e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2024; 16(11); 449-453

Original Research Article

Risk of Renal Damage Associated with the Use of the Intravitreal Anti-VEGF Therapy for the Treatment of Diabetic Retinopathy

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Received: 25-08-2024 / Revised: 23-09-2024 / Accepted: 26-10-2024

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Conflict of interest: Nil

Abstract:

Background: Diabetic macular oedema is the most common cause of blindness among diabetic retinopathy patients. Early recognition and treatment of the patient with diabetic macular oedema help prevent the development of complications and improve the patient's quality of life.

Aim: To assess the treatment of the anti-VEGF among patients with diabetic macular oedema associated with the development of renal damage.

Methods: This single-centred retrospective study was conducted in a tertiary care centre between May 2022 to May 2024. All the patients with diabetic macular oedema were included in the study. All the patients who received anti-VEGF therapy were grouped in one group, and those who didn't were taken as controls. And all the renal parameters were evaluated at the baseline and one month after the completion of the therapy.

Results: A total of 208 patients with diabetic macular oedema participated in the study. 104 patients who received anti-VEGF therapy were grouped in one group, and those who didn't receive it were grouped in another group. The study showed a significant increase in the HbA1c values ($p<0.001$), eGFR ($p<0.001$), serum creatinine ($p<0.001$), serum urea ($p<0.001$) and systemic blood pressure level ($p<0.001$) between the baseline and after the treatment.

Conclusion: The study showed that diabetic patients with diabetic macular oedema could be treated with anti-VEGF treatment. Various parameters such as renal function, blood pressure, and HbA1C should be closely monitored during the treatment.

Keywords: Diabetic retinopathy, Macular oedema, Anti-VEGF, Renal parameters.

Introduction

Diabetes mellitus is one of the common metabolic diseases encountered in day-to-day practices [1]. And. The change in the lifestyle of people and the rapid growth of urbanisation have led to a recent increase in the incidence of diabetes in both developed and developing countries [2]. In India, the percentage of people with diabetes mellitus increased from 7.1% in 2009 to 8.9% in 2019. At the global level, India ranks second after China, with 77 million found to be affected by the disease [3]. Since diabetes mellitus is a metabolic and endocrine disease, it can affect the other system of the body, which causes an increase in morbidity and mortality among the patients [4]. Diabetic retinopathy is one of the severe manifestations of patients with Diabetes Mellitus and leads to visual loss and business among patients. It is the fourth leading cause of blindness in the world [5]. Studies have shown that 34.6% of diabetic patients worldwide complain of some form of diabetic retinopathy. The prevalence of diabetic retinopathy in India ranged from 10% to 25% in various studies [6]. The presence of hyperglycaemia plays an essential role in the development of hyperglycaemia-induced vascular damage. Additionally, the hexosamine route, the polyol pathway, and the activation of protein kinase-C are metabolic processes that play a significant role in the development of the disease [7]. Diabetic macular oedema was the most frequent cause of vision loss in people with diabetic retinopathy [8]. To treat diabetic macular oedema, the vascular

endothelial growth factor inhibitor (anti-VEGF) had to show promising results. The anti-VEGF acts by suppressing the plasma levels of the VEGF, which plays a vital role in the development of macular oedema [9]. It has been demonstrated that intravitreal anti-VEGR stops the disease's progression and enhances the patient's eyesight. However, the major disadvantage of this drug is the development of systemic side effects. Renal damage due to glomerular injury after the systemic injection has been described extensively in the literature [10]. Recent pharmacokinetic studies have shown that the intravitreal injection of the agent can also lead to the development of renal damage [11]. On the other hand, the effects of anti-VEGF on the kidneys are not well documented in the literature. So, this study was planned to assess the treatment of the anti-VEGF associated with the development of renal damage.

Materials and Methods

This single-centre retrospective study was conducted at a tertiary care centre from May 2022 to May 2024. Patients with diabetic macular oedema who had baseline GFR data and follow-up GFR data at one month, and who were willing to participate, were included in the study. Patients without available GFR data, those with renal failure requiring haemodialysis, or those who had received intravitreal corticosteroid treatment were excluded. A total of 104 patients who received anti-VEGF therapy during the study period were included, along with a control group of 104 patients with diabetic macular oedema.

The patients were initially assessed for age, sex, socioeconomic status, locality, presenting complaints, and the duration of diabetes. They were further evaluated for the presence of hypertension, ischemic heart disease, peripheral vascular disease, diabetic foot, and diabetic polyneuropathy. Additionally, information was collected on the use of medications for chronic diseases, including aspirin, statins, renin-angiotensin system inhibitors, oral antidiabetic drugs, and insulin. Data was also gathered on the timing of the first intravitreal injection, the most recent dose, the total number of injections received, and glycated haemoglobin (HbA1c) levels before and after the final injection. All patients in the study received either bevacizumab, ranibizumab, or aflibercept throughout the two-year treatment period. Each patient was evaluated for their response to treatment, with each type of anti-VEGF medication administered as a single therapy. Simultaneous bilateral injections were counted as two separate injections. Various renal parameters, such as HbA1c, eGFR, serum creatinine, serum urea, and systolic blood pressure, were compared at baseline and one month after treatment.

For statistical analysis, data were entered and stored in Microsoft Excel and analysed using SPSS (Statistical Package for the Social Sciences) version 20. Categorical variables were expressed as frequencies and percentages, and the paired t-test was used to assess differences in continuous variables. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 208 patients with diabetic macular edema participated in the study, with 104 patients randomized to the intervention group and an equal number in the control group. Of the participants, 45.2% were over the age of 50, followed by 29.8% who were between 41 and 50 years old. Males comprised 66.3% of the study population. According to the modified BG Prasad classification, 39.4% of the patients belonged to Class I socioeconomic status, followed by 27.9% in Class II socioeconomic status. In terms of comorbidities, 53.8% of the patients had hypertension, while diabetic polyneuropathy and cerebrovascular disease were observed in 39.9% and 30.3% of the patients, respectively (as shown in Table 1).

Regarding medication usage, the study found that 60.1% of the participants were taking oral antidiabetic drugs, 44.2% were on insulin, and 39.4% were using renin-angiotensin inhibitors. Statin use was observed in 35.1% of the patients (as shown in Table 2).

Evaluation of various renal parameters in relation to anti-VEGF therapy revealed a significant increase in HbA1c ($p < 0.001$), eGFR ($p < 0.001$), serum creatinine ($p < 0.001$), serum urea ($p < 0.001$), and systolic blood pressure ($p < 0.001$) between baseline and after treatment (as shown in Table 3).

Table 1: Socio-demographic details of the patients

Variable	Intervention group n (%)	Control group n (%)	Total n (%)
Age (in years)			
18-30	10 (9.6)	8 (7.6)	18 (8.6)
31-40	18 (17.3)	16 (15.4)	34 (16.3)
41-50	32 (30.8)	30 (28.8)	62 (29.8)
>50	44 (42.3)	50 (48.1)	94 (45.2)
Gender			
Male	64 (61.5)	70 (67.3)	138 (66.3)

Female	40 (38.4)	34 (32.7)	74 (35.7)
Socioeconomic status			
Class I	44 (42.3)	38 (36.5)	82 (39.4)
Class II	30 (28.8)	28 (26.9)	58 (27.9)
Class III	20 (19.2)	27 (25.9)	47 (22.6)
Class IV	10 (9.6)	11 (10.6)	21 (10.1)
Hypertension			
Present	54 (51.9)	58 (55.7)	112 (53.8)
Absent	50 (48.1)	46 (43.8)	96 (46.2)
Diabetic polyneuropathy			
Present	39 (37.5)	44 (42.3)	83 (39.9)
Absent	65 (62.5)	60 (57.6)	125 (60.1)
Cerebrovascular disease			
Present	29 (27.9)	34 (32.7)	63 (30.3)
Absent	75 (72.1)	70 (67.3)	145 (69.7)

Table 2: Distribution of the patients based on the drug intake

Variable	Intervention group n (%)	Control group n (%)	Total n (%)
Oral antidiabetic drug			
Yes	70 (67.3)	55 (52.9)	125 (60.1)
No	34 (32.7)	50 (48.1)	84 (39.9)
Insulin			
Yes	44 (42.3)	48 (46.1)	92 (44.2)
No	60 (57.6)	56 (53.9)	116 (55.8)
Renin-angiotensin inhibitor			
Yes	39 (37.5)	45 (43.3)	84 (39.4)
No	65 (62.5)	59 (56.7)	124 (59.6)
Statin treatment			
Yes	33 (31.7)	40 (38.5)	73 (35.1)
No	71 (68.3)	64 (61.5)	135 (64.9)

Table 3: Various renal parameters before and after the anti-VEGF therapy

Variable	Group	Baseline	Post-treatment	p-value
HbA1C	Intervention group	7.4 ± 0.15	8.5 ± 0.23	<0.001
	Control group	7.5 ± 0.19	7.7 ± 0.16	
eGFR	Intervention group	77.2 ± 2.12	65.7 ± 1.15	<0.001
	Control group	80.6 ± 2.71	76.9 ± 0.69	
Serum creatinine	Intervention group	1.1 ± 0.13	1.8 ± 0.13	<0.001
	Control group	1.1 ±0.18	1.2 ±0.13	
Serum urea	Intervention group	26.5 ±1.8	38.8 ± 2.15	<0.001
	Control group	29.8 ± 1.27	32.4 ± 1.39	
Systolic Blood Pressure	Intervention group	130 ± 2.29	142 ± 2.33	<0.001
	Control group	133 ± 1.73	140 ± 1.89	

***p-value less than 0.05 is taken as significant**

Discussion

Diabetic retinopathy is one of the common complications seen among patients with uncontrolled diabetes mellitus. Patients with diabetic retinopathy typically experience blindness due to diabetic macular oedema. Despite the abundance of accessible therapeutic choices, none was completely safe and effective. The anti-VEGR has been used for cancer treatment for a long time, and it has been shown to either cause or exacerbate renal function, proteinuria, and hypertension [13]. Anti-VEGF therapy is one of the newer treatment regimens that provide promising results, and it was found to be safe because of its low systemic absorption. Still, studies have shown that this treatment was also found to be associated with renal damage [14,15]. In our study, diabetic macular oedema was seen more commonly among patients with more than 50 years (45.2%), followed by 41 to 50 years (29.8%). Males were more commonly affected (66.3%), and the socio-economic status was higher (39.4%).

The study by Nguyen et al.[16] Showed that the mean age of the patients with diabetic retinopathy was 62 years, and males were commonly affected (53.5%). Another study by Haliyur et al.[17] Also

showed that the mean age of patients with diabetic macular oedema was 62 years. Still, the study showed that females (55%) were more commonly affected by the disease). Malhotra et al.[18] Showed that low socioeconomic status was associated with a higher risk of diabetic macular oedema. In our study, 53.8% of the patients had hypertension and diabetic polyneuropathy, and cerebrovascular disease was noted in 39.9% and 30.3% of the patients, respectively. Similar to our study, the study by del Cura et al.[11] Also showed that about 80.3% of the patients with diabetic macular oedema had hypertension, but diabetic polyneuropathy and cerebrovascular disease was noted in 10.6% and 13.6% of the patients. Under normal circumstances, the ocular barrier, which sequestrates the drug locally, delays or prevents the systemic absorption of anti-VEGF. Patients with diabetic retinopathy and vascular occlusion-induced macular degeneration and macular oedema were shown to have disruption to this barrier, which allowed the medication to pass through and be more widely absorbed [19]. Also, the kidneys expressed the VEGF receptors more, and the podocytes expressed it. The function of the glomerular capillary and tubular endothelial cells regulated it [20]. Studies have shown that the glomerular endothelium is developed and maintained in large part by VEGF. It is essential for the survival and proliferation of mesangial cells, which further facilitates vasodilation, as well as for the proliferation and differentiation of fenestrated endothelial cells. It also played a part in the interstitial matrix's remodelling [21].

Studies has demonstrated that the intravascular depletion of VEGF caused by continuous anti-VEGF injections impacts endothelial cell and podocyte signalling, ultimately leading to inflammation through the renin-angiotensin-aldosterone pathway. When compared to the patient's baseline data, our study shows a relative increase in the various kidney parameters following the conclusion of anti-VEGF medication. And similar to our study, the study by Hanna et al.[22] also showed a deterioration in the renal parameters, which was supported by the study by Rivero et al.[23] Which also showed similar findings. These results suggest a possible increased risk of worsening renal function in patients with diabetes—however, the study by Kameda et al.[24] and O'Neill et al.[25] There was no change in renal filtration or microalbuminuria deterioration among the patients who received anti-VEGF therapy.

The studies have shown that not all the VEGF blocking agents were found to have the same risk of causing renal dysfunction. And among the agents, ranibizumab was found to be the safest drug [26]. The study also demonstrates that switching patients from aflibercept plus bevacizumab to ranibizumab can reduce the likelihood of systemic side effects and decrease absorption following intravitreal injections [27]. The present study is not without limitations. The study was done retrospectively on a small population in a single centre.

Conclusion

The study showed that diabetic patients with diabetic macular oedema could be treated with anti-VEGF treatment. Various parameters such as renal function, blood pressure, and HbA1C should be closely monitored during the treatment. By this, the early effects of the drug on the renal system of the body can be easily identified and prevented in the earlier stage. The study also recommends having a multicentre, prospective study with a larger sample size to confirm the study's findings.

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