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CLINICAL RESEARCH

Effect of Intravitreal Anti-Endothelial Growth Factor Agents on Renal Function in Patients With Diabetes Mellitus

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Introduction: Intravitreal administration of vascular endothelial growth factor inhibitors (anti-VEGF) is the treatment of choice in retinal pathology associated with type 2 diabetes mellitus (DM2). We aimed to analyze the effect of intravitreal anti-VEGF administration on renal function in patients with DM2.

Methods: This is a single-center retrospective and observational study of patients with DM2 with and without chronic kidney disease (CKD). We analyzed the evolution of renal function after anti-VEGF onset, compared with a control group.

Results: We included 45 patients (55.6% male) who received anti-VEGF therapy. Mean age was 74.4±11.5 (50–91) years. These were compared with 45 patients with similar characteristics. After 12 months, 76.3% had CKD with a mean reduction in estimated glomerular filtration rate (eGFR) of 19.4%. Nine patients (20%) had a >25% reduction in eGFR, and 3 patients (6.7%) had a >50% reduction in GFR. At 24 months, 80% of patients had CKD with a mean eGFR decrease of 28%. The mean eGFR slope of patients who had received anti-VEGF treatment was 10 ml/min/year compared to 1.5 ml/min/year in the control group ($P < 0.05$). After the first administration, 5 patients (17.2%) in the CKD group required renal replacement therapy during follow-up (mean time 22±12 months). Main risk factors for need of dialysis were age, presence of previous CKD, and baseline proteinuria.

Conclusion: Intravitreal anti-VEGF administration is a risk factor for CKD and rapid progression to end-stage kidney disease in patients with previous CKD. Knowing these drugs' implications is crucial to avoid CKD progression and opportunely limit their use in certain patients.

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Diabetes mellitus (DM) is an increasingly prevalent disease in our environment. During the past decades, the prevalence of DM has been increasing exponentially because of DM2.[1] Approximately 35% of patients with diabetes present with diabetic retinopathy (of which up to 80% present with concomitant diabetic renal disease), with intravitreal administration of anti-VEGF being the treatment of choice.[2]

In recent years, intravitreal anti-VEGF agents have revolutionized the treatment of various retinal pathologies, including age-related macular degeneration, central retinal vein thrombosis, proliferative diabetic retinopathy, and diabetic macular edema.[3,4] Intravitreal anti-VEGF has been shown to halt the progression of these diseases and improve the vision of treated patients, exponentially increasing its use in the field of ophthalmology in recent years.[5]

The renal damage produced by systemic administration of anti-VEGF is widely known, presenting a wide range of renal lesions ranging from increased proteinuria, arterial hypertension (AHT),[6] various glomerular diseases,[7] and thrombotic microangiopathy.[8,9]

Recent pharmacokinetic studies[10] have shown that intravitreal agents are absorbed systemically and may

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cause renal damage.[11-13] However, there is scarce information in the literature on the renal effect of these agents.[14,15] Isolated case series have recently been published describing renal involvement after the use of intravitreal anti-VEGF,[4,16-19] and, given the increasingly widespread use of these drugs, studies with a more significant number of patients are needed to clarify the adverse effects of these drugs, in order to make safer use of these agents.[20-23]

Our study aimed to analyze the effect of these drugs on renal function in patients with DM, the effect on the progression of renal disease, the evolution of other parameters such as blood pressure, and other adverse effects.

METHODS

Study Design and Patient Selection

We conducted a retrospective, observational, single-center, case-control study in which we selected diabetic patients, with or without CKD, who received intravitreal anti-VEGF from January 2018 to December 2019 with a follow-up of 24 months. The selected patients were diabetic subjects who attended the ophthalmology consultation at Hospital Universitario 12 de Octubre, diagnosed with diabetic retinopathy or macular edema requiring treatment with intravitreal anti-VEGF. The control group included patients with DM2 with and without CKD who had not received anti-VEGF treatment with similar baseline characteristics. Patients undergoing renal replacement therapy or renal transplantation were excluded. This clinical study was approved by the hospital's ethics and clinical trials committee.

Study Variables

Demographic variables, including gender, age, weight, and height, were analyzed. We recorded several clinical parameters including the following: AHT (considering those patients with a previous diagnosis of AHT, blood pressure >140/90 mm Hg or patients on antihypertensive treatment); time of DM; type of retinopathy; previous CKD (defined as eGFR <60 ml/min, albuminuria, or a CKD stage according to Kidney Disease: Improving Global Outcomes classification equal to or greater than 3); use of renin-angiotensin-aldosterone system (RAS) blockade; insulin; oral antidiabetics; and analytical parameters, including glycemia, glycated hemoglobin, hemogram, serum creatinine, estimate renal GFR (calculated by CKD Epidemiology Collaboration equation), and albuminuria (expressed as an albumin-to-creatinine ratio [ACR], in mg/g). Other parameters were also recorded, such as the type of anti-VEGF drug administered, the number of doses, and other adverse events. Data were collected on the evolution of treated patients from 12 months prior to the administration of intravitreal anti-VEGF until 24 months later. For the control group, data was collected during the same study time period.

Statistical Analysis

Continuous variables were expressed as mean±SD or the median (interquartile range) as appropriate. Statistical analysis was performed using Student *t*-test or Mann-Whitney U test as appropriate. Qualitative variables were shown as absolute values and relative frequencies and were compared with the chi-square test. The correlation between variables was calculated using Pearson's correlation. Survival analysis was determined by the Kaplan-Meier method and compared with the log-rank test. We performed a multivariate analysis using the Cox regression model, including all variables with clinical relevance and *P*-values <0.10 in univariate analysis. Results are shown as the hazard ratio with the corresponding 95% confidence intervals. We considered *P*-values <0.05 as statistically significant. The statistical analysis was performed with SPSS version 24.0 for iOS (IBM, Armonk, NY).

RESULTS

Patients' Characteristics

The study comprised a total of 90 patients (In Table 1, we show the baseline characteristics of the patients in both groups). A total of 45 patients on anti-VEGF therapy were analyzed; 55.6% were males. The mean age was 75.5 years, with a mean time of evolution of DM of 14.3 years. Ninety-one percent were hypertensive, and 64.4% had previously known CKD.

Table 1. Overall baseline characteristics

Characteristics	Anti-VEGF (*n* = 45)	Control (*n* = 45)	*P*-value
Age (yr)	75.5 (64.5–84.8)	74.1 (59.5–87.2)	0.90
Gender (males)	25 (55.6%)	23 (51.1%)	0.67
Diabetes (%)	45 (100%)	45 (100%)	1
Insulin	30 (66.6%)	14 (31.1%)	0.001
Oral antidiabetic drugs	35 (77.7%)	45 (100%)	0.001
AHT (%)	41 (91.1%)	45 (100%)	0.41
RAS blockade (%)	38 (84%)	37 (82.2%)	0.77
DME (%)	36 (80%)	-	-
AMD (%)	9 (20%)	-	-
BMI (kg/m2)	29.3 (25.6–32.7)	29.1 (25.8–32.5)	0.8
Glycated Hb (g/dl)	7.2 (6.1–7.6)	7.3 (6.1–8.2)	0.9
Baseline sCr (mg/dl)	1.6 (0.8–2.1)	1.1 (0.6–1.8)	0.001
Baseline eGFR (ml/min per 1.73 m^2)	42.2 (26.2–71.2)	51.7 (28.0–88.5)	0.007
Baseline ACR (mg/g)	145 (2–2955)	110 (1.3–920.8)	0.007
Bevacizumab (%)	26 (57.8%)	-	-
Ranibizumab (%)	19 (42.2%)	-	-

ACR, albuminuria-to-creatinine ratio; AHT, hypertension; AMD, age-related macular degeneration; BMI, body mass index; DME, diabetic macular edema; eGFR, estimate glomerular filtrate rate; Hb, hemoglobin; RAS, renin-angiotensin system; sCR, serum creatinine; VEGF, vascular endothelial growth factor.

Table 2. Baseline characteristics of patients on anti-VEGF therapy

Characteristics	Total ($N = 45$)	CKD ($n = 29$)	Non-CKD ($n = 16$)	*P*-value
Age (yr)	75.5 (64.5–84.8)	75.2 (63.9–84.5)	76.7 (65–85.3)	0.7
Gender (males)	25 (55.6%)	19 (65.5%)	6 (37.5%)	0.07
Diabetes (%)	45 (100%)	29 (100%)	16 (100%)	1
Insulin	30 (66.6%)	20 (69%)	10 (62.5%)	0.3
Oral antidiabetic drugs	35 (77.7%)	21(72.4%)	14 (87.5%)	0.4
AHT (%)	41 (91.1%)	27 (93.1%)	14 (87.5%)	0.4
RAS blockade (%)	24.5 (60%)	24 (87.9%)	10.5 (75%)	0.3
DME (%)	36 (80%)	22 (75.9%)	14 (87.5%)	0.3
AMD (%)	9 (20%)	7 (24.1%)	2 (12.5%)	0.3
BMI (kg/m2)	29.33 (25.6–32.7)	29.3 (25.8–32.7)	30 (25.5–33)	0.8
Glycated Hb (g/dl)	7.1 (6.1–8.2)	6.5 (6.1–7.6)	8.2 (7.5–9.5)	0.001
Baseline sCr (mg/dl)	1.5 (0.8–2.1)	1.8 (1.5–2.5)	0.8 (0.6–0.8)	0.000
Baseline GFR (ml/min per 1.73 m^2)	42.2 (26.2–71.2)	29.5 (22.5–40.5)	77 (68–86.5)	0.000
Baseline ACR (mg/g)	145 (49.5–695.4)	526.5 (100–1275)	51.3 (19.4–75.4)	0.001
Bevacizumab (%)	26 (57.8%)	16 (55.2%)	10 (62.5%)	0.4
Ranibizumab (%)	19 (42.2%)	13 (44.8%)	6 (37.5%)	0.4

ACR, albuminuria-to-creatinine ratio; AHT, hypertension; AMD, age-related macular degeneration; BMI, body mass index; DME, diabetic macular edema, GFR, glomerular filtrate rate; Hb, hemoglobin; RAS, renin-angiotensin system; sCR, serum creatinine; VEGF, vascular endothelial growth factor.

Of treated patients with CKD, 93.1% had AHT (87.9% of them treated with RAS blockade), and 87.5% of the patients without CKD also had AHT (75% of them treated with RAS blockade), with no significant differences between the 2 groups (CKD and non-CKD) in terms of frequency of AHT and treatment with RAS blockade.

As for metabolic control, most patients had a mean total glycated hemoglobin of 7.1%, with worse control in patients without CKD (mean glycated hemoglobin of 8.2%), compared to a mean glycated hemoglobin of 6.5% in patients with CKD, with statistically significant differences between the 2 groups. In patients without CKD, 62.5% were on insulin treatment at baseline, compared to 69% in patients with CKD, with no significant differences between the 2 groups. Regarding treatment with oral antidiabetic drugs, 87.5% of the patients without CKD were on treatment with oral antidiabetic drugs, whereas 72.4% were treated with oral antidiabetic drugs in the CKD group.

Regarding weight, patients with CKD had a body mass index of 29.3 kg/m^2, with no statistically significant differences compared to patients without CKD, who had a body mass index of 30 kg/m^2.

The retinal pathology for which anti-VEGF treatment was initiated was diabetic macular edema in 80% of the patients. In comparison, 20% of the patients had age-related macular degeneration, with no significant differences between patients with and without CKD. The type of anti-VEGF drug used was bevacizumab in 57.8% and ranibizumab in 42.2% of patients. The mean number of doses administered was 7.7, with a minimum of 1 and a maximum of 22 (Table 2).

For the control group, 45 patients were analyzed. Mean age was 74.1 years, 51.1% were males. Twenty-nine (64.4%) had previous CKD. All patients had previous AHT and 82.2 % were on RAS blockade treatment. All patients were on oral antidiabetic drugs and 31.1 % were treated with insulin. Mean body mass index was 29.1 kg/m^2.

Overall Evolution of Renal Function

The median eGFR at baseline was 42.2 ml/min for patients on anti-VEGF therapy versus 51.7 ml/min in the control group; and the median albumin-to-creatinine was 145 mg/g versus 110 mg/g, respectively.

After 6 months, patients on anti-VEGF had a median eGFR of 35.5 ml/min, representing a decrease in eGFR of 6.7 ml/min, whereas patients in the control group had a median eGFR of 48.1 ml/min, representing a decrease of 3.6 ml/min ($P = 0.002$).

At 12 months, patients on anti-VEGF agents had a median eGFR of 32.5 ml/min versus 50.2 ml/min in the control group, this represents a decrease of 9.7 ml/min versus 1.5 ml/min ($P = 0.0001$).

At 24 months, patients treated with anti-VEGF had a median eGFR of 28.5 ml/min; this represented a decrease of 13.7 ml/min. On the other hand, patients in the control group had a median eGFR of 47.1 ml/min, representing a decrease of 4.6 ml/min ($P = 0.01$) (Figure 1).

Regarding the magnitude of eGFR decrease over time in patients treated with anti-VEGF, there was a reduction in eGFR >25% of 13.3%, 20%, and 26.7% at 6, 12, and 24 months follow-up, respectively. Furthermore, there was a 50% reduction in 6.7% and 13.3% at 12 and 24 months, respectively. The eGFR of

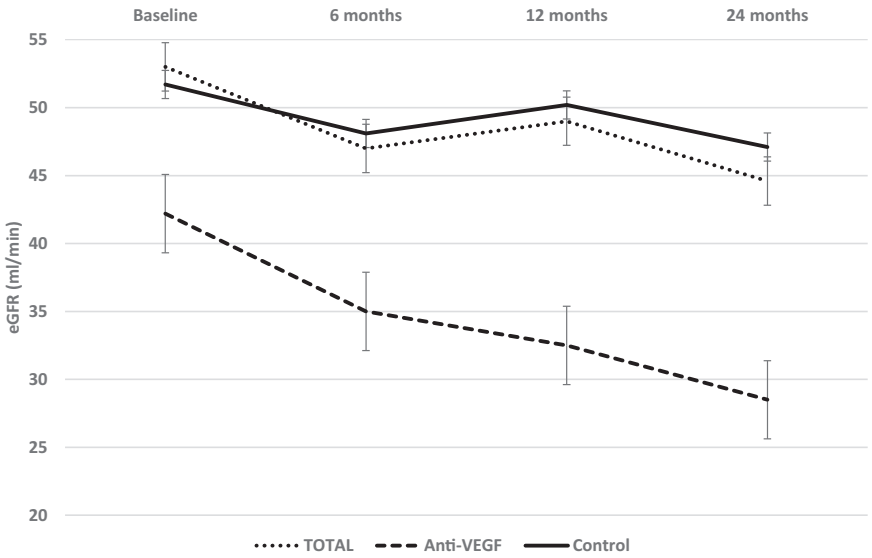

Figure 1. Renal function evolution per group. Anti-VEGF, vascular endothelial growth factor inhibitor; eGFR, estimated glomerular filtration rate.

these patients was analyzed 12 months before the start of anti-VEGF administration. The median eGFR in the 12 months prior to drug initiation was 49.1 ml/min. During the 12 months before the start of treatment, the decrease in eGFR was 6.9 ml/min in 1 year, with a decrease of >25% eGFR in this year in 1 patient. No patient presented with a decrease of >50% eGFR in the 12 months prior to drug administration.

Evolution of Renal Function of Treated Patients With CKD and Non-CKD

Overall, 64.4% ($n = 29$) had CKD (GFR <60 ml/min) at the start of anti-VEGF administration, with a median eGFR of 29.5 ml/min, whereas the rest of the patients who did not have CKD had a median GFR of 77 ml/min.

In the group of patients with CKD, the median eGFR in the 12 months prior to drug initiation was 35.5 ml/min. At drug initiation, the median GFR was 29.5 ml/min, with a median eGFR of 23 ml/min at 6 months and a median eGFR of 20 ml/min at 12 and 24 months of treatment. Therefore, a median eGFR decrease of 6.5 ml/min was observed at 6 months, with a median eGFR decrease of 9.5 ml/min at 12 and 24 months.

In the group of patients without CKD, the median GFR in the previous 12 months was 80.9 ml/min. The median eGFR was 77 ml/min at baseline, 65 ml/min at 6 months, 56 ml/min at 12 months, and 55 ml/min at the end of follow-up (24 months). A median eGFR decrease of 12 ml/min, 21 ml/min, and 22 ml/min was observed at 6, 12, and 24 months, respectively (Table 3).

The decrease in eGFR was significantly greater at 12 and 24 months after anti-VEGF administration compared to 12 months before drug administration in both groups.

In Table 4, we show the decrease in eGFR in patients with CKD and those without CKD. In the CKD group, there was a reduction in eGFR >25% of 17.9%, 21.4%, and 28.6% at 6, 12 and 24 months follow-up,

Table 3. Evolution of eGFR before and after anti-VEGF therapy[a]

	Previous 12 mo	Baseline	6 mo	12 mo	24 mo
Total					
eGFR (mil/min per 1.73 m^2)	49.1 (15.2–90)	42.2 (26.2–71.2)	35.5 (20.7–63)	32.1 (21–49.9)	28.5 (19.2–53.5)
eGFR decrease (mil/min per 1.73 m^2)	-	6.9 ml/min	6.7ml/min	10 ml/min	13.7ml/min
P vs. 12 mo	-	-	0.06	0.04	0.03
eGFR (mil/min per 1.73 m^2)	35 (15.5–58.3)	29.5 (15–59)	23 (13–53)	20 (9–46)	20 (4–42)
CKD					
eGFR (mil/min per 1.73 m^2) decrease	-	5.5 ml/min	6.5 ml/min	9.5 ml/min	9.5 ml/min
P vs. 12 mo	-	-	0.07	0.03	0.03
eGFR (mil/min per 1.73 m^2)	80.9 (64–114)	77 (63–106)	65 (42–90)	56 (42–83)	55 (19–90)
Non-CKD					
eGFR decrease (mil/min per 1.73 m^2)	-	3.5 ml/min	12 ml/min	21 mil/min	22 mil/min
P vs. 12 mo	-	-	0.002	0.003	0.02

CKD, chronic kidney disease, eGFR, estimated glomerular filtration rate, VEGF, vascular endothelial growth factor.
[a]Dash lines represent data non-available.

Table 4. Percentage of eGFR reduction among treated patients with and without CKD

eGFR reduction >25%				
	Total *N* (%)	CKD *n* (%)	Non-CKD *n* (%)	*P*-value CKD vs. no CKD
−12 mo	-	-	-	-
Baseline	1 (0.02)	1 (0.02)	0 (0)	0.04
6 mo	6 (13.3)	5 (17.9)	1 (6.3)	0.001
12 mo	9 (20)	6 (21.4)	3 (18.8)	0.02
24 mo	12 (26.7)	8 (28.6)	4 (25)	0.02
eGFR reduction >50%[a]				
	Total *N* (%)	CKD *n* (%)	Non-CKD *n* (%)	*P*-value CKD vs. no CKD
−12 mo	-	-	-	-
Baseline	0 (0)	0 (0)	0 (0)	-
6 mo	0 (0)	0 (0)	0 (0)	-
12 mo	3 (6.7)	2 (7.1)	1 (6.3)	0.04
24 mo	6 (13.3)	4 (14.3)	2 (12.5)	0.03

CKD, chronic kidney disease; eGFR, estimated glomerular filtration.
[a]Dash lines represent data non-available.

respectively. In the group of patients without CKD, there was a reduction in eGFR >25% of 6.3, 18.6, and 25%, respectively. There was a 50% reduction in the CKD group of 7.1 and 14.3% at 12 and 24 months, respectively, versus 6.3 and 12.5% in the non-CKD group.

Evolution to End-Stage Renal Disease

Of the treatment group, 5 patients (17.2%) with CKD required renal replacement therapy during follow-up (mean time 22 ± 12 months) after administration of the first dose. In Figure 2, we show the risk of progression to end-stage CKD in this group of patients. The median age in this group at the start of the study was significantly older than the overall median age (79 years), presenting a median eGFR of less than 28 ml/min at the start of treatment, with an ACR >1000 mg/g at the start of follow-up (Table 5). No patient in the control group required renal replacement therapy.

Multivariate logistic regression analysis showed that the main risk factors associated with the need for starting dialysis were age >75 years and the presence of CKD before starting treatment (Table 6).

Evolution of Proteinuria

Overall mean proteinuria at baseline was 320 mg/g. We have no data on proteinuria in the 12 months prior to drug administration, probably because this parameter was only requested once the patients were referred to the nephrology department.

Mean proteinuria at baseline was 145 mg/g in patients with anti-VEGF therapy. Increase in the ACR to 396 mg/g, 381 mg/g, and 537 mg/g were observed at 6, 12, and 24 months, respectively. This increase in proteinuria was significantly higher at 12 and 24 months compared to baseline. Patients with CKD had a median ACR of 526.5 mg/g, whereas patients without CKD had a median ACR of 51.3 mg/g, showing significant differences between the 2 groups (Table 7).

In the group of treated patients with CKD, there was an increase in proteinuria with ACR 615 mg/g, 572 mg/

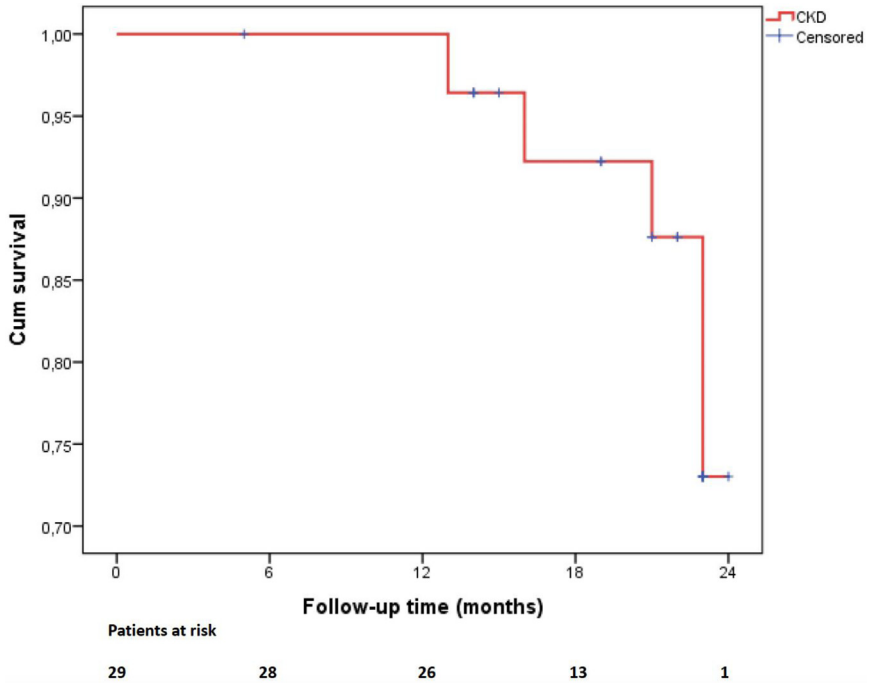

Figure 2. Risk for progression to ESKD in treated CKD patients. CKD, chronic kidney disease; ESKD, end-stage kidney disease.

Table 5. Differences between patients who require kidney replacement therapy and those who do not (24 mo)

Variable	KRT (n = 5)	No KRT (n = 40)	*P*-value
Age (yr)	78.9 (50–91)	61.97 (54–74)	0.01
Gender (males %)	4 (80)	21 (52.1)	0.243
AHT (%)	4 (80)	37 (92.5)	0.35
Anti-VEGF type: avastin (%)	1 (20)	25 (62.5)	0.07
Treat >6 mo (%)	2 (40)	20 (50)	0.63
BMI (kg/m^2)	27 (17.5–32)	29.8 (20.9–37.6)	0.157
Glycated Hb	6.1 (5.6–8.5)	7.1 (5.6–9.8)	0.418
eGFR (mil/min per 1.73 m^2) 12 mo before baseline	30.4 (15.5–56.6)	66.5 (27.1–92.3)	0.01
Previous SCr (mg/dl)	2.3 (1.2–3.9)	1 (0.4–2.5)	0.003
Initial CKD (%)	5 (100)	24 (60)	0.06
eGFR (mil/min per 1.73 m^2) at anti-VEGF onset	26 (15–28)	51 (15–106)	0.002
sCR (mg/dl) at anti-VEGF onset	2.4 (1.9–3.9)	1.3 (0.5–3.5)	0.015
ACR (mg/g) at anti-VEGF onset	1816 (1226–2955)	102 (2–1659)	0.02

ACR, albuminuria-to-creatinine ratio; AHT, hypertension; BMI, body mass index; CKD, chronic kidney disease; Hb, hemoglobin; eGFR, estimate glomerular filtrate rate; KRT, kidney replacement therapy; sCR, serum creatinine; Treat >6 months, treatment at 6 months; VEGF, vascular endothelial growth factor.

g, and 687 mg/g, at 6, 12, and 24 months, respectively. In patients without previous CKD, the evolution of proteinuria was 58 mg/g at 6 months, 51 mg/g at 12 months, and 202 mg/g at 24 months.

The increase in proteinuria was more significant at 24 months in treated patients without CKD compared to those with previous CKD, in whom it increased slightly initially but remained stable during follow-up.

Patients in the control group had a median proteinuria of 110 mg/g at baseline. At 12 months, 60% of patients showed stability or slight increase in ACR, whereas 28.9% suffered an increase in ACR greater of 50%. This increase was more frequent in those patients with CKD.

Blood Pressure and Other Effects

An increase in systolic blood pressure was observed at 6 and 12 months in both groups, although this difference was not statistically significant. There were no cases of thrombotic microangiopathy as an adverse side effect.

Visual Outcomes

Visual outcomes were assessed overall 24 months after the first administration of the drugs. The parameters to establish visual improvement were gain or stability of visual acuity, decrease of macular thickness, and disappearance or improvement of subretinal choroidal neovascular membranes. It was also considered whether the administration regimen was spaced out over the follow-up due to good response.

Of the 45 patients treated, 30 (66%) showed stability or improvement of visual parameters, whereas 15 subjects (33%) showed no improvement. Regarding treated patients with CKD, 17 (37.7%) showed stability or improvement of visual parameters.

Table 6. Risk factors for need of dialysis

Variable	OR	Confidence interval (CI 95%)	*P*-value
Gender: males	3.6	0.37–35.29	0.243
Age >75 yr	1.3	0.6–0.98	0.015
HT	3.08	0.02–3.91	0.354
Previous CKD	1.4	1.03–1.43	0.04
RAS blockade	1.4	0.06–7.4	0.7
Treatment >6 mo	1.49	0.1–4.4	0.673
Anti-VEGF type (avastin)	6.6	0.68–65.36	0.06

CKD, chronic kidney disease; HT, hypertension; OR, odds ratio; RAS, renin-angiotensin system; VEGF, vascular endothelial growth factor.

DISCUSSION

The main finding of our study was that patients with DM with or without CKD had significant deterioration of renal function after intravitreal administration of an anti-VEGF.

The effect on increased proteinuria, worsening of AHT, and deterioration of renal function after systemic administration of anti-VEGFs is widely proven.[3,8,9] It is well known that vascular endothelial growth factor (VEGF) is an essential signaling protein involved in angiogenesis. Specifically, VEGFR-2 predominates in the mesangium, endothelial cells, and tubular capillaries. The interaction of podocytes and endothelial cells by VEGF expression is essential for developing and maintaining glomerular filtration by inducing endothelial fenestrations and maintaining glomerular permeability.[24] Blockade of VEGFR-2 leads to the appearance of proteinuria, AHT, or impaired glomerular filtration.

VEGF inhibitors have become the treatment of choice for several retinal pathologies.[2,10] This type of ophthalmologic therapy is based on local administration into the vitreous humor by intraocular injection and involves a dose approximately 400 times lower than that used for oncological disease.[8,14] However, some studies show that several of these drugs are absorbed systemically and produce adverse effects.[10,16]

Table 7. Evolution of proteinuria among patients with anti-VEGF therapy[a]

Proteinuria	−12 mo	Baseline	6 mo	12 mo	24 mo
ACR (mg/g) Total patients	-	145 (49–695)	396 (50–1140)	381[b] (71–1211)	537[b] (89–1353)
ACR (mg/g) CKD	-	526 (100–1275)	615 (180–1405)	572 (187–1763)	687 (170–1944)
ACR (mg/g) non-CKD	-	51 (19–75)	58 (11–529)	51 (2–430)	202[b] (4–827)

ACR, albuminuria-to-creatinine ratio, CKD, chronic kidney disease, VEGF: vascular endothelial growth factor.
[a]Dash lines represent data non-available.
[b]$P < 0.05$ respect to baseline.

There is increasing evidence in the literature that the intravitreal use of these agents may contribute to AHT and proteinuria[5,17,22]; this is especially highlighted in diabetic patients who often have previous hypertension, proteinuria, and CKD.[4,14,25] Three cases of chronic thrombotic microangiopathy associated with initiating intravitreal VEGF blockade with bevacizumab and aflibercept have also been described recently.[2,16] In Table 8, we show several clinical cases reported in the literature showing renal involvement by intravitreal administration of antiangiogenic drugs.

Conversely, there are studies conducted by the Diabetic Retinopathy Clinical Research Committee where renal damage by intravitreal administration of antiangiogenic drugs is called into question. These studies analyzed the ACR in 654 patients who received ranibizumab, aflibercept, or bevacizumab, during a 52-week follow-up. The average number of injections administered during treatment was between 9 and 10. In all 3 treatment groups, more than 77% of patients maintained their proteinuria value close to the baseline. In contrast, 10% and 16% of patients experienced a worsening ACR in the follow-up period. This study concluded that these drugs had no deleterious influence on patients' proteinuria control.

In our group of treated patients, 71.4 % had a worsened proteinuria during follow-up; this increase was significantly higher at 24 months in both groups and in the subgroup without previous CKD. The main risk factors identified for the development of end-stage renal disease were advanced age, the presence of previous CKD, and baseline albuminuria; this was in line with the limited data published, where the risks of intravitreal anti-VEGF inhibition may approximate 14% for worsening hypertension and 14% to 45% for increased proteinuria. The risks are lower compared with systemic administration of VEGF inhibitors (where 23.6% of patients have worsening hypertension and 21% to 63% have increased proteinuria), but this should not preclude close follow-up of patients.

In our series, 56.6% of patients exposed to anti-VEGF presented with a significant progressive deterioration of renal function (understood as a decrease >25% initial eGFR), in contrast with the control group that showed much more stable eGFR, although a decline in eGFR was still observed. This decrease was significantly greater in the group of patients with CKD.

Table 8. Clinical characteristics and kidney outcomes of patients with anti-VEGF therapy and renal manifestations reported in the literature[a]

Reference	Age-sex	Previous disease	Ocular disease	Drug used	Presentation	Histological findings	Kidney outcome
1	77-M	AHT	ME	ranibizumab	Severe AHT + AKI	TMA +MPGN	PR
2	54-M	MCD on remission	EM	bevacizumab	NS	-	CR
3	56-M	DM2	DR	ranibizumab	AKI + proteinuria	-	PR
4	-	DM2	DR	bevacizumab	AKI	-	-
5	16-F	MCD	SCN	bevacizumab	NS	-	CR
6	68-F	DN	DR	ranibizumab	AKI and proteinuria	-	HD
	59-M	DN	DR	bevacizumab	-		HD
7	67-M	KT	AMD	bevacizumab	Proteinuria	MGN	-
	52-M	KT	AMD	ranibizumab	AKI and proteinuria	-	
	54-F	DN	DR	bevacizumab	Proteinuria	NAS+DN	HD
8	53-M	AHT, DM2, CKD	DR	bevacizumab	AKI and proteinuria	-	HD
	65-F	None	AMD	bevacizumab→ aflibercept	AHT	-	HD
9	67-M	AHT, DM2, CKD	DR	ranibizumab	AKI and AHT	-	HD
Effect of intravitreal anti-endothelial growth factor and DM. Rivero *M et al.*	45 patients	DM2 100%	ME 80%	Ranibixumab	AKI and proteinuria	-	5 HD
		AHT 91%					12 PR
		CKD 64%	AMD 20%	bevacizumab			

AHT, arterial hypertension; AKI, acute kidney injury; AMD, age-related macular degeneration; CKD, chronic kidney disease; CR, complete remission; DM2, type 2 diabetes mellitus; DR, diabetic retinopathy; HD, hemodialysis; KT, kidney transplant; MCD, minimal change disease; ME, macular edema; MGN, membranous glomerulonephritis; MPGN, membranous-proliferative glomerulonephritis; NAS, nephroangiosclerosis; ND, diabetic nephropathy; NS, nephrotic syndrome; PR, partial remission; TMA, thrombotic microangiopathy; VEGF, vascular endothelial growth factor.
[a]Dash lines represent data non-available.

Proteinuria increased in 71.4% of treated patients at the end of follow-up (24 months); however, there was also a significant increase in proteinuria in the control group subjects with CKD at 12 months, but this increase was of minor extent. Five patients (17.2%) of the CKD treated group required kidney replacement therapy during follow-up after administration of the first dose; these patients were significantly older, had an estimated GFR <30 ml/min, and had higher baseline proteinuria compared to treated subjects who did not need kidney replacement therapy.

Furthermore, we observed that bevacizumab may have a more harmful effect than ranibizumab; although there was no significant difference, there was a trend. Therefore, studies with a larger number of patients would be necessary to support this statement.

Regarding visual outcomes, in our series, two-thirds of patients showed stable or improved visual acuity and better optical coherence tomography parameters during follow-up. On the other hand, one-third of the patients showed no improvement in visual parameters. Notably, 37% of patients with CKD noted visual improvement or stability; this substantial percentage of patients with visual improvement makes the decision to discontinue anti-VEGF therapy in patients with CKD very difficult, especially if we consider that the eGFR decrease at 24 months in this particular group was 13.7 ml/min and that the need for kidney replacement therapy, although not inexistent, was low. These findings reinforce the need for studies with larger numbers of patients to draw firm conclusions.

Our work has significant limitations. It is a retrospective single-center study with a small number of patients. However, among its strengths is that it is a study that reflects real-world clinical practice with patients with and without CKD compared with a similar control group.

In conclusion, in diabetic patients with CKD who will receive intravitreal anti-VEGF treatment, renal function, proteinuria, and blood pressure should be closely monitored after administration. In this way, we will be able to detect early the effects of these drugs on renal function and even contraindicate their use in patients with a high risk for CKD development or worsening. Prospective studies are needed to provide further scientific evidence for this finding.

DISCLOSURE

All the authors declared no competing interests.

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