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SHORT REPORT

Renal function after intravitreal administration of vascular endothelial growth factor inhibitors in patients with diabetes and chronic kidney disease

Yusuke Kameda[1], Tetsuya Babazono[2]*, Yasuko Uchigata[2], Shigehiko Kitano[1]

Departments of [1]Ophthalmology and [2]Medicine, Diabetes Center, Tokyo Women's Medical University School of Medicine, Tokyo, Japan

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***Correspondence**
Tetsuya Babazono
Tel.: +81-3-3353-8111
Fax: +81-3-3358-1941
E-mail address:
babazono.dmc@twmu.ac.jp

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ABSTRACT

The present study aimed to determine whether intravitreal administration of vascular endothelial growth factor inhibitors is associated with deterioration of renal function, as seen with systemic administration, in patients with diabetes and chronic kidney disease. Estimated glomerular filtration rates before and after 160 intravitreal injections of vascular endothelial growth factor inhibitors (aflibercept, bevacizumab or ranibizumab) were compared in 69 patients with diabetes and with a baseline estimated glomerular filtration rate <60 mL/min/1.73 m^2. We also determined the incidence of acute kidney injury. The data showed no significant difference in the estimated glomerular filtration rate before and after vascular endothelial growth factor inhibitor administration in all patients and in patient subgroups based on each inhibitor. Furthermore, no episodes of acute kidney injury occurred. In conclusion, intravitreal administration of vascular endothelial growth factor inhibitors is unlikely to be associated with a deterioration of renal function in patients with diabetes and chronic kidney disease.

INTRODUCTION

Vascular endothelial growth factor (VEGF) inhibitors, which were first used in immunotherapy for several solid cancers, have now attracted attention in the field of ophthalmology as therapies for both macular edema and proliferative retinopathy in patients with diabetes[1]. Recently, safety concerns regarding renal adverse effects have been raised for the use of systemic anti-VEGF therapies, possibly limiting their clinical use in patients with pre-existing chronic kidney disease (CKD)[2–6]. However, information regarding whether intravitreal administration of VEGF inhibitors is associated with renal complications, except in rare instances, is lacking; the intravitreal dose is approximately 150-fold lower than the systemic dose[7,8]. In the clinic, diabetes patients who are candidates for intravitreal anti-VEGF therapy are likely to have CKD, as diabetic retinopathy and nephropathy usually progress in parallel as a result of long-term diabetic microvasculopathy[9]. We carried out the present observational study to determine whether intravitreal VEGF inhibitors are associated with a deterioration in renal function in patients with diabetes and CKD.

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METHODS

Study design and participants

This was a single-center, historical cohort study. The protocol was approved by the ethics committee of Tokyo Women's Medical University School of Medicine, Tokyo, Japan. The study included consecutive patients with diabetes who received one of the three commonly used intravitreal VEGF inhibitors; that is, aflibercept (Eylea; Regeneron Pharmaceuticals Inc., Tarrytown, NY, USA), bevacizumab (Avastin; Genentech Inc., South San Francisco, CA, USA) and ranibizumab (Lucentis; Genentech Inc.), at the Department of Ophthalmology, Diabetes Center, Tokyo Women's Medical University School of Medicine, between 1 August 2008 and 30 September 2016; those who had both baseline (within 30 days before injection) and follow-up (within 30 days after injection) measurements of serum creatinine were identified. Finally, those with a baseline estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 were included in the present study. If patients received multiple intravitreal injections

of VEGF inhibitors, they were analyzed independently on a per-subject basis. After providing written informed consent, each patient was injected with either 2.0 mg of aflibercept, 1.25 mg of bevacizumab or 0.5 mg of ranibizumab, into the vitreous cavity through the pars plana, 3.0–4.0-mm posterior to the limbus, using a 30-G needle under sterile conditions.

Measurements and study end-point

Renal function was assessed by eGFR, which was proposed by the Japanese Society of Nephrology: eGFR = 194 × age (years)$^{-0.287}$ × serum creatinine level (mg/dL) $^{-1.094}$ × (0.739, if female)[10]. The primary end-point was the change in eGFR after the injections. The secondary end-point was the incidence of acute kidney injury (AKI) events, which were defined as an increase in serum creatinine levels ≥0.3 mg/dL within 48 h after the injection, or ≥1.5-fold the baseline value within 7 days post-injection, according to the Kidney Disease Improving Global Outcomes Clinical Practice Guideline for AKI[11].

Statistical analysis

Statistical analysis was carried out using JMP software, version 12.1.0 (SAS Institute Inc., Cary, NC, USA). All data are expressed as the mean ± standard deviation (and range). A paired *t*-test was used to compare the pre- and post-injection values. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 69 diabetes patients (47 men and 22 women) who received 160 injections met the inclusion criteria for enrollment. The mean age (±standard deviation) was 54 ± 14 years (range 26–81 years). Among them, 32 aflibercept injections were given to 13 patients, 90 bevacizumab injections to 36 patients and 38 ranibizumab injections to 20 patients. Serum creatinine levels were determined 11 ± 10 days (range 0–30 days) before the injection, and 16 ± 10 days (range 1–30 days) after the injection.

Overall, no significant changes in eGFR were observed after the 160 injections (32.1 ± 14.9 mL/min/1.73 m^2 and 32.3 ± 15.6 mL/min/1.73 m^2, respectively; $P = 0.594$) in 69 patients when compared with before the injections (Table 1).

In the CKD stage subgroup analysis, no significant differences were observed in eGFR before and after the injections, respectively: 45.6 ± 8.87 mL/min/1.73 m^2 and 46.2 ± 9.66 mL/min/1.73 m^2 for 77 injections in 40 patients with stage 3 CKD ($P = 0.380$), 21.6 ± 4.05 mL/min/1.73 m^2 and 21.4 ± 4.74 mL/min/1.73 m^2 for 66 injections in 31 patients with stage 4 CKD ($P = 0.539$), and 12.0 ± 2.36 mL/min/1.73 m^2 and 11.7 ± 2.58 mL/min/1.73 m^2 for 17 injections in 11 patients with stage 5 CKD ($P = 0.445$).

The subgroup analysis of each VEGF inhibitor also showed no significant differences in the eGFR (Table 1). No cases of AKI developed in association with 51 injections in 32 patients including 12 injections in nine patients within 2 days post-injection, in whom serum creatinine levels were measured within 7 days after the injections. The eGFR also did not significantly decrease after the injections in these subgroups, respectively: 28.8 ± 13.3 mL/min/1.73 m^2 and 30.1 ± 14.0 mL/min/1.73 m^2 for the group measured within 7 days after the injection ($P = 0.006$), and 30.0 ± 13.9 mL/min/1.73 m^2 and 31.0 ± 13.9 mL/min/1.73 m^2 for the group measured within 2 days after the injection ($P = 0.332$).

DISCUSSION

The current study showed that the mean eGFR did not change after intravitreal administration of any of the three VEGF inhibitors, suggesting that anti-VEGF therapy used in the field of ophthalmology does not affect renal function, even in patients with diabetes and pre-existing reduced eGFR.

Renal adverse effects associated with systemic anti-VEGF therapy are well documented, although the mechanisms are still debated[2–6]. *In vitro* studies have reported that VEGF in the kidney, which was highly expressed by the podocytes and activates VEGF receptor 2 on glomerular capillary endothelial cells, plays an important role in maintaining normal glomerular structure and function, and its inhibition might be associated with endothelial dysfunction and podocyte dysregulation[2–5,12]. The doses of the intravitreously administered VEGF inhibitors in the present study were much lower than those administered intravenously[13]; however, aflibercept and ranibizumab could be detected in the glomerular capillaries in monkeys after one intravitreal injection[14]. In addition, a few cases of AKI events after intravitreal anti-VEGF therapy have been reported, although we were unable to explain the differences observed between the current study and the AKI cases[7,8]. Therefore,

Table 1 | Changes in estimated glomerular filtration rate before and after intravitreous vascular endothelial growth factor inhibitor injection

VEGF inhibitors	No. injections	No. patients	eGFR (mL/min/1.73 m^2)		*P*-value
			Before injection	After injection	
Overall	160	69	32.1 ± 14.9	32.3 ± 15.6	0.594
Aflibercept	32	13	27.4 ± 14.2	27.1 ± 15.2	0.593
Bevacizumab	90	36	32.0 ± 13.6	32.4 ± 14.2	0.410
Ranibizumab	38	20	36.5 ± 17.4	36.5 ± 18.1	0.952

Estimated glomerular filtration rate (eGFR) before and after intravitreous injection of each vascular endothelial growth factor (VEGF) inhibitor was compared using paired *t*-test.

monitoring of renal function should be recommended, even in patients receiving intravitreal anti-VEGF therapy. In the current historical cohort study, we were unable to obtain data on clinical characteristics, such as blood pressure and proteinuria, which were associated with outcomes induced by systemic anti-VEGF therapy.

The current study had some limitations. First, the number of patients was relatively small, especially those who received aflibercept and ranibizumab injections. Second, because this was a historical study, an *a priori* power analysis was not carried out. Third, we used follow-up serum creatinine values that were measured at varying intervals after the injections, raising the possibility that we missed the peak creatinine value. Finally, we measured eGFR within just 30 days after intravitreal administration of VEGF inhibitors; therefore, we did not follow any longitudinal changes in renal dysfunction.

Nevertheless, the current study suggested that intravitreal VEGF inhibitors can be administered safely to diabetes patients who have a decreased eGFR. Prospective studies are required to confirm these results and to assess the long-term effects.

DISCLOSURE

The authors declare no conflict of interest.

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