The Effects of Intravitreal Agents on Systemic Vascular Diseases in Patients with Diabetic Retinopathy

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Abstract

Purpose: To assess the risk for cerebrovascular disease (CVD) and coronary artery disease (CAD) in diabetic patients who were treated with intravitreal anti-VEGF agents and compare the rates of CVD and CAD with diabetic controls.

Methods: A retrospective chart review of diabetic patients was performed. The need for intravitreal injection and type of agent were noted. If clinically significant or center-involving diabetic macular edema (DME) were determined, intravitreal anti-VEGF agents were used. The CVD and/or CAD occurred within 6 months of the intravitreal injection were accepted as the main outcomes of the study. The records of diabetic patients who were followed up but not needed intravitreal injections were accepted as the control group of the study. Comparisons between these groups were performed.

Results: The number of patients enrolled in the study was 9751 (5243 female, 4508 male patients). Of these patients, 1261 patients were received various intravitreal injections. Patients who had CVD history were divided into two groups according to whether they received intravitreal injection or not. There was statistically significant difference between these groups in terms of CVD history ($p < 0,001$). There was statistically significant difference in the hazard of CVD between different anti-VEGF treatments ($p < 0,001$). Patients who had CAD history were divided into two groups according to whether they received intravitreal injection or not. There was no statistically significant difference between these groups in terms of CAD history ($p = 0,31$).

Discussion: The risk for CVD was seen to increase with the intravitreal anti-VEGF treatment in diabetic patients. The rate of CVD was higher in patients who received intravitreal bevacizumab treatment.

Introduction

Diabetic retinopathy (DR) is the most common complication of diabetes and is expected that 642 million people will suffer from DR by 2040 [1]. The most common cause of visual impairment due to DR is diabetic macular edema (DME)[2]. The intravitreal administration of anti-vascular endothelial growth factors (VEGF) is commonly used for the treatment of center-involving DME with decreased vision [3]. Two mg every 8 weeks after 5 initial monthly injections of aflibercept and 0,3 mg monthly injection of ranibizumab were approved by US Food and Drug Administration based on VIVID-VISTA and RISE-RIDE clinical trials results, respectively [4, 5]. Off-label use of 1,25 mg intravitreal bevacizumab is also common all over the World [6]. Besides, intravitreal administrations of anti-VEGF agents have been used for proliferative DR [7].

The frequency of intravitreal injections of anti-VEGF agents in diabetic patients has been increased because of the expanding indications. While the increasing rates of intravitreal anti-VEGF injections, the ocular and systemic complications of such a widely performed procedure have been commonly reported [8–10]. Systemic side effects and overall mortality due to anti-VEGF agents were not found to be increased in the short and medium term when compared with either sham group or photocoagulation

treatment in patients with DME [11]. Besides, adverse systemic diseases in patients with proliferative DR were not found to be different when compared with controls [8]. On the other hand, a recent meta-analysis that focused on the patients which had highest-level exposure to anti-VEGF agents, revealed a possible increased risk of death and cerebrovascular accidents. In the same meta-analysis report, no increased risk of myocardial infarction was detected [10].

The aim of the current study was to assess the risk for cerebrovascular diseases (CVD) and coronary artery disease (CAD) in diabetic patients who were treated with intravitreal anti-VEGF agents and compare the rates of CVD and CAD with diabetic controls.

Materials-methods

The present, retrospective study was conducted in a tertiary university hospital. Prior approval from the Institutional Review Board was taken (IRB number:

E-71522473-050.01.04-6071-49 and informed consent was obtained from each subject. The study was performed in adherence to the Declaration of Helsinki.

A retrospective chart review of diabetic patients at the Retinal Disease Department was performed. The chart reviews included medical records between January 2010 and December 2020. The age, sex, serum HbA1c levels, and duration of diabetes mellitus of patients were noted. The need for intravitreal injection and type of agent were also noted. The stage of diabetic retinopathy was noted as proliferative and non-proliferative DR. If clinically significant or center-involving DME were determined, intravitreal anti-VEGF agents were used. The preference of anti-VEGF agent was done according to ophthalmologist decision. The diagnosis of clinically significant DME was done due to ETDRS [12]. Center-involving DME was defined as thickening of the retina at or within 500 μ of the center of the macula [13].

The histories of CVD or CAD in patients after intravitreal injections were noted. The CVD and/or CAD occurred within 6 months of the intravitreal injection were accepted as the main outcomes of the study. The records of diabetic patients who were followed up in Retina Department but not needed intravitreal injections were accepted as the control group of the study. The histories of CVD and CAD in these patients were also noted.

Cerebrovascular diseases were composed of ischemic stroke and hemorrhagic stroke. Coronary artery diseases were composed of myocardial infarction and unstable angina.

Patients with the age below 18 years old, any intraocular surgeries, chronic ocular diseases such as uveitis, glaucoma were excluded from the study. Patients with other retinal diseases such as age related macular degeneration, santral, branch retinal vein occlusion, and choroidal neovascularization.

Statistical analysis was performed by using SPSS statistical software (IBM SPSS Statistics, Version 23.0. Armonk, NY: IBM Corp.) Descriptive analyses were performed to provide information on the general characteristics of the study population. Kolmogorov-Smirnov test was used to evaluate whether the

distributions of numerical variables were normal. The numeric variables were presented as mean $\pm$ standard deviation. Categorical variables were compared by the Chi-Square test. A p-value <0.05 was considered significant.

Results

The number of patients enrolled in the study was 9751 (5243 female, 4508 male patients). The mean age was $65,2 \pm 11,0$ years. The mean HbA1c was $7,6 \pm 1,1$ mmol/l. Of these patients, 1261 patients were received various intravitreal injections because of DME with or without proliferative DR. Of these patients, 855 was diagnosed as CSME and 406 was diagnosed as center-involving DME. (Table 1).

Table 2 reveals the number of patients who had CVD. 25 patients had a diagnosis of ischemic CVD and 1 patient had hemorrhagic CVD diagnosis. Patients who had CVD history were divided into two groups according to whether they received intravitreal injection or not. There was statistically significant difference between these groups in terms of CVD history ($p < 0,001$).

Table 3 reveals the number of patients who had CAD. All patients underwent coronary angiography and coronary stent implantation was performed 28 patients, coronary by pass grafting performed 2 patients. Patients who had CAD history were divided into two groups according to whether they received intravitreal injection or not, again. There was no statistically significant difference between these groups in terms of CAD history ($p = 0,31$).

The possible effect of different anti-VEGF treatment modalities on CVD was also assessed. There was statistically significant difference in the hazard of CVD between different anti-VEGF treatments ($p < 0,001$) (Table 4).

The possible effect of different anti-VEGF treatment modalities on CAD was also assessed and no statistically significant difference was found in the hazard of CVD between different anti-VEGF treatments ($p = 0,84$) (Table 5).

Table 1
Number of diabetic patients who received various intravitreal agent treatments.

	Frequency (n)	Percent (%)
No Intravitreal Agent Use	8490	87,1
Bevacizumab treatment	179	1,8
Ranibizumab treatment	455	4,7
Aflibercept treatment	364	3,7
Bevacizumab+Ranibizumab Treatment	139	1,4
Bevacizumab+aflibercept treatment	44	0,5
Ranibizumab+Aflibercept Treatment	66	0,7
Bevacizumab+Ranibizumab+Aflibercept treatment	14	0,1
Total	9751	100

Table 2
The number of patients who had cerebrovascular diseases history

	No CVD history (n)	CVD history(n)	Percent
No intravitreal treatment	8423	67	0,8
Intravitreal treatment	1235	26	2,1
CVD: cerebrovascular disease. According to Chi-square test, there was significant difference between these groups. $p < 0,001$.			

Table 3
The number of patients who had coronary artery disease history

	No CAD history (n)	CAD history(n)	Percent
No intravitreal treatment	8242	248	2,9
Intravitreal treatment	1228	33	2,6
CAD: coronary artery disease. According to Chi-square test, there was no significant difference between these groups. $p = 0,310$.			

Table 4
Cerebrovascular disease in patients who were received different treatment modalities

	No CVD history (n)	CVD history(n)	Percent (%)
No intravitreal treatment	8422	67	0,8
Bevacizumab treatment	171	8	4,5
Ranibizumab treatment	443	12	2,6
Aflibercept treatment	360	4	1,1
Bevacizumab+Ranibizumab Treatment	137	2	1,4
Bevacizumab+aflibercept treatment	44	0	0
Ranibizumab+Aflibercept Treatment	66	0	0
Bevacizumab+Ranibizumab+Aflibercept treatment	14	0	0
CVD: cerebrovascular disease. According to Chi-square test, there was statistically significant difference among groups ($p<0,001$).			

Table 5
Coronary artery diseases in patients who were received different treatment modalities

	No CAD history (n)	CAD history(n)	Percent (%)
No intravitreal treatment	8242	247	2,9
Bevacizumab treatment	173	6	3,4
Ranibizumab treatment	441	14	3,1
Aflibercept treatment	353	11	3
Bevacizumab+Ranibizumab Treatment	137	2	1,4
Bevacizumab+aflibercept treatment	44	0	0
Ranibizumab+Aflibercept Treatment	65	1	1,5
Bevacizumab+Ranibizumab+Aflibercept treatment	14	0	0
CAD: Coronary artery disease. According to Chi-square test, there was no statistically significant difference among groups (p=0,84).			

Discussion

In the current study, the rate of CVD was higher in diabetic patients who had treated with anti-VEGF agents than diabetic controls. The percentage of patients who had CVDs was 2,1%. Wu et al. was reported that CVDs were seen in 0,5% percent of patients who received intravitreal Bevacizumab treatment. The diagnosis of patients were variable in this study [14]. In a recent meta-analysis, possible increased risk for cerebrovascular accidents was revealed in patients with DME who were treated with intravitreal anti-VEGF agents for 2 years [10]. In our study, the control group was composed of diabetic patients. As reported previously that the risk for cerebrovascular diseases (stroke) was higher in diabetic patients, the comparison between diabetics who received intravitreal anti-VEGF treatment and diabetic controls gave us more accurate results [15]. Maloney et al. compared CVD between diabetic patients who received anti-VEGF agents, argon laser treatment, and steroid treatment. They did not find any increased risk of cerebrovascular diseases within 6 months after intravitreal anti-VEGF treatment. In this study, the cerebrovascular diseases were consisted of ischemic, hemorrhagic stroke and transient ischemic attack [2]. In our study, we investigated only ischemic and hemorrhagic stroke.

In the current study, the risk of CVD was found to be higher in diabetic patients who were treated with intravitreal Bevacizumab. Maloney et al. compared the risk of cerebrovascular diseases after intravitreal bevacizumab, ranibizumab, and aflibercept treatments in diabetic patients. They did not find any

difference among different intravitreal anti-VEGF agents [16]. Cerebrovascular diseases were composed of hemorrhagic, ischemic stroke and transient ischemic attack. Wang et al. compared the incidence of systemic adverse diseases of intravitreal bevacizumab and ranibizumab in patients with age related macular degeneration. They did not find any difference [17]. The severity of diabetes mellitus, the differences in the inclusion criteria and investigation on different retinal diseases might cause variety in the results.

In this current study, the risk of coronary artery diseases after intravitreal anti-VEGF treatment did not increase. In a recent meta-analysis, 24 clinical trials were included which were investigated major cardiovascular diseases in diabetic patients. They did not find any difference in diabetic patients in regards of cardiovascular diseases [18]. In another meta-analysis, ranibizumab and aflibercept treatments were found to not affect the risk for myocardial infarction and arteriotrombotic diseases [10]. Maloney et al. also did not find any increased risk for CAD in diabetic patients treated with intravitreal anti-VEGF agents [2]. All these studies and our study revealed no increased risk for CAD in diabetic patients treated with anti-VEGF agents.

In this study, different types of anti-VEGF agents were also investigated whether they affect the risk for CAD. There was no significant difference between ranibizumab, bevacizumab and aflibercept treatments. Maloney et al. also did not find any increased risk for acute myocardial infarction and cardiovascular diseases with all these treatments [16].

The limitation of this current study was the numeric differences between groups. the retrospective design did not allow us to reach more information about the treatment of diabetic controls. On the other hand, to investigate only one disease (Diabetes Mellitus) treated with intravitreal agents gave us more accurate and reliable results.

In conclusion, the risk for cerebrovascular diseases was increased with the intravitreal anti-VEGF treatment in diabetic patients. The rate of CVD was higher in diabetic patients who received intravitreal bevacizumab treatment. On the other hand, the risk for coronary artery disease did not affect from intravitreal anti-VEGF treatment in diabetic patients.

Statements and Declarations:

Declarations

Funding : This study was not funded by any company.

Compliance with ethical standards: Conflict of interest All authors declare that they have no conflict of interest.

Ethical standard: Prior approval from the Sakarya University Institutional Review Board IRB: 71522473-050.01.04-6071-49 was taken. The study was performed in adherence to the 1964 Declaration of Helsinki.

Informed consent: Written informed consent was obtained from the parents of each subject in the study

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