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The Association of Intravitreal Anti-VEGF Injections With Kidney Function in Diabetic Retinopathy

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Purpose: To examine whether patients with diabetic retinopathy receiving intravitreal anti-VEGF injections are at increased risk of kidney function decline.

Design: Retrospective cohort study.

Participants: Included 187 patients who received intravitreal anti-VEGF injections for proliferative diabetic retinopathy (PDR) and/or diabetic macular edema (DME), and 929 controls with non-PDR who did not receive injections, at a large tertiary care center in Chicago, Illinois.

Methods: We queried our institutional enterprise data warehouse to identify patients with diabetic retinopathy, determined whether they received intravitreal anti-VEGF injections, and followed kidney function for all patients over time.

Main Outcome Measures: We assessed time to sustained 40% decline in estimated glomerular filtration rate (eGFR) from baseline in patients receiving intravitreal anti-VEGF injections and compared it with controls using Kaplan-Meier and multivariable adjusted Cox proportional hazards regression models.

Results: This study included 1116 patients (565 female [50.6%]; mean [standard deviation {SD}] age, 57.3 [13.6] years; mean [SD] eGFR, 65.3 [32.1] ml/min/1.73 m^2). Of these, 187 patients received $\geq$ 1 intravitreal anti-VEGF injection (mean [SD], 11.4 [13.1] injections) for PDR and/or DME, and 929 controls with non-PDR received no injections. Intravitreal anti-VEGF injection use was not associated with an increased risk of kidney function decline (hazard ratio [HR], 1.44; 95% confidence interval [CI], 0.97−2.15). Subgroup analyses revealed that use of intravitreal anti-VEGF injections was associated with increased risk of kidney function decline in male patients (HR, 1.87; 95% CI, 1.11−3.14) but not female patients (HR, 0.97; 95% CI, 0.50−1.89). Intravitreal anti-VEGF injection use was also associated with an increased risk of kidney function decline in patients with baseline eGFR $>$ 30 ml/min/1.73 m^2 (HR, 1.86; 95% CI, 1.15−3.01), but not in individuals with baseline eGFR $\leq$ 30 ml/min/1.73 m^2 (HR, 0.97; 95% CI, 0.45−2.10). Among patients who received injections, receiving $\geq$ 12 injections was not associated with risk of kidney function decline (HR, 1.13; 95% CI, 0.52−2.49).

Conclusions: Intravitreal anti-VEGF injections for patients with diabetic retinopathy are overall well-tolerated with respect to kidney function, but the use of intravitreal anti-VEGF injections was associated with an increased risk of kidney function decline in certain subgroups of patients.

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Intravitreal anti-VEGF therapy has revolutionized the treatment paradigms for numerous retinal conditions and is now widely used in the treatment of sight-threatening complications of diabetic retinopathy, including proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME).[1−5] Aflibercept and ranibizumab have been approved by the United States Food and Drug Administration to treat both PDR and DME, while bevacizumab is commonly used off-label as a cost-effective alternative. Since there is widespread adoption of these agents in the treatment of diabetic retinopathy, investigation of the potential toxicities related to their use is essential to improve the care of patients with diabetic retinopathy.

Prior studies demonstrated that patients who received systemic administration of anti-VEGF agents developed arterial thromboembolic events, proteinuria, and worsening hypertension.[6,7] Possible mechanisms of kidney injury include glomerular thrombotic microangiopathy, endothelial dysfunction, and microvascular dysfunction.[8] Though these agents are administered intravitreally in relatively small doses, limited case reports suggested a potential association between intravitreal anti-VEGF administration and kidney

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function decline.[9–12] While a recent retrospective cohort study suggested that there is no increased risk of major adverse cardiovascular events with intravitreal therapy,[13] less is known about the risk of kidney function decline in a large cohort of patients with proliferative diabetic retinopathy and/or DME. To address this, we performed an institutional retrospective cohort study of patients with diabetic retinopathy to examine the association of intravitreal anti-VEGF injections with the risk of kidney function decline.

Methods

Study Population

We queried the Northwestern Medicine Enterprise Data Warehouse from February 1, 2008, to September 30, 2017, and identified all patients over 18 years of age with type 1 or type 2 diabetes mellitus using *International Classification of Diseases, Ninth or 10th Revision* codes base 250 and base E11. Records were reviewed until the time of death, date of last contact with the health care system, or the study end date, whichever came first. We excluded pregnant patients, dialysis patients, and kidney transplant recipients. The study is in accordance with the principles of the Declaration of Helsinki and was approved by the institutional review board at Northwestern University with a waiver of informed consent. All data except dates were de-identified.

Injection Cohort

The injection cohort consisted of patients who received $\geq$ 1 unilateral or bilateral intravitreal injections of bevacizumab, ranibizumab, or aflibercept for PDR and/or DME, determined by identification of a current procedural terminology code 67028 associated with a primary diagnosis of PDR and/or DME. To define baseline kidney function and account for glycemic control, we included patients who had a serum creatinine and hemoglobin A1C (HbA1C) value within a year prior to their first injection.

Control Cohort

The control cohort consisted of patients with nonproliferative diabetic retinopathy (NPDR) by *International Classification of Diseases, Ninth or 10th Revision* codes who did not receive intravitreal injections (Table S3). To assess baseline kidney function and account for glycemic control, we included patients who had a serum creatinine and HbA1C value within a year prior to their first evaluation of NPDR.

Exposure and Outcomes

The primary exposure was the use of intravitreal anti-VEGF injections for treatment of PDR and/or DME compared to no injection for the NPDR control group. The primary outcome was kidney function decline, defined as a sustained 40% decline in estimated glomerular filtration rate (eGFR) from baseline, which is consistent with expert consensus and utilized in international clinical trials for the outcome of kidney failure.[14] We used the creatinine-based Chronic Kidney Disease Epidemiology Collaboration 2009 equation to calculate eGFR.[15] Sustained 40% eGFR decline was defined as 3 consecutive eGFR values that were at least 40% lower from the baseline eGFR value over a period of $\geq$ 3 months.

Covariate Ascertainment

We collected patients' information at the time of the baseline visit, including demographics (age, sex, and race), medical history (hypertension, heart failure, and proteinuria), pertinent laboratory data (HbA1C and eGFR), and medications that may impact kidney function (anti-hypertensive medications, nonsteroidal anti-inflammatory drugs, diuretics, antidiabetic agents, antimicrobials, antireflux agents, immunosuppressants, systemic anti-VEGF agents, aspirin, digoxin, lithium, pamidronate, probenecid, phenytoin, and contrast dye). We used *International Classification of Diseases, Ninth or 10th Revision* codes to define comorbid conditions (Table S4). Table S5 shows generic names used to classify medications.

Statistical Analysis

Descriptive statistics were summarized as mean $\pm$ standard deviation (SD) for continuous variables, and frequency distribution is presented with percentages for categorical variables. We used Fisher exact test and chi-square tests to compare frequency distributions of categorical variables between 2 and multiple group comparisons, respectively. For evaluations between continuous variables and cohorts, we used *t* tests. We performed Kaplan-Meier time-to-event analyses to examine the risk for the outcome with differences assessed by the log-rank test. We used Cox proportional hazards regression models to investigate the association of intravitreal anti-VEGF injection use for PDR and/or DME compared to no injection use for NPDR with the outcome. We adjusted for baseline covariates including age, sex, race, hypertension, medications, HbA1C, proteinuria, and baseline eGFR. We performed prespecified subgroup analyses to assess whether the association between the use of intravitreal anti-VEGF injections and kidney function decline differed by sex or baseline eGFR ($>$ 30 vs. $\leq$ 30 ml/min/1.73 m^2). Among patients who received intravitreal anti-VEGF injections, we performed an additional prespecified subgroup analysis to evaluate whether the use of $>$ 12 intravitreal injections was associated with kidney function decline. We confirmed no violations of the proportional hazards assumption through assessment of Schoenfeld residuals. All statistical tests were 2-sided, and P values < 0.05 were considered significant. All analyses were conducted using R version 3.6.0.

Results

Baseline Characteristics of Study Population

We identified a total of 187 patients (97 female [51.9%]) who received $\geq$ 1 intravitreal anti-VEGF injection for PDR and/or DME, and 929 patients (468 female [50.4%]) with NPDR who did not receive intravitreal anti-VEGF therapy, from February 2008 to September 2017. Patients who had PDR and/or DME received a mean (SD) of 11 (13) injections over a mean (SD) of 21 (24) months. Median (interquartile range) time from baseline eGFR measurement to first intravitreal anti-VEGF injection was 53 (18.5–104.5) days. Median (interquartile range) time between injections was 35 (28–56) days.

Table 1 shows the baseline characteristics of patients who did and did not receive intravitreal anti-VEGF injections. Patients who had PDR and/or DME and received intravitreal anti-VEGF injections were older (mean [SD] age, 59.3 [12.5] vs. 57.0 [13.8] years; $P = 0.03$), had a lower baseline eGFR (58.0 [31.0] vs. 66.8 [32.2] ml/min/1.73 m^2; $P = 0.001$), and had a greater prevalence of hypertension (94.1% vs. 75.1%; $P < 0.001$), heart failure (16.6% vs. 10.4%; $P = 0.02$), chronic kidney disease (CKD)

Table 1. Baseline Characteristics of Study Participants

	Injection Cohort (n = 187)	Control Cohort (n = 929)	*P* Value
Age, mean (SD), years	59.3 (12.5)	57.0 (13.8)	0.027
Female (%)	97 (51.9)	468 (50.4)	0.770
Race (%)			0.062
White	79 (42.4)	438 (47.1)	
Black	69 (36.9)	263 (28.3)	
Other	39 (20.9)	228 (24.5)	
Medical history (%)			
Hypertension	176 (94.1)	698 (75.1)	< 0.001
Heart failure	31 (16.6)	97 (10.4)	0.023
Proteinuria	62 (33.2)	93 (10.0)	< 0.001
Medications (%)			
Anti-hypertensives	167 (89.3)	784 (84.4)	0.107
NSAIDs	132 (70.6)	621 (66.8)	0.362
Other nephrotoxic medications*	118 (63.1)	624 (67.2)	0.322
HbA1C, %	8.06 (1.93)	8.37 (2.16)	0.069
Baseline eGFR, ml/minutes/1.73 m^2	58.0 (31.0)	66.8 (32.2)	0.001

DME = diabetic macular edema; eGFR = estimated glomerular filtration rate (calculated via Chronic Kidney Disease Epidemiology Collaboration 2009 formula); HbA1C = hemoglobin A1C value; NPDR = nonproliferative diabetic retinopathy; NSAIDs = non-steroidal anti-inflammatory drugs; PDR = proliferative diabetic retinopathy; SD = standard deviation.
The injection cohort consists of patients who received anti-VEGF injections for PDR and/or DME. The control cohort consists of patients with NPDR who did not receive anti-VEGF injections.
Data presented as count (percentage) and mean (SD).
*Diuretics, antidiabetic agents, antimicrobials, anti-reflux agents, immunosuppressants, systemic anti-VEGF agents, aspirin, digoxin, lithium, pamidronate, probenecid, phenytoin, and contrast dye.

(50.8% vs. 37.6%; $P = 0.001$), and proteinuria (33.2% vs. 10.0%; $P < 0.001$) compared to patients with NPDR who did not receive intravitreal anti-VEGF injections.

Association of Intravitreal Anti-VEGF Injections with Kidney Function Decline

The mean follow-up time was approximately 46 months in the control cohort and 34 months for the injection cohort. During the study period, 33 patients with PDR and/or DME (17.6%) and 131 patients with NPDR (14.1%) experienced a sustained 40% eGFR decline. Intravitreal anti-VEGF use in patients with PDR and/or DME was associated with an increased risk of kidney function decline (log rank $P = 0.006$) (Fig 1). Figure 2 shows the multivariable adjusted association of intravitreal anti-VEGF therapy with kidney function decline. Age, sex, hypertension, use of nephrotoxic medications, baseline eGFR, baseline HbA1C, and proteinuria were significantly associated with kidney function decline and confounded the association between the use of intravitreal anti-VEGF injections and kidney function decline. In the fully multivariable adjusted model, the use of intravitreal anti-VEGF injections was associated with a nominally higher, but statistically nonsignificant, risk of kidney function decline (hazard ratio [HR], 1.44; 95% confidence interval [CI], 0.97−2.15).

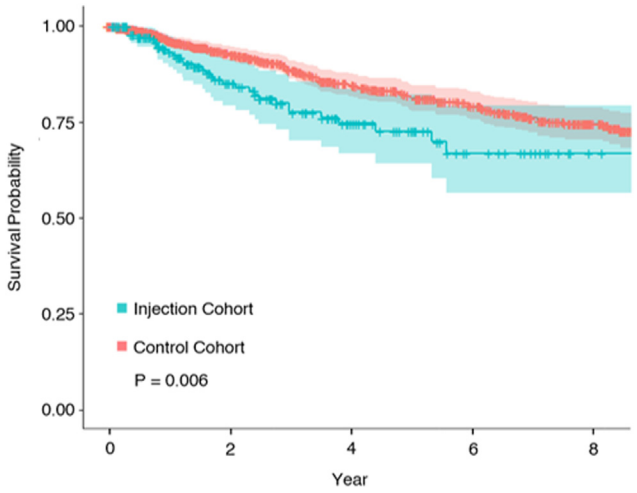

Figure 1. Time to sustained 40% decline in estimated glomerular filtration rate by intravitreal anti-VEGF injection use.

Subgroup Analyses

We performed prespecified subgroup analyses to understand whether the association of intravitreal anti-VEGF therapy with kidney function decline differed by sex or baseline kidney function. Table 2 shows the multivariable adjusted associations of intravitreal anti-VEGF injection use with kidney function decline stratified by sex, baseline kidney function (> 30 vs. ≤ 30 ml/min/1.73 m^2), and number of injections. Intravitreal anti-VEGF injection use was associated with kidney function decline in males (HR, 1.87; 95% CI, 1.11−3.14) but not females (HR, 0.97; 95% CI, 0.50−1.89) in multivariable adjusted models. Intravitreal anti-VEGF injection therapy was also associated with kidney function decline in patients who had a baseline eGFR > 30 ml/min/1.73 m^2 (HR, 1.86; 95% CI,

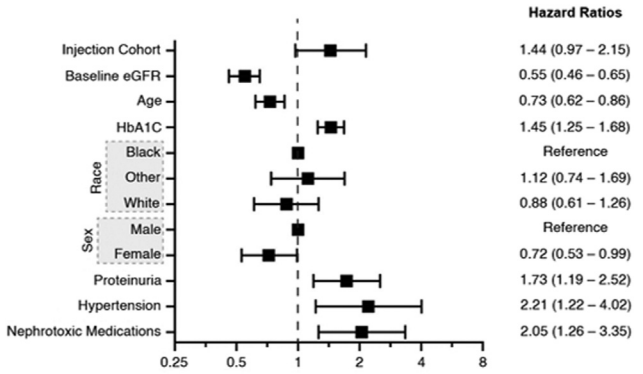

Figure 2. Association of anti-VEGF therapy with kidney function decline. eGFR = estimated glomerular filtration rate; HbA1C = hemoglobin A1C.

1.15−3.01), but not in patients who had a baseline eGFR $\leq$ 30 ml/min/1.73 m^2 (HR, 0.97; 95% CI, 0.45−2.10). Among patients who received injections for PDR and/or DME, there was no significant difference between patients who received $\geq$ 12 or $<$ 12 injections (HR, 1.13; 95% CI, 0.52−2.49).

Discussion

In this retrospective cohort study of individuals with diabetic retinopathy, the use of intravitreal anti-VEGF injections was not significantly associated with kidney function decline. In exploratory prespecified analyses, we found that specific subgroups including male patients and those with a baseline eGFR $>$ 30 ml/min/1.73 m^2 may have an increased risk of kidney function decline. Our findings warrant additional research to investigate whether intravitreal anti-VEGF injections worsen kidney function in specific subgroups of patients with diabetic retinopathy.

Intravitreal anti-VEGF injections are effective treatments for PDR and DME that function by inhibiting VEGF-induced neovascularization and increased vascular permeability. Prior studies have demonstrated that intravitreal anti-VEGF injections may enter the systemic circulation, which results in significant suppression of serum VEGF levels[16−18] and poses an increased risk to highly vascular organs dependent on VEGF signaling. In the kidney, VEGF is physiologically expressed by podocytes and activates receptors on glomerular endothelial cells.[19] Disruption of this interaction results in endotheliosis, impairment of glomerular filtration, and proteinuria.[8] Kidney biopsies of patients treated with systemic anti-VEGF therapy demonstrated features of subacute thrombotic microangiopathy, which may suggest a potential mechanism for the pathogenesis of anti-VEGF-induced kidney injury.[20] Thus, anti-VEGF agents may impair kidney function in susceptible patients even when administered via intravitreal injection. Given the widespread use of intravitreal anti-VEGF injections, with potential expansion to other indications such as moderately severe to severe NPDR,[21] further research is needed to determine whether additional monitoring is necessary to reduce the risk of kidney function decline.

A recent cohort study analyzed the effects of intravitreal anti-VEGF injections on cardiovascular outcomes and found no association with increased risk of myocardial infarction or stroke.[13] Our findings also suggest that anti-VEGF injections are overall well-tolerated with respect to kidney function. Interestingly, we did not identify a dose effect, as the subgroup receiving $\geq$ 12 intravitreal anti-VEGF injections did not demonstrate an increased risk of sustained decline in kidney function compared with the subgroup receiving $<$ 12 injections. This may suggest an association with kidney function decline in certain predisposed individuals, regardless of the number of injections received.

Our exploratory subgroup analyses found that the use of intravitreal anti-VEGF injections may be associated with kidney function decline in men and patients without advanced CKD (eGFR $>$ 30 ml/min/1.73 m^2). Our finding of a sex-related disparity is consistent with other studies that have also shown sex-related disparities in CKD progression

Table 2. Association of Intravitreal Anti-VEGF Injection Use With Kidney Function Decline Among Subgroups

	N	N Events	HR	95% CI	*P* Value
Sex*					
Male	551	85	1.87	1.11−3.14	0.02
Female	565	79	0.97	0.50−1.89	0.92
eGFR*					
$>$ 30	923	117	1.86	1.15−3.01	0.01
$\leq$ 30	193	47	0.97	0.45−2.10	0.95
Number of injections†					
$\geq$ 12 vs. $<$ 12	187	33	1.13	0.52−2.49	0.76

CI = confidence interval; DME = diabetic macular edema; eGFR = estimated glomerular filtration rate (calculated via Chronic Kidney Disease Epidemiology Collaboration 2009 formula); HbA1C = hemoglobin A1C value; HR = hazard ratio; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy.

*HR compares patients receiving intravitreal anti-VEGF injections for PDR and/or DME to control patients with NPDR not receiving injections. Models adjusted for baseline eGFR, age, HbA1C, race, proteinuria, heart failure, hypertension, and use of nephrotoxic medications.

†HR compares patients receiving $\geq$ 12 anti-VEGF injections for PDR and/or DME to those receiving $<$ 12 injections for PDR and/or DME. Model adjusted for baseline eGFR, age, HbA1C, sex, and proteinuria.

where women have a lower risk of progression compared with men, possibly due to differential effects of sex hormones or sex-related differences in lifestyle factors.[22–24] Our finding of a stronger association among those without advanced CKD is interesting, as patients with more advanced CKD are generally at greater risk of progression.[25] A potential explanation is that in the setting of more preserved eGFR, any deleterious effect of intravitreal anti-VEGF therapy may be more significant than that at lower levels of kidney function, when other factors that contribute to CKD progression may be more important. Further research is needed to identify subgroups of patients who receive intravitreal anti-VEGF injections at risk of kidney function. If our findings are confirmed, follow-up studies should determine whether frequent monitoring of kidney function is warranted in certain at-risk subpopulations, and whether treatment adjustments such as reduced frequency of injections may be appropriate.

The strengths of our study include the use of a large cohort of patients with diabetic retinopathy and follow-up data to assess change in kidney function over time. However, our study has several limitations that need consideration. Although we adjusted for multiple covariates, the retrospective nature and use of administrative codes may lead to residual confounding of unmeasured covariates. Our results emanated from a single academic center and must be interpreted with caution. Although our study included a relatively large sample size, the follow-up time was relatively short, which may limit our ability to detect the long-term implications of intravitreal anti-VEGF agents on kidney function. We were unable to evaluate the effects of the different intravitreal anti-VEGF agents on kidney function due to our sample size, though this should be investigated in follow-up studies. We were further unable to account for severity of NPDR among controls, or for severity of PDR and/or DME among those receiving injections. Since individuals with more severe ophthalmic microvascular disease may also be at increased risk of kidney microvascular disease, this should also be investigated in future studies.

Conclusions

In this exploratory analysis, use of intravitreal anti-VEGF injections was not associated with kidney function decline in all patients with diabetic retinopathy but may be associated with kidney function decline in men and patients without advanced CKD. Ophthalmologists should have heightened awareness of the potential for kidney injury and consider co-ordinating care with nephrologists and primary care physicians to monitor kidney function in patients receiving these injections. Ultimately, further prospective studies are needed to confirm these findings and identify specific cohorts of patients at particularly high risk for kidney function decline with intravitreal anti-VEGF therapy.

Footnotes and Disclosures

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HUMAN SUBJECTS:

Human Subjects data were used in this study. The study is in accordance with the principles of the Declaration of Helsinki and was approved by the institutional review board at Northwestern University with a waiver of informed consent. All data except dates were de-identified. No animal subjects were used in this study.

Author Contributions:

Conception and design: Bunge, Dalal, Gray, Culler, Brown, Quaggin, Srivastava, Gill

Data Collection: Bunge, Dalal, Culler

Analysis and interpretation: Bunge, Dalal, Gray, Culler, Brown, Quaggin, Srivastava, Gill

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Abbreviations and Acronyms:
CI = confidence interval; **CKD** = chronic kidney disease; **DME** = diabetic macular edema; **eGFR** = estimated glomerular filtration rate; **HbA1C** = hemoglobin A1C; **HR** = hazard ratio; **NPDR** = nonproliferative diabetic retinopathy; **PDR** = proliferative diabetic retinopathy; **SD** = standard deviation.

Keywords:
diabetic retinopathy, diabetic macular edema, intravitreal injections, anti-vascular endothelial growth factor, anti-VEGF.

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References

1. Diabetic Retinopathy Clinical Research Network, Elman MJ, Aiello LP, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema. *Ophthalmology*. 2010;117:1064−1077.e35.
2. Writing Committee for the Diabetic Retinopathy Clinical Research Network, Gross JG, Glassman AR, et al. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA*. 2015;314:2137−2146.
3. Gross JG, Glassman AR, Liu D, et al. Five-year outcomes of panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA Ophthalmol*. 2018;136:1138−1148.
4. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology*. 2012;119:789−801.
5. Heier JS, Korobelnik JF, Brown DM, et al. Intravitreal aflibercept for diabetic macular edema: 148-week results from the VISTA and VIVID studies. *Ophthalmology*. 2016;123:2376−2385.
6. Scappaticci FA, Skillings JR, Holden SN, et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. *J Natl Cancer Inst*. 2007;99:1232−1239.
7. Li M, Kroetz DL. Bevacizumab-induced hypertension: clinical presentation and molecular understanding. *Pharmacol Ther*. 2018;182:152−160.
8. Izzedine H, Massard C, Spano JP, et al. VEGF signalling inhibition-induced proteinuria: mechanisms, significance and management. *Eur J Cancer*. 2010;46:439−448.
9. Hanna RM, Barsoum M, Arman F, et al. Nephrotoxicity induced by intravitreal vascular endothelial growth factor inhibitors: emerging evidence. *Kidney Int*. 2019;96:572−580.
10. Hanna RM, Abdelnour L, Hasnain H, et al. Intravitreal bevacizumab-induced exacerbation of proteinuria in diabetic nephropathy, and amelioration by switching to ranibizumab. *SAGE Open Med Case Rep*. 2020;8:2050313X20907033.
11. Touzani F, Geers C, Pozdzik A. Intravitreal injection of anti-VEGF antibody induces glomerular endothelial cells injury. *Case Rep Nephrol*. 2019;2019:2919080.
12. Cheungpasitporn W, Chebib FT, Cornell LD, et al. Intravitreal antivascular endothelial growth factor therapy may induce proteinuria and antibody mediated injury in renal allografts. *Transplantation*. 2015;99:2382−2386.
13. Dalvin LA, Starr MR, AbouChehade JE, et al. Association of intravitreal anti-vascular endothelial growth factor therapy with risk of stroke, myocardial infarction, and death in patients with exudative age-related macular degeneration. *JAMA Ophthalmol*. 2019;137:483−490.
14. Levey AS, Inker AL, Matsushita K, et al. GFR decline as an end point for clinical trials in CKD: a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. *Am J Kidney Dis*. 2014;64:821−835.
15. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604−612.
16. Avery RL, Castellarin AA, Steinle NC, et al. Systemic pharmacokinetics following intravitreal injections of ranibizumab, bevacizumab or aflibercept in patients with neovascular AMD. *Br J Ophthalmol*. 2014;98:1636−1641.
17. IVAN Study Investigators, Chakravarthy U, Harding SP, et al. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. *Ophthalmology*. 2012;119:1399−1411.
18. Zehetner C, Kirchmair R, Huber S, et al. Plasma levels of vascular endothelial growth factor before and after intravitreal injection of bevacizumab, ranibizumab and pegaptanib in patients with age-related macular degeneration, and in patients with diabetic macular oedema. *Br J Ophthalmol*. 2013;97:454−459.
19. Schrijvers BF, Flyvbjerg A, De Vriese AS. The role of vascular endothelial growth factor (VEGF) in renal pathophysiology. *Kidney Int*. 2004;65:2003−2017.
20. Pfister F, Amann K, Daniel C, et al. Characteristic morphological changes in anti-VEGF therapy-induced glomerular microangiopathy. *Histopathology*. 2018;73:990−1001.
21. Brown DM, Wykoff CC, Boyer D, et al. Evaluation of intravitreal aflibercept for the treatment of severe nonproliferative diabetic retinopathy: results from the PANORAMA randomized clinical trial. *JAMA Ophthalmol*. 2021;139:946−955.
22. Cobo G, Hecking M, Port FK, et al. Sex and gender differences in chronic kidney disease: progression to end-stage renal disease and haemodialysis. *Clin Sci (Lond)*. 2016;130:1147−1163.
23. Ricardo AC, Yang W, Sha D, et al. Sex-related disparities in CKD progression. *J Am Soc Nephrol*. 2019;30:137−146.
24. Sofia B, Ahmed SR. Sex hormones in women with kidney disease. *Nephrol Dial Transplant*. 2016;31:1787−1795.
25. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2013;3:1−150.