Introduction: In this study, the risk factors that may influence visual improvement after intravitreal ranibizumab (IVR) treatment for exudative age-related macular degeneration (AMD) were examined.

Patients and Methods: From April 2008 to February 2012, 420 patients (448 eyes) with exudative AMD were prospectively registered at Seoul National University Hospital. From this group of patients, 125 eyes were included in this study. All patients were treated with 3 consecutive IVR injections. The best-corrected visual acuity (VA) was evaluated at baseline and 1 month after the third ranibizumab injection. To evaluate the risk factors associated with VA improvement after IVR, patient demographic data and systemic risk factors were analyzed. Patients were divided into a nonresponder group and a responder group, with reference to the median visual improvement in all eyes.

Results: Among 125 eyes, 66 eyes (52.8%) were included in the responder group and 59 eyes (47.2%) in the non-responder group. The median VA improvement after 3 monthly ranibizumab injections was -0.05 logMAR. Multivariate analyses revealed that current smoking (adjusted OR, 7.540; 95% CI, 1.732–32.823) was independently associated with poor VA improvement after IVR treatment for exudative AMD.

Conclusion: Cigarette smoking is an independent risk factor for lower VA gains with IVR treatment for exudative AMD. Therefore, we believe that smoking cessation is important for a better visual outcome in AMD patients who are current smokers.

Keywords: exudative age-related macular degeneration, ranibizumab, cigarette smoking

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INTRODUCTION

Exudative age-related macular degeneration (AMD) is a leading cause of visual loss in the elderly (1), and vascular endothelial growth factor (VEGF) is known to play a key role in the development of choroidal neovascularization (CNV) in eyes with AMD (2). Intravitreal ranibizumab (IVR) injections result in the regression of CNV and improvements in visual acuity (VA) (3, 4). The majority of exudative AMD patients benefit from IVR, but the degree of vision recovery after IVR is variable (5-7). Several studies have suggested potential predictors of visual outcome. The suggested factors include baseline VA, CNV subtype, CNV lesion size, age at the time of ranibizumab treatment, and genetic polymorphism (3, 4, 7-9).

None of the factors that have been suggested to predict visual outcome can be modified by the treating physicians or by the patients. Identifying potential systemic or behavioral risk factors that can influence the visual outcome after anti-VEGF treatment in exudative AMD patients can be as important as the IVR treatment itself. Therefore, we conducted this investigation to identify modifiable systemic and behavioral risk factors that influence visual improvement after IVR in exudative AMD patients.

PATIENTS AND METHODS

The medical records for 448 eyes from 420 patients prospectively registered in an exudative AMD patient cohort between April 2008 and February 2012 at Seoul National University Hospital were reviewed. Inclusion criteria for this study were as follows: (1) exudative AMD that was confirmed by physical examination, fluorescein angiography (FA), and optical coherence tomography (OCT) (CirrusTM; Carl Zeiss Meditec, Dublin, CA, USA); (2) 3 monthly intravitreal ranibizumab (Lucentis®; Novartis, Basel, Switzerland) injections; and (3) an OCT examination 1 month after the third injection. The exclusion criteria included the following: (1) poor compliance to treatment or loss from follow-up, (2) ranibizumab therapy in combination with any other AMD therapy (e.g., photodynamic therapy, intravitreal triamcinolone), (3) any ocular intervention within 3 months of the initial intravitreal ranibizumab injection, and (4) patient refusal to undergo blood sampling.

Hypertension, diabetes mellitus and smoking status, demographic data, and body type data (waist circumference, height, body weight, and body mass index [BMI]) were collected at baseline. Additionally, venous blood samples were drawn from all patients after 12 hours of fasting to examine systemic levels of C-reactive protein (CRP), total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides. Smoking status was also recorded; a current smoker was defined as a patient who was an active smoker at enrollment. Non-smokers included both former smokers (ex-

smoker) and patients who had never smoked (never-smoker).

Best-corrected VA was measured before treatment (pre-treatment) and 1 month after the third IVR injection (post-treatment). All VA measurements were converted to the logarithm of the minimal angle of resolution (logMAR) values for statistical analyses. The change in VA was calculated by subtracting the pre-treatment logMAR VA from the post-treatment value. Based on the median VA change, patients were divided into 2 groups: those who showed a smaller VA improvement than the median value (poor VA improvement group) and those who showed a VA change equal to or better than the median (good VA improvement group).

The CNV subtype was determined using findings from FA, spectral domain OCT and, if applicable, indocyanine green (ICG) angiography. Central macular thickness (CMT), as measured by OCT, was defined as the distance from the internal limiting membrane to Bruch's membrane at the fovea.

Statistical analyses were performed using SPSS software (Ver. 18, SPSS, Chicago, IL, USA). One-way analysis of variance (ANOVA), Student's t-tests, and Fisher's exact tests were performed on data, as applicable. Linear regression analysis and multivariate logistic regression analysis were also performed, adjusting for age, gender, diabetes mellitus and hypertension status, waist circumference, BMI, anticoagulant status, total cholesterol, and initial CMT. This study adhered to the tenets of the Declaration of Helsinki. The institutional review board of Seoul National University Hospital approved the study protocol and all participants provided informed consent

before any study procedures were performed.

RESULTS

Among the 420 registered patients, 123 patients (125 eyes) who underwent blood sampling were included in this analysis. There were 59 eyes (47.2%) that demonstrated a smaller improvement than the median (poor VA improvement group) and 66 eyes (52.8%) that showed an equal or larger improvement than the median (good VA improvement group). The mean and median VA changes after 3 monthly IVR injections were -0.15 ± 0.40 and -0.05 logMAR, respectively.

There were no significant differences in age, gender, waist circumference, height, body weight, BMI, CRP levels, total cholesterol or lipid (triglyceride, low-density lipoprotein, high-density lipoprotein) values, diabetes mellitus status, or hypertension status (Table 1). The proportions of patients taking anticoagulant drugs were also similar between the 2 groups. The only statistically different factor between the 2 groups was the patient's current smoking status (unadjusted OR, 4.81; 95% CI, 1.27–18.2). Eleven (18.6%) patients were current smokers among the 59 patients in the poor VA improvement group, in contrast to 4 (6.1%) among the 66 patients in the good VA improvement group (Figs. 1 and 2).

Although the initial CMT was lower in the good VA improvement group than in the poor VA improvement group, the difference was not statistically significant ($p = 0.09$). However, the final CMT was significantly larger in the poor VA improvement group ($p < 0.001$). The incidences of pigment epithelial detachment, subretinal fluid accumulation, and subretinal

hemorrhage were not significantly different between the 2 groups. The proportions of CNV subtypes were not significantly different between the 2 groups (data not shown).

Multivariate linear regression analysis after adjusting for age, gender, diabetes mellitus and hypertension status, waist circumference, BMI, anticoagulant status, and total cholesterol levels, showed that current smokers had a higher risk of a poor VA improvement ($p = 0.004$). In model 1, stepwise logistic regression revealed an independent association between current smoking (adjusted OR for age, gender, diabetes mellitus and hypertension status, waist circumference, BMI, anticoagulant status, and total cholesterol, 7.303; 95% CI, 1.698–31.414) and poor VA improvement (Table 2). In model 2, stepwise logistic regression suggested an independent association between current smoking (adjusted OR for age, gender, diabetes mellitus and hypertension status, waist circumference, BMI, anticoagulant status, total cholesterol, and baseline CMT, 7.540; 95% CI, 1.732–32.823) and poor VA improvement (Table 2).

Demographic data and risk factors were compared between never-smoker, ex-smoker, and current smoker (Table 3). As a result, male was dominant in ex-smoker and current smoker groups. Waist circumference, height, and body weight were larger in ex-smoker and current smoker than in never-smoker, but there was no difference between these groups with only male patients (data not shown). Total cholesterol, triglyceride, and low-density lipoprotein were significantly higher in current-smoker than never-smoker and ex-smoker in male patients (data not shown). As a result of

separate analysis, there was a significant association between current smoking and poor VA improvement in male patients (adjusted OR, 19.645; 95% CI, 1.709–225.823).

Table 1. Comparison of the poor and good VA improvement groups, divided by median visual acuity improvement (-0.05 log[minimum angle of resolution]).

	Poor VA improvement	Good VA improvement	p-value
Eyes (n)	59	66	---
Age (years)	69.2 ± 7.9	70.7 ± 7.8	0.27*
Gender (M:F)	33:26	38:28	0.86†
Diabetes Mellitus (n)	12	18	0.37†
Hypertension (n)	36	34	0.29†
WC (cm)	86.5 ± 9.2	86.9 ± 9.7	0.80*
Height (cm)	161.8 ± 7.5	160.9 ± 9.7	0.56*
Body weight (kg)	63.8 ± 9.6	61.4 ± 10.2	0.18*
BMI	24.3 ± 2.7	23.7 ± 3.6	0.33*
Anticoagulant users (n)	14	11	0.38†
Ex-smokers (n)	21	27	1.00†
Current smokers (n)	11	3	0.01†
CRP (mg/L)	0.6 ± 1.3 (n = 34)	0.4 ± 0.6 (n = 26)	0.43*
Total cholesterol (mg/dL)	179.0 ± 41.9	186.3 ± 38.3	0.31*
TG (mg/dL)	144.8 ± 86.6	136.2 ± 60.8	0.52*
LDL (mg/dL)	107.0 ± 35.5	109.9 ± 35.8	0.65*
HDL (mg/dL)	50.6 ± 11.4	54.2 ± 15.4	0.13*
Baseline logMAR	0.76 ± 0.59	0.83 ± 0.60	0.52*
Final logMAR	0.90 ± 0.64	0.43 ± 0.42	<0.001*
Change in logMAR VA	0.13 ± 0.24	-0.41 ± 0.34	<0.001*
Baseline CMT (μm)	454.1 ± 309.4	375.1 ± 202.3	0.09*
Final CMT (μm)	372.7 ± 284.7	247.2 ± 135.9	<0.01*
PED (n)	27	26	0.48†
SRF (n)	30	39	0.36†
SRH (n)	35	39	0.98†

BMI = body mass index, CMT = central macular thickness, CRP = C-reactive protein, F = female, HDL = high-density lipoprotein, LDL = low-density lipoprotein, M = male, MAR = minimum angle of resolution, PED = pigment epithelium detachment, SRF = subretinal fluid, SRH = subretinal hemorrhage, VA = visual acuity, WC = waist circumference, *independent t-test, †Fisher's exact test

Table 2. Independent risk factors for poor visual acuity (VA) improvement after intravitreal ranibizumab treatment for exudative age-related macular degeneration.

Risk factor	Model 1		Model 2	
	Poor VA improvement OR (95% CI)*	p-value	Poor VA improvement OR (95% CI)*	p-value
Age	1.032 (0.978–1.089)	0.249	1.033 (0.978–1.092)	0.245
Sex (male)	1.097 (0.405–2.971)	0.856	1.193 (0.433–3.287)	0.732
Diabetes mellitus	0.517 (0.189–1.415)	0.199	0.537 (0.194–1.491)	0.233
Hypertension	1.719 (0.719–4.113)	0.223	1.700 (0.701–4.126)	0.241
WC (per cm)	1.046 (0.974–1.123)	0.219	1.056 (0.982–1.136)	0.142
BMI	0.882 (0.717–1.085)	0.235	0.873 (0.708–1.077)	0.204
Anticoagulant	1.604 (0.538–4.786)	0.397	1.375 (0.448–4.215)	0.578
Smoking status				
Nonsmoker	1		1	
Current smoker	7.303 (1.698–31.414)	0.008	7.540 (1.732–32.823)	0.007
Total cholesterol	1.009 (0.998–1.021)	0.121	1.010 (0.998–1.022)	0.090
Baseline CMT	-	-	0.999 (0.997–1.000)	0.082

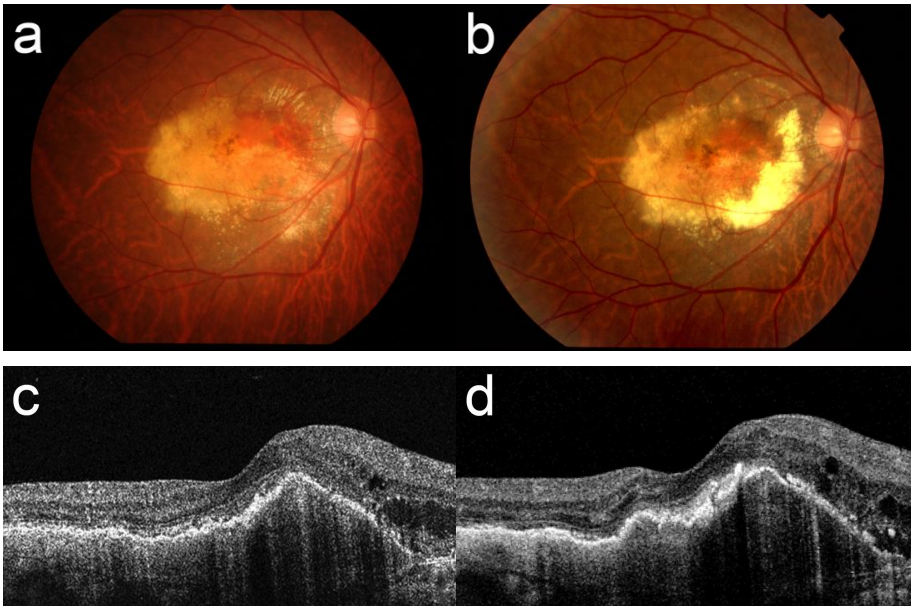
BMI = body mass index, CI = confidence interval, CMT = central macular thickness, OR = odds ratio, WC = waist circumference

Table 3. Comparison of the non-smoker, ex-smoker, and current smoker.

	Never-smoker	Ex-smoker	Current smoker	p-value
Eyes (n)	63	48	14	---
Age (years)	68.4 ± 8.3	72.1 ± 6.9	69.9 ± 8.2	0.051*
Gender (M:F)	13:50	47:1	11:3	<0.001†
Diabetes Mellitus (n)	15	13	2	0.69†
Hypertension (n)	42	23	5	0.04†
WC (cm)	84.5 ± 8,9	89.7 ± 8.9	86.5 ± 10.9	0.014*
Height (cm)	156.9 ± 8.2	166.6 ± 5.6	162.8 ± 9.4	<0.001*
Body weight (kg)	59.4 ± 8.9	66.4 ± 8.5	63.6 ± 14.4	0.001*
BMI	24.2 ± 3.5	23.9 ± 2.5	23.8 ± 3.7	0.850*
Anticoagulant users (n)	9	14	2	0.15†
CRP (mg/L)	0.26 ± 0.7 (n = 32)	0.73 ± 1.4 (n = 19)	0.69 ± 1.3 (n = 9)	0.26*
Total cholesterol (mg/dL)	188.5 ± 33.4	169.0 ± 39.9	204 ± 53.1	0.003*
TG (mg/dL)	135.9 ± 53.6	125.0 ± 57.8	211.8 ± 140.9	<0.001*
LDL (mg/dL)	112.9 ± 30.2	97.9 ± 34.7	125.4 ± 50.3	0.14*
HDL (mg/dL)	52.6 ± 11.0	52.7 ± 16.8	51.8 ± 13.7	0.98*
Baseline logMAR	0.78 ± 0.61	0.77 ± 0.54	0.99 ± 0.71	0.42*
Final logMAR	0.60 ± 0.61	0.64 ± 0.53	0.89 ± 0.63	0.24*
Change in logMAR VA	0.17 ± 0.40	0.13 ± 0.39	0.10 ± 0.44	0.79*
Baseline CMT (μm)	407.4 ± 258.1	425 ± 291.9	391.1 ± 139.9	0.89*
Final CMT (μm)	313.2 ± 230.3	301.7 ± 249.3	292.3 ± 116.8	0.94*
PED (n)	26	23	4	0.47†
SRF (n)	30	30	9	0.23†
SRH (n)	42	24	8	0.19†

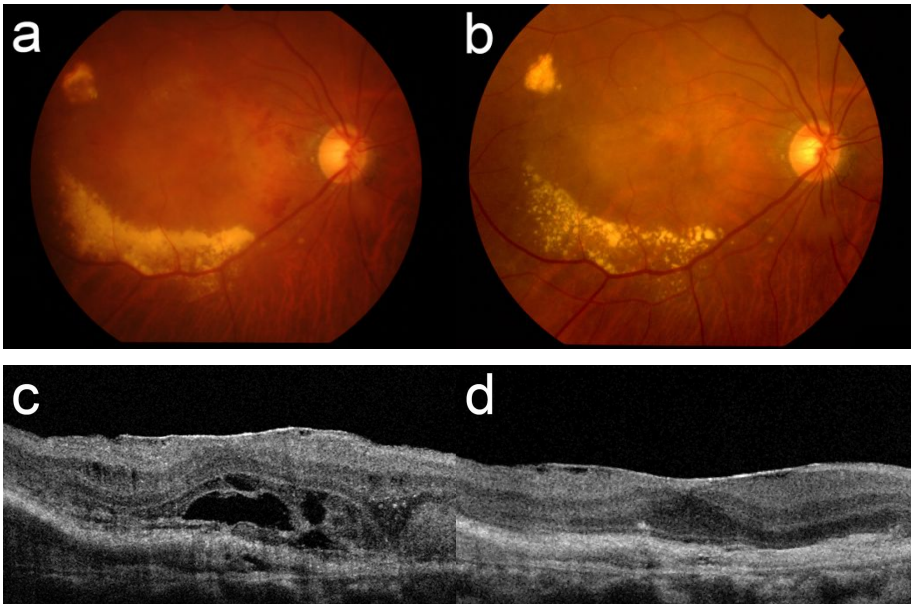
BMI = body mass index, CMT = central macular thickness, CRP = C-reactive protein, F = female, HDL = high-density lipoprotein, LDL = low-density lipoprotein, M = male, MAR = minimum angle of resolution, PED = pigment epithelium detachment, SRF = subretinal fluid, SRH = subretinal hemorrhage, VA = visual acuity, WC = waist circumference, *one-way ANOVA, †Fisher's exact test

Figure 1. Fundus photographs and optical coherence tomography (OCT) images from a 57-year-old male smoker.



a. A baseline fundus photograph shows submacular hemorrhage and exudate. **b.** A post-treatment fundus photograph shows persistent submacular hemorrhage, extensive macular retinal pigment epithelial atrophy, and a disciform scar. Pre- (**c**) and post-treatment (**d**) OCT images show virtually no anatomical improvements following intravitreal ranibizumab treatment.

Figure 2. Fundus photographs and optical coherence tomography (OCT) images of a 73-year-old male ex-smoker.



a. A baseline fundus photograph shows submacular hemorrhage, the choroidal neovascular membrane, and exudate. **b.** A post-treatment fundus photograph shows resolution of the submacular hemorrhage, but choroidal neovascularization and exudate persists. **c.** A baseline OCT image reveals subretinal fluid and a thickened choroidal neovascular membrane. **d.** A post-treatment OCT image shows resolution of the previously observed subretinal fluid and thinning of a now inactive choroidal neovascular membrane.

DISCUSSION

Our data show that current cigarette smoking in exudative AMD patients is associated with a poor VA improvement following IVR therapy. Cigarette smoking increases the risk of developing AMD, with heavier smokers showing an increasingly greater risk of developing AMD (10-12). Additionally, a positive association between current and past smoking history and the development of exudative AMD has been reported (13). Fortunately, smoking cessation reduces the risk of developing AMD and of progression to neovascular AMD (12).

The mechanisms by which cigarette smoking negatively affects the retina are not well known. However, several hypotheses have been suggested. First, cigarette smoking is associated with increased oxidative stress, lipid peroxidation, fibrinogen levels, and platelet aggregation. It is also associated with reduced plasma high-density lipoprotein and antioxidant levels (11, 14, 15). Second, cigarette smoking can cause non-oxidative chemical damage to the retina. Nicotine promotes angiogenesis, both in vitro and in vivo, through nicotine-induced up-regulation of VEGF, a key molecule in the pathogenesis of neovascular AMD (16-19). Cigarette smoking also causes inflammation by activating complement C3 and other inflammatory mediators and reducing serum levels of complement factor H (18). Lastly, cigarette smoking can damage choroidal vessels and diminish choroidal blood flow through atherosclerosis and vasoconstriction, both of which are thought to play a role in AMD development (10, 20).

The effect of cigarette smoking on the response of exudative AMD to IVR treatment has not been widely studied. In our study, current smokers were more than 7 times more likely (adjusted OR, 7.540; 95% CI, 1.732–32.823) to have a poor VA improvement after IVR treatment than their non-smoking counterparts. In contrast, McKibbon et al. (7) reported that smoking status did not significantly affect VA change after IVR treatment, but patients who had never smoked tended to distinguish more letters in vision tests. These varying results may be the result of multiple compounding factors, such as genetic and/or racial differences.

In the present study, significant differences in CMT changes before and after therapy were not observed between current smokers and non-smokers. In addition, the baseline CMT values were not significantly different between the 2 groups. These results are consistent with those of previous reports that indicated that OCT findings are not sufficient to predict functional outcomes (21, 22).

The MARINA and ANCHOR studies showed that important predictors of VA outcomes are baseline VA, CNV lesion size, and age at the time of ranibizumab treatment (3, 4). There were no differences in baseline CMT, baseline logMAR VA and age between never-smoker, ex-smoker, and current smoker. Furthermore, there were no differences in presentation of pigment epithelium detachment, subretinal hemorrhage, and subretinal fluid between these groups. Thus, in current study, the independent risk factor for poor VA improvement is current smoking other than non-modifiable risk factors such as baseline VA, baseline macular lesion, or age. Total cholesterol,

triglyceride, and low-density lipoprotein were high in current smoker in this study. They are not presumed to be predictors of poor visual outcome after IVR treatment. They may have some roles for poor visual outcome, but it is beyond the scope of this study.

Recent studies have also suggested an association between treatment response and genetic polymorphisms (7-9), which are, in most circumstances, not modifiable. In contrast, the present study suggests that an emphasis on smoking cessation before and even during treatment can improve the chances of a good VA response to IVR treatment.

The strength of our study is that it involved a prospective cohort study design, with all patients treated using a standardized protocol of 3 consecutive monthly injections and extensive analysis of numerous potential risk factors, including systemic and behavioral patterns among the exudative AMD patients.

The study, however, also has some limitations. The relatively small number of patients examined in this prospective study may have resulted in missed risk factors that might emerge from analyses of larger groups of patients. And many patients were excluded from initially eligible 420 patients, thus they could not represent the population. Additionally, smoking status was not quantified as pack-years, so we could not determine a smoking dose-response relationship. The relatively short follow-up period also did not allow long-term results to be examined. These limitations indicate that longer studies, involving larger groups of patients, are needed.

In conclusion, current cigarette smoking, a modifiable lifestyle

choice, is an independent risk factor for a poor VA response to IVR used in the treatment of exudative AMD. Therefore, patients should be encouraged to stop smoking as early in their treatment course as possible.

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국문 초록

서론: 본 연구에서는 삼출성연령관련황반변성에서 유리체강내 라니비주맙 치료에 대한 반응에 영향을 주는 교정 가능한 위험인자들을 찾아보고자 한다.

방법: 2008 년 4 월부터 2012 년 2 월 까지 서울대학교병원의 삼출성연령관련황반변성 코호트에 전향적으로 등록된 환자 420 명 448 안 중 125 안의 의무기록을 조사하였다. 환자들은 1 개월 간격으로 3 회 연속으로 유리체강내 라니비주맙 치료를 시행 받았다. 최대교정시력을 주사 전과 3 회 째 주사치료 1 개월 후에 측정하였다. 유리체강내 라니비주맙 치료에 의한 시력호전 정도와 연관을 가진 위험인자를 확인하기 위하여 인구학적 자료 및 전신적인 위험인자를 분석하였다. 환자들은 시력호전정도의 중간값을 기준으로 크게 호전된 군과 적게 호전된 군의 두 군으로 나누어 비교하였다.

결과: 125 안 중에서 66 안 (52.8%)은 크게 호전된 군에 포함되었으며 59 안 (47.2%)는 적게 호전된 군에 포함되었다. 1 개월 간격으로 3 회 연속 유리체강내 라니비주맙 치료 후 시력호전정도의 중간값은 −0.05 logMAR 였다. 다변량분석 결과,

현재 흡연 상태가 삼출성연령관련황반변성에 대한 유리체강내 라니비주맙 치료 후 적은 시력 호전을 보이는 독립적인 위험인자였다 (adjusted OR, 7.540; 95% CI, 1.732–32.823).

결론: 흡연은 삼출성연령관련황반변성에서 유리체강내 라니비주맙 치료에 의한 시력호전을 저해시키는 독립적인 위험인자이다. 그러므로 현재 흡연을 하는 연령관련황반변성 환자는 흡연을 중단하는 것이 나은 시력예후를 위하여 중요하다.

주요어: 라니비주맙, 삼출성연령관련황반변성, 흡연

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