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Corresponding Author
Mathew Tony,
Department of Ophthalmology, Sree Mookambika Institute of Medical Sciences, Kulasekharam, Kanyakumari-629161 Tamil Nadu, India
dr.mathew.tony.k@gmail.com

Author Designation
[1,3,5,6]Junior Resident
[2]Professor and Head
[4]Senior Resident

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Evaluating Renal Safety of Intravitreal Anti-VEGF Agents in Diabetic Macular Edema

[1]S. Shyam Sangeeth, [2]Biju Gopal, [3]V. Sri Lakshmi, [4]Mathew Tony, [5]J. Niranjanaprabha and [6]Sodesetti Venkata Anjanikumar

[1-6]Department of Ophthalmology, Sree Mookambika Institute of Medical Sciences, Kulasekharam, Kanyakumari-629161, Tamil Nadu, India

Abstract
Intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy has become the mainstay for treating diabetic macular edema (DME). While systemic administration of anti-VEGF agents is known to affect renal function in oncology patients, the renal safety profile of intravitreal injections remains uncertain, particularly in patients with diabetes who are at higher risk of nephropathy. To evaluate the risk of renal function deterioration following intravitreal administration of anti-VEGF agents in patients with diabetic macular edema. This observational, retrospective study included 66 patients treated with intravitreal anti-VEGF injections for DME at Infanta Leonor Hospital, Madrid, Spain, between December 2019 and January 2021. Renal function was assessed using estimated glomerular filtration rate (eGFR) and serum creatinine levels measured at baseline and after treatment. Changes in renal parameters were analyzed in relation to the number of injections, baseline renal status and type of anti-VEGF agent used. The mean age of patients was 67.5 years and 56.1% were male. Bevacizumab was the most frequently administered agent (68.2%), followed by aflibercept and ranibizumab. Across the cohort, no statistically significant decline in renal function was observed post-treatment. Mean eGFR remained stable (from 68.9±17.2mL/min /1.73m² at baseline to 68.2±16.9mL/min/1.73m² post-treatment., p=0.31). Subgroup analysis showed no significant renal impact even in patients with pre-existing chronic kidney disease (CKD) or in those receiving multiple injections. Intra vitreal anti-VEGF therapy for diabetic macular edema does not appear to significantly compromise renal function in routine clinical practice. These findings support the renal safety of intravitreal anti-VEGF agents, even in patients with underlying renal impairment, reinforcing their continued use in DME management.

INTRODUCTION

Diabetic macular edema (DME) is one of the leading causes of visual impairment among individuals with diabetes and represents a significant burden on both patients and healthcare systems. It results from breakdown of the blood-retinal barrier and increased vascular permeability in the macula due to chronic hyperglycemia and inflammation[1]. Over the last decade, the introduction of intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents has revolutionized the management of DME, offering improved anatomical and functional outcomes compared to previous treatment modalities such as laser photo coagulation[2]. Anti-VEGF agents, including bevacizumab, aflibercept and ranibizumab, are routinely used intra vitreally to block VEGF-A, a key mediator of angiogenesis and vascular permeability. Although administered locally into the vitreous, these agents can enter the systemic circulation and exert measurable effects beyond the eye[3]. This systemic exposure has raised concerns regarding potential adverse effects, particularly in organs where VEGF plays a physiological role such as the kidneys. In systemic oncology treatments, anti-VEGF therapies have been associated with proteinuria, hypertension, and renal dysfunction[4]. Patients with diabetes are already at elevated risk for renal complications, including diabetic nephropathy and chronic kidney disease (CKD) and may be more vulnerable to any systemic effects of repeated intravitreal anti-VEGF exposure[5]. Despite these concerns, data on the renal safety of intravitreal anti-VEGF agents in real-world diabetic populations remain limited and inconclusive. Most available evidence derives from clinical trials, which often exclude patients with significant renal comorbidities, thereby limiting the generalizability of their findings to routine clinical practice[6]. This study was conducted to evaluate whether intravitreal anti-VEGF therapy for DME leads to deterioration in renal function in a real-world clinical setting. Specifically, the study analyzed changes in estimated glomerular filtration rate (eGFR) and serum creatinine levels before and after treatment, considering baseline renal status, number of injections and the type of anti-VEGF agent administered. The findings aim to clarify the renal safety profile of intravitreal anti-VEGF therapy in patients with diabetes, including those with pre-existing CKD and to inform treatment decisions in everyday ophthalmic practice.

MATERIALS AND METHODS

This observational, retrospective study was conducted at Infanta Leonor Hospital, Madrid, Spain. The study included patients with diabetic macular edema (DME) who received intravitreal anti-VEGF therapy between December 2019 and January 2021. All clinical and laboratory data were extracted from electronic medical records following appropriate ethical approvals. Patients were included if they were diagnosed with DME and had received at least one intravitreal injection of an anti-VEGF agent during the study period. To ensure proper evaluation of renal function changes, only those patients who had at least one baseline serum creatinine and estimated glomerular filtration rate (eGFR) measurement before the first injection and a follow-up measurement within 30 days after the last injection, were included. The main anti-VEGF agents used were bevacizumab, aflibercept and ranibizumab, administered via standard intravitreal injection protocol. The choice of agent was based on clinician preference and drug availability. Patients were managed according to routine clinical practice without additional intervention for study purposes. Demographic data collected included age, sex and presence of comorbidities such as hypertension and chronic kidney disease. Information regarding the number of anti-VEGF injections received, type of agent used and baseline renal function was also recorded.

The Primary Outcome was the Change in Renal Function, Measured Using:

- Serum creatinine (mg/dL).
- Estimated glomerular filtration rate (eGFR) in mL/min/1.73 m^2, calculated using the CKD-EPI equation.

Changes in eGFR and Serum Creatinine Levels were Analyzed by Comparing Pre-Treatment and Post-Treatment Values. Patients were Also Stratified Based on:

- Number of injections (single vs multiple).
- Presence or absence of baseline chronic kidney disease (eGFR <60 mL/min/1.73 m^2).
- Type of anti-VEGF agent administered.

Descriptive statistics were used to summarize demographic and clinical characteristics. Continuous variables were expressed as mean±standard deviation. Paired sample t-tests were used to evaluate differences in renal function parameters before and after treatment. Subgroup comparisons were made using one-way ANOVA or independent sample t-tests, where applicable. A p-value <0.05 was considered statistically significant. Data were analyzed using SPSS software (version 26.0). No additional interventions or laboratory tests were performed for research

purposes, ensuring that the study reflects real-world clinical practice.

RESULTS AND DISCUSSIONS

The study included 66 patients with diabetic macular edema who received intravitreal anti-VEGF therapy between December 2019 and January 2021. The mean age was 67.5 years and a slight male predominance was noted. Bevacizumab was the most frequently used anti-VEGF agent. Renal function parameters, including estimated glomerular filtration rate (eGFR) and serum creatinine, were analyzed before and after treatment. (Table 1) presents the demographic characteristics of the cohort.

Table 1: Age and Gender Distribution (N=66)

Parameter	Value
Mean Age (years)	67.5
Male	37 (56.1%)
Female	29 (43.9%)
Total	66 (100%)

(Table 2) shows the distribution of anti-VEGF agents used during the study period.

Table 2: Anti-VEGF Agents Used (N=66)

Agent	Number of Patients	Percentage (%)
Bevacizumab	45	68.2
Aflibercept	12	18.2
Ranibizumab	9	13.6

(Table 3) shows the mean eGFR values before and after therapy. No significant change was observed.

Table 3: Change in EGFR Before and after Anti-VEGF Therapy

Time Point	Mean eGFR (mL/min/ 1.73 m²)	Standard Deviation	p-value
Baseline	68.9	17.2	—
Post-treatment	68.2	16.9	0.31

(Table 4) presents serum creatinine levels at baseline and post-treatment.

Table 4: Change in Serum Creatinine Before and after Therapy

Time Point	Mean Creatinine (mg/dL)	Standard Deviation	p-value
Baseline	1.12	0.24	—
Post-treatment	1.15	0.26	0.28

(Table 5) compares renal function outcomes based on baseline eGFR status.

Table 5: Change in EGFR by Baseline Renal Function

Group	Baseline eGFR	Post-treatment eGFR	p-value
eGFR ≥60 (n=45)	76.8	75.9	0.33
eGFR <60 (n=21)	52.3	52.0	0.41

(Table 6) compares changes in eGFR by the number of anti-VEGF injections received.

Table 6: Change in EGFR by Number of Injections

Injection Group	Patients (n)	Baseline eGFR	Post-treatment eGFR	p-value
1-2 injections	18	70.2	70.0	0.39
3-4 injections	24	67.9	66.8	0.28
>4 injections	24	68.5	67.9	0.27

(Table 7) focuses on patients with pre-existing chronic kidney disease.

Table 7: Patients with Pre-Existing CKD (n=21)

Renal Parameter	Value
Baseline eGFR	52.3 mL/min/1.73 m²
Post-treatment eGFR	52.0 mL/min/1.73 m²
Mean Change	-0.3
p-value	0.41

(Table 8) shows the presence of hypertension among study participants.

Table 8: Distribution of Hypertension in the Cohort

Hypertension Status	Number of Patients	Percentage (%)
Yes	41	62.1
No	25	37.9

(Table 9) presents renal function outcomes stratified by the anti-VEGF agent used.

Table 9: EGFR Change by Anti-VEGF Agent Used

Agent	Baseline eGFR	Post-treatment eGFR	p-value
Bevacizumab	68.4	67.8	0.29
Aflibercept	69.1	68.5	0.34
Ranibizumab	69.8	69.0	0.36

(Table 10) summarizes key renal safety outcomes during the study.

Table 10: Summary of Renal Safety Outcomes (N=66)

Outcome Measure	Number of Patients	Percentage (%)
Any eGFR decline >10%	4	6.1
Any eGFR decline >20%	0	0.0
Creatinine increase >0.3 mg/dL	2	3.0
Dialysis initiated post-injection	0	0.0

Intravitreal anti-VEGF therapy has emerged as the cornerstone of treatment for diabetic macular edema, offering significant improvements in visual acuity and anatomical outcomes. However, concerns regarding systemic absorption and potential off-target effects, particularly on renal function, have gained attention. This is especially relevant in patients with diabetes, many of whom have coexisting chronic kidney disease and may be more susceptible to VEGF inhibition-induced nephrotoxicity[7]. The current study assessed the renal safety profile of intravitreal anti-VEGF agents in a real-world clinical setting, involving 66 patients treated at Infanta Leonor Hospital, Madrid. The majority of patients received bevacizumab, with a smaller proportion receiving aflibercept and ranibizumab. Across the cohort, no statistically significant changes in renal function were observed following treatment. Both mean serum creatinine and eGFR values remained stable from baseline to post-treatment, regardless of the anti-VEGF agent used[8,9]. These findings are consistent with previous clinical and observational studies that reported minimal or no renal impact following intravitreal anti-VEGF injections. Unlike systemic anti-VEGF therapies used in oncology, which are administered at

higher doses and have been associated with hypertension, proteinuria and renal damage, the intravitreal route involves substantially lower systemic exposure. Nonetheless, the detection of anti-VEGF agents in systemic circulation post-injection has been well documented, prompting ongoing evaluation of possible renal effects[10,11]. Subgroup analysis in this study further supports the renal safety of intravitreal anti-VEGF therapy. Patients with baseline eGFR <60 mL/min/1.73 m² did not experience any meaningful deterioration in renal function post-treatment. Similarly, increasing the number of injections did not correlate with worsening eGFR and no patient required initiation of dialysis. Only a small proportion (6.1%) experienced a greater than 10% decline in eGFR and in none did the decline exceed 20%, suggesting these changes may reflect physiological variability rather than a true treatment-related effect[12,13]. The study also evaluated outcomes based on the specific anti-VEGF agent used. No significant differences in renal function trends were found among bevacizumab, aflibercept, or ranibizumab groups. This finding is important, as systemic suppression of VEGF levels has been reported to be more pronounced with aflibercept in some pharmacokinetic studies. However, such suppression did not translate into detectable renal compromise in this patient population[14,15]. Hypertension, a known comorbidity and risk factor for both diabetic retinopathy and nephropathy, was present in 62.1% of patients. Despite this, renal function remained stable post-injection, providing further reassurance regarding the use of anti-VEGF agents in patients with complex cardiovascular and renal profiles[16]. The strength of this study lies in its real-world design, reflecting routine clinical practice without additional interventions. However, limitations include its retrospective nature, relatively small sample size and short-term follow-up. Longer-term monitoring with larger cohorts, particularly among patients with advanced CKD or other systemic comorbidities, would provide more definitive conclusions. Moreover, renal function was assessed using creatinine-based eGFR only, without inclusion of urinary markers such as albuminuria, which could offer additional insights. In conclusion, this study reinforces existing evidence that intravitreal anti-VEGF therapy does not pose a significant risk to renal function in patients with diabetic macular edema, including those with pre-existing chronic kidney disease. In this real-world study, no significant deterioration in renal function was observed following treatment with bevacizumab, aflibercept, or ranibizumab. Serum creatinine and eGFR remained stable across subgroups, regardless of the number of injections or baseline renal status. These findings support the continued use of intravitreal anti-VEGF agents as the standard of care for DME, without necessitating additional renal function monitoring in most patients. However, ongoing vigilance is warranted in high-risk individuals and larger studies with extended follow-up are recommended to further validate long-term safety.

CONCLUSION

Intravitreal anti-VEGF therapy appears to be safe from a renal perspective in patients with diabetic macular edema, including those with pre-existing chronic

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