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Mini Observational	:	Characteristics of Diabetic Macular Edema Patients Who Undergo Intravitreal Vascular Endothelial Growth Factor Inhibitors Treatment
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CHARACTERISTICS OF DIABETIC MACULAR EDEMA PATIENTS WHO UNDERGO INTRAVITREAL VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS TREATMENT

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ABSTRACT

Introduction: Diabetes mellitus (DM) is a group of metabolic disorders with diabetic retinopathy as the most common microvcascular complication. An important manifestation of DR is diabetic macular edema (DME) that occurs across all DR severity levels. Intravitreal vascular endothelial growth factor (VEGF) inhibitors for DME treatment have emerged as preferred therapy in the past few years.
Purpose: to describe the characteristics of diabetic macular edema patients who undergo intravitreal VEGF inhibitors treatment.
Method: A total of 31 consecutive patients with DME diagnosis who undergo intravitreal VEGF inhibitors treatment from Januari to December 2018 were included. Data from medical records on patient demographics, comorbidities, ocular history, ophthalmic examination findings including type of DME, and central macular thickness (CMT) via spectral domain (SD) optical coherence tomography (OCT).
Results: SD-OCT (90.32%) was the most common diagnostic method. Diffuse DME with and without cyst found in 88.89%. There were 80.56% of patients had a good anti-VEGF respons. Average HbA1c level was 8,37 (0.32) % in the poor responsive group.
Conclusion: Type 2 diabetes mellitus was the cause of DME in all patients of this study. Most of the DME patients were diffuse DME. Anti-VEGF High HbA1c level was found in poor responsive group.

Keywords: Diabetic Macular Edema, Intravitreal Vascular Endothelial Growth Factor Inhibitor

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic disorders characterised by high blood glucose levels. High blood glucose levels in persistent condition cause various complications such as generalized vascular damage affecting the heart, eyes, kidneys and nerves. The global prevalence of diabetes in adults has been increasing over recent decades. The International Diabetes Federation (IDF) estimated the global prevalence to be 151 million in 2000. The number increase to 451 million (age 18–99 years) people with diabetes worldwide in 2017.[1,2]

Indonesia is the fifth largest adult-onset diabetes population in the world. WHO estimated an increasing number from current estimate of around 6.5 million to more than 20 million by 2030 in Indonesia. This number did not include people with

undiagnosed diabetes, who accounted for nearly 50% of the total diabetic cases in the population.[1,3]

Diabetic retinopathy (DR) is the most common microvascular complication of diabetes. An important manifestation of DR is diabetic macular edema (DME) that occurs across all DR severity levels of both NPDR and PDR. DME represents the most common cause of vision loss in patients with DR and affects the central vision.[4,5]

There are two modalities of treatment for DME, laser photocoagulation and intravitreal vascular endothelial growth factor (VEGF) inhibitors or anti-VEGF. Focal and/or grid laser photocoagulation of leaking microaneurysms and areas of retinal thickening had been the standard of care for DME since the 1980s. Intravitreal VEGF inhibitors have emerged as preferred therapy for many patients with DME within the past few years. The prevalence of DME was reported as 6.81% among patients with diabetes worldwide. Some study estimated in the year 2030, 350 million people worldwide will have diabetes and 100 million of them will have DME as the result of their diabetes.[5,6]

The purpose of this study is to describe the characteristics of diabetic macular edema patients who undergo intravitreal VEGF inhibitors treatment.

METHODS

This is a retrospective observational study. The data of this study were taken from medical records in Cicendo Eye Center National Eye Hospital. We collected all 31 cases of diabetic macular edema patients who undergo intravitreal vascular endothelial growth factor inhibitors within periode of January to December 2018.

All medical records were evaluated and data on demographics and medical history were recorded. This included history of diabetes (type, treatment, time from onset to DME diagnosis, and follow-up care), hypertension and receipt of antihypertensive treatment, blood biochemistry (fasting blood glucose, HbA1c, lipid profile), ocular history (reason for visiting an ophthalmologist, concomitant ocular diseases, and previous eye operations), ophthalmic examination findings including uncorrected visual acuity (UCVA) using Snellen chart, type of DME, central macular thickness using spectral domain (SD) optical coherence tomography (OCT), CMT at the time of diagnosis, and planned pharmacological treatments (corticosteroids, antivascular endothelial growth factor [anti-VEGF] agents) and nonpharmacological treatments (laser photocoagulation, vitrectomy). Data

in this study were analyzed using Microsoft Excel 2016.

RESULTS

We reviewed 31 consecutive patients [mean (SD) age: 54.3 (6.75) years, 58% female]. All patients with type 2 diabetes. The time from onset of diabetes to diagnosis of DME was less than 5 years in 29% of patients, 10-14 years in 25.8% of patients, and was more than 20 years in 3.2% of patients. We found 61.3% patients were receiving treatment for diabetes. Blood biochemistry data were available only for 25 patients (80.6%). These data indicate that the mean (SD) fasting blood glucose level was 132.76 (20.36) mg/dL, HbA1c level was 7.88 (1.1) %, and total cholesterol level was 259.2 (119.3) mg/dl.

Table 1: Baseline characteristics of patients

Age	
Mean	54.3
SD	6.75
Min-Max	36-66
Sex, n (%)	
Male	13 (42)
Female	18 (58)
Systolic Blood Pressure (mmHg), mean (SD)	135.7 (22.9)
Diastolic Blood Pressure (mmHg), mean (SD)	80.67 (9.9)
Hypertention, n (%)	
Present	16 (51.6)
Diabetes, n (%)	
Type 2	31 (100)
Undertreatment	19 (61.3)
Time from onset of diabetes to DME diagnosis, n (%)	
Less than 5 years	9 (29)
5–9 years	7 (22.6)
10–14 years	8 (25.8)
15–19 years 193 (20.4)	6 (19.4)
More than 20 years	1 (3.2)
Blood biochemistry (N = 25)	
Fasting blood glucose (mg/dL)	
Number of patients (n)	25
Mean (SD)	132.76 (20.36)
HbA1c (%)	
Number of patients (n)	11
Mean (SD)	7.88 (1.1)
Total cholesterol (mg/dL)	
Number of patients (n)	5
Mean (SD)	259.2 (119.3)
LDL (mg/dL)	
Number of patients (n)	5
Mean (SD)	156.2 (85.57)
HDL (mg/dL)	
Number of patients (n)	5
Mean (SD)	37.7 (9.6)
Triglyceride (mg/dL)	
Number of patients (n)	4
Mean (SD)	125 (69.1)

LDL: Low-density lipoprotein, HDL: High-density lipoprotein

Most patients came due to vision problems (52.2%) after reffered from secondary hospital as showed in Table 2. The most common concomitant eye disease was cataract (58.06%). There were 3 patients (9.67%) had previous ocular operations. 4 patients underwent eye operation with vitrectomy was the most common eye operation as a treatment for their vitreous haemorrhage.

Anti-VEGF treatment had been given in 41 eyes of 31 patients. The UCVA was measured using a Snellen chart in all patients. The mean (SD) Snellen score was 0.2 (0.17) for the right eye and 0.16 (0.13) in the left eye group. Intraocular pressure was measured by a pneumatic method for all patients. The mean (SD) intraocular pressure in right eye group was 16.13 mmHg (4.76) and in left eye was 16.71 mmHg (2.97) as seen in Table 3.

Table 2: Ocular history of patients

Reason for visiting ophthalmologist, n (%)	
Routine control	4 (12.9)
Vision problem	27 (87.1)
Concomitant eye diseases, n (%)	
Cataract	18 (58.06)
Glaucoma	2 (6.45)
Other	1 (3.23)
Previous eye operations, n (%)	3 (9.67)
Total eye operations, n (%)	4 (12.9)
Glaucoma surgery	1 (25)
Vitrectomy	3 (75)

Table 3. Ophthalmic examination findings

Anti-VEGF Treatment (n)	41
Snellen - uncorrected visual acuity score	
Mean (SD)	0.16 (0.15)
Median (min-max)	0.1 (1/300 - 0.63)
Intraocular pressure (mmHg), mean (SD)	16.38 (4.06)
OCT Examination, n (%)	36 (87.80)
DME type, n (%)	
Focal Macular Thickening	3 (8.33)
Diffuse Thickening without Cysts	21 (58.33)
Diffuse Cystoid Macular Edema	11 (30.56)
Tractional Macular Edema	1 (2.78)
Total	36 (100.00)
Central macular thickness (μm)	
Mean (SD)	383.31 (138.48)
n (%)	
≤300 μm	12 (33.33)
>300 μm	24 (66.67)

SD-OCT was performed in 36 eyes (90.32%). Diffuse DME without Cysts was diagnosed in 58.33% of eyes, diffuse cystoid macular edema in 30.56% of eyes, focal DME in 8.33% of eyes, and 2.78% of eyes had tractional DME. The mean (SD) CMT at the time of diagnosis was 383.31 (138.48) μm and a CMT greater than 300 μm was present in 24 eyes (66.67%).

There were several changes after intravitreal anti-VEGF injection. SD-OCT was performed to see any changes in CMT.

The results showed 80.56% of patients had a good anti-VEGF respons. The mean (SD) CMT after the injection was decreased to 343.03 (138.48) μm. CMT greater than 300 μm was decreased to 20 eyes (55.0%). The results showed 80.56% of patients had a good anti-VEGF respons. Otherwise, there were 7 unresponsive eyes (19.44%) after the injection of anti-VEGF.

Table 4. Findings after anti-VEGF treatment

Snellen - uncorrected visual acuity score	
Mean (SD)	0.25 (0.19)
Median (min-max)	0.16 (1/300-0.63)
Central macular thickness (μm)	
Mean (SD)	343.03 (133.38)
n (%)	
≤300 μm	16 (45.0)
>300 μm	20 (55.0)
	n (%)
Good responsive	29 (80.56)
Poor responsive	7 (19.44)

DISCUSSION

DME is the most common cause of vision loss in patients with DR. The mean age of our study was 54.3 years with type 2 diabetes mellitus as the cause of all the DME. This result is similar with Liew et al in their cohort study of DME with the mean age is 58.2 years with most of the subjects are type 2 diabetes mellitus. Only 61.3% of our patients were receiving antidiabetic treatment. There are 58% female who had DME in this study. It is similar with Sasongko et al in Indonesia, but different with another study such as Luxmi et al in India and Eldem et al in Turkey. Male had more numbers in their studies.[3,7,8]

Chronic hypertension is one of risk factor associated with increased risk of developing DME. There are endothelial cells damage leading to changes in the structure of blood vessels and other vascular dysfunctions. Many studies have implicated elevated blood pressure with an increased risk of DME. There were 16 patients (51.6%) in this study who also had hypertension with blood pressure above 140/90.[4,5,9]

Time for onset DME in our study showed that 29% patients got DME in less than 5 years and 25.8% in 10-14 years. Liew et al study in Sydney found that the participants in their study having a mean duration of diabetes of 12.5 years. The previous study reported increase in the prevalence of DME with longer duration of diabetes mellitus. Most of the patients in this study had a short time of onset probably because the eye complains became their first symptom to come to the clinic, rather than their high blood sugar level.[8,9]

The average HbA1c level was 7.88%. This finding supported the previously reported association of elevated levels of HbA1c with DME prevalence and deterioration, particularly for patients whose HbA1c level is above 7%. The other blood biochemistry was lipid profile. The association between

DME and lipid levels has been equivocal. Our study found a higher mean total cholesterol level with 259.2 mg/dl with a lower mean of HDL (37.7 mg/dl).[5,9]

The symptoms of DME range from slight visual blurring to complete blindness if left untreated. DME triggered from diabetes-induced breakdown of the blood-retinal barrier (BRB). The breakdown produces consequent vascular leakage of fluid and proteins into the neural retina. The extravasation of fluid into the neural retina creates abnormal retinal thickening and sometimes cystoid edema of the macula. SD-OCT was used in our study to confirmed retinal thickening. A previous study stated that pattern of edema classification on SD-OCT can have a significant impact on treatment decisions and subsequent visual outcome. Diffuse DME with or without cyst was the most type of DME with 88.89% in our study, similar with Eldem et al findings in Turkey. [9–11]

We found that 66.67% eyes had baseline CMTs greater than 300 μm before the injection. Patients with diffuse DME and with a higher baseline CMT (>300 μm) were less likely to have received antidiabetic treatment. Higher CMTs found significantly in untreated than treated patients with diabetes.[9,12]

The results after intravitreal anti-VEGF injection was good. There was an increasing average visual acuity to 0.25 (0.19) using Snellen chart after one-month follow-up. The SD-OCT results showed 80.56% of patients had a good anti-VEGF respons with a decreased number of CMT. The mean (SD) CMT after the injection was decreased to 343.03 (138.48) μm. CMT greater than 300 μm was decreased to 20 eyes (55.0%). Most of the patients just got one injection of anti-VEGF. Otherwise, there were 7 poor respons eyes (19.44%) from 7 different patients after the injection of anti-VEGF.

The poor responsive group patients consist of 5 patients who just got 1 injection, 1 patient got 2 injection, and 1 patient got 3 injection of anti-VEGF. All of them had a poor glycemic control with average (SD) fasting blood sugar was 130.2 (25.48) mg/dL. Average HbA1c was 8,37 (0.32) % in this group. Matsuda et al found the role of systemic factors on the outcomes of anti-VEGF treatment for DME. The important metabolic parameter for anti-VEGF treatment was HbA1c. They found HbA1c level more than 7.0% had a less reduction in CMT after injection. Glucose control influences the different outcomes among patients.[13,14]

CONCLUSION

All patients in our study had type 2 diabetes mellitus. Most of the patients had poor glycemic control with DME in less than

5 years. Vision problem was the most frequent reason for seeking care from an ophthalmologist. More than half of patients had baseline CMT values greater than 300 μm, and most of the patients had diffuse DME. Anti-VEGF treatment was found succesfull in reducing DME in most of the patients. Small group of patients were not had a good response after the injection of anti-VEGF. High HbA1c level was found in this group.

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