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The outcome of bevacizumab treatment for diabetic macular oedema at the Charlotte Maxeke Johannesburg Academic Hospital

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The outcome of bevacizumab treatment for diabetic macular oedema at the Charlotte Maxeke Johannesburg Academic Hospital

Dr Irfaan Hasrod

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Masters of Medicine in Ophthalmology

Johannesburg 2018

Declaration

I Irfaan Hasrod declare that this Research Report is my own, unaided work. It is being submitted for the Degree of Master of Medicine in the branch of Ophthalmology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

……

(Signature of candidate)

……day of …….20…….in……

Dedication

To my wife Aayesha, my parents Yousuf and Abida and son Umar for their unwavering support, love and motivation

Presentations arising from research project

none

Publications arising from research project

none

Abstract

Aim: The aim of this study is to examine the outcomes of treatment of diabetic macular oedema using bevacizumab at Charlotte Maxeke Johannesburg Academic Hospital by analysing the change in visual acuity and a change in retinal macular thickness at three months following the first intravitreal bevacizumab injection.

Method: A retrospective study of the records of all patients treated with intravitreal bevacizumab for diabetic macular oedema from 1st January 2013 to 31 December 2015 was done.

Results: A total of 178 eyes (from 151 patients) were treated for diabetic macular oedema during the period of 1st January 2013 to 31st December 2015. Seventeen of these eyes were treated with 1 injection, 33 with 2 injections and 128 eyes with 3 injections from baseline to three months. From the patients who were treated with 3 injections, 80 completed treatment at three months and 48 went on to receive more injections. Thus dividing the eyes into 4 groups.

Patients who received 1 injection showed no median change in VA, logMAR 1.0 interquartile range ”IQR” (0.6LogMAR; 2.0 LogMAR) at baseline to LogMAR 1.0 IQR (0.48logMAR; 2.0LogMAR) at three months. Patients who received 2 injections also showed no median change in VA, logMAR 0.77 IQR (0.6logMAR; 0.77logMAR) at baseline to logMAR 0.77 IQR (0.6logMAR; 1.0logMAR) at three months.

Patients who received 3 injections showed an increase of visual acuity, LogMAR 0.77 IQR (0.6logMAR; 1.0logMAR) at baseline to logMAR 0.60 IQR (0.48logMAR; 0.77logMAR) at three months. The patients who received 3 injections at baseline and went on to receive further injections also showed an increase in median visual acuity, logMAR 0.77 IQR (LogMAR0.6; logMAR1.00) at baseline to logMAR 0.60 IQR (logMAR0.48; logMAR1.00) at three months.

There was a decrease in macula thickness in all 4 groups. In patients receiving three injections at three months there was a significant p-value of 0.018 for the change in macula thickeness from baseline of 313 micrometres IQR (256micrometres; 419micrometres) to three months of 266 micrometres IQR (219micrometres; 356micrometres). For patients who

received three injections at three months but went on to receive further injections, a significant p-value of P=0.0061 for the change in macula thickness from baseline of 398 micrometres IQR (328micrometres; 452micrometres) to three months of 321 micrometres IQR (262micrometers; 387 micrometers).

Conclusion: Bevacizumab is useful in the treatment of Diabetic macular oedema in terms of an increase in visual acuity and decrease in macular thickness, provided patients receive a loading dose of three intravitreal injections in the first three months of treatment.

Acknowledgements

To my Supervisor, Dr Aubrey Makgotloe, for his immense time, patience, effort and help to ensure the success of this project, thank you for the guidance in both this project and for the guidance in life as a whole.

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Nomenclature

ANOVA	Analysis of Variance
CFT	Central foveal thickness
CME	Cystoid macular oedema
CMJAH	Charlotte Maxeke Johannesburg academic hospital
CSMO	Clinically significant macular oedema
DMO	Diabetic macular oedema
DRT	Diffuse retinal thickening
IQR	Interquartile range
logMAR	Logarithm minimal angle of resolution
OCT	Optical coherence tomography
SD	Standard deviation
SRD	Serous retinal detachment
VEFG	Vascular endothelial growth factor

CHAPTER 1

1 Introduction and literature review

1.1 Background

Diabetic macular oedema "DMO" is a consequence of micro vascular changes in the retina and results in the central loss of vision in patients with diabetic retinopathy. Damaged retinal vessels leak, thereby causing swelling of the macula. The leakage is caused, amongst other factors, by the up regulation of vascular endothelial growth factor.[1] Bevacizumab is an anti vascular endothelial growth factor "VEGF" which binds to receptors in the retina causing a decrease in leakage and thus an improvement of vision.[2] Various studies have been published on the outcome of bevacizumab treatment of DMO, demonstrating visual acuity improvement. In Charlotte Maxeke Johannesburg academic hospital 'CMJAH', bevacizmab is the predominant treatment for DMO, however the outcome of treatment has never been studied. This study analysis the visual outcome of patients treated with bevacizumab for DMO.

1.2 Literature review

1.2.1 Introduction

Diabetic macular oedema is a leading cause of blindness in the world and its prevalence is increasing with the increasing prevalence of diabetes. In diabetic patients, blindness is considered to be the third most common cause of morbidity, following cardiovascular accidents and amputations.[3] At the time of diagnosis of diabetes mellitus, diabetic retinopathy is present in up to 30 percent of individuals.[3] Twenty-six percent of individuals with diabetic retinopathy present with diabetic macular oedema.[4]

1.2.2 Epidemiology

The prevalence of type 2 diabetes in South Africa was 9% in 2009, this increased by 3,5% from 2005.[5] In 2017, the national prevalence of diabetes in South Africa is estimated to be 5.4% with a confidence interval of (3.2%-10.8%).[6] Diabetic macular oedema increases from about 3% in recently diagnosed type 2 diabetics to 29% in those suffering from diabetes for more than 20 years.[7]

1.2.3 Pathophysiology

In the retinal circulation, capillaries are non-fenestrated and capillary endothelial cells have tight junctions and hence they normally do not leak fluid or blood. The primary reason for diabetic macular oedema is the leakage of fluid from surrounding vessels. The two pathophysiologic mechanisms largely responsible for this leakage are anatomical and biochemical mechanisms.[8]

The anatomical changes are endothelial cell loss. This loss of endothelial cells is often preceded by marked dysfunction and loss of surrounding pericyte cells, thickening of the basement membrane, loss and dysfunction of the glial cells.[8]

Molecular changes include an increase of reactive oxygen species and pro-inflammatory factors such as, advanced glycation end products, intracellular adhesion molecule (ICAM-1), complement C5-9 deposition and cytokines and up regulation of VEGF.[8]

VEGF is thought to increase vascular permeability by phosphorylating tight junction proteins in the blood retinal barrier. These proteins include occludin and zonula occludens-1.[9]

1.2.4 Risk Factors for Diabetic Macular Oedema

Risk factors for developing diabetic macular oedema includes : the type and duration of diabetes, glycaemic control, hypertension, dyslipidemia, nephropathy.[10,11]

Diabetic macular oedema has been shown to be twice as common in type 1 diabetes than type 2 diabetes independant of the duration of diabetes.[10] Diabetic macular oedema ranges from 3 percent in patients who have had diabetes for 10 years, to twenty percent in patients with 20 years or more of diabetes. [10]

Tight control of diabetes has been shown to decrease the incidence of diabetic macular oedema. In the Diabetes Control and Complications Trial (DCCT), tight glycaemic control was associated with a 46% reduction in diabetic macular oedema.[12] An important marker for glycaemic control is glycated haemoglobin (HbA1c). It was shown in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) that an elavated baseline HbA1c was associated with an increased risk of diabetic macular oedema.[13]

Concomitant hypertension is another risk factor for the development of diabetic macular oedema. Hypertension is thought to compromise vascular permeability in the already damaged diabetic vasculature by increasing perfusion pressure, thus causing more leakage and leading to diabetic macular oedema.[11] It has been shown in the Wisconsin Epidemiologic Study of Diabetic Retinopathy that hypertension increased the prevalence of diabetic macular oedema three fold.[14]

Dyslipidemia affects the retinal circulation in two ways. First the formation of atherosclerotic plaques which can occlude vessels leading to ischaemia and hypoxia. Secondly by causing endothelial dysfunction though local inflammatory responses. Both of which leads to VEGF upregulation.[15] A study by Raman et al showed that dyslipidemia is independently associated with diabetic macular oedema.[16]

Nephropathy has also been shown in a 15-year follow up study to be associated with the development of diabetic macular oedema.[17] It is beleived that lower serum protein concentration in renal dysfuction reduces the plasma colloidal osmotic pressure, increasing oedema and fluid retention, thus contributing to diabetic macular oedema.[18]

1.2.5 Diagnosis

Diabetic macular oedema is a pathological swelling of the layers of the neurosensory retina at the macula secondary to diabetes. It can be diagnosed both clinically by means of slit-lamp biomicroscopy and by ophthalmic imaging techniques such as fluoroscein angiography and fundus stereo photography. Optical coherence tomography (OCT) being the most commonly used modality.[19] OCT allows a micron-level, high-resolution diagnostic tool that uses infrared light within 800-840nm wavelength to provide a real-time non-invasive image of the retina.[20]

Diabetic macular oedema can be categorised by OCT findings into 4 different patterns. These are namely, diffuse retinal thickening “DRT”, cystoid macular oedema “CME”, serous retinal detachment “SRD” and vitreomacular interface abnormalities “VMIA”.[19]

Diffuse retinal thickening is characterized by a sponge-like thickened retina. The outer retinal layers show low reflective areas and displace the inner retinal layers anteriorly. Cystoid macular oedema is characterized by intraretinal cystic structures extending in a radial fashion from the foveola. Histopathological examinations reveal that the intraretinal cysts are due to intracytoplasmic swelling and necrosis of Muller cells with further neuronal degeneration. Serous retinal detachment is defined as a detachment of the neurosensory retina from the retinal pigment epithelium associated with a clear space between the two. Vitreomacular interface abnormalities can be characterized by either an epiretinal membrane or vitreomacular traction. Both of which are presented with a highly reflective membrane at the vitreoretinal surface .[19]

1.2.6 Classification

The Early Treatment Diabetic Retinopathy Study defined the presence of clinically significant macular oedema “CSMO” as: retinal thickening within 500 micrometers of the centre of the fovea, hard exudates within 500 micrometers of the centre of the fovea with adjacent retinal thickening or at least 1 disc area of retinal thickening of any part of which is within 1 disc diameter of the fovea.[21,22]

1.2.7 Treatment of diabetic macular oedema

Treatment of diabetic macular oedema involves both controlling the risk modifiable risk factors such as hypertension, hyperglycaemia, and dyslipidemia and by specific therapies.[11]

Argon laser photocoagulation has been the main modality of treatment of macular oedema since the publication of the results of the Early treatment Diabetic Retinopathy study (ETDRS) in the 1980s. Argon laser photocoagulation was used as a focal treatment of microaneurysms and other areas of focal leakage with a 50-100um spot size to create a whitening around the area of leakage, or as a grid treatment of permeable capillaries of leakage within two disc diameters of the centre using a spot size of 500-200um, 1 burn width apart. This study showed that there was an approximately 50% reduction in the rate of

moderate visual loss at 3 years following argon laser photocoagulation compared to no treatment. However, in patients with oedema involving the centre of the macular, the risk of moderate visual loss at three years was 15% with treatment. Laser photocoagulation has the side effects of visual field defects, retinal fibrosis and retinal scars. Recent studies also show that certain patients suffer severe visual loss although having aggressive treatment.[3,23]

Intravitreal steroids and anti-vascular endothelial growth factor (VEGF) agents are also used in the management of diabetic macular oedema following randomized clinical trials which showed that they have better efficacy compared to laser.[3,23] Intravitreal steroids have potent anti-inflammatory effects, and have a beneficial therapeutic effect on both retinal thickness and visual acuity in short term treatment of diabetic macular oedema. Intravitreal steroid implants are also available in sustained release formulas for the treatment of diabetic macular oedema.[3,23] The first intravitreal corticosteroid used for diabetic macular oedema was intravitreal triamcinolone. A study by the Diabetic Retinopathy Clinical Research Network involving 840 study eyes compared the efficacy of 1mg and 4 mg intravitreal triamcinolone compared to focal/grid laser photocoagulation for the treatment of diabetic macular oedema. They found that 4mg intravitreal triamcinolone had the best effect within 4 months of application, but it was short lived and by one year had the same effect as 1mg and focal/grid laser.[24] It has been show that intravitreal triamcinolone has a longer-lasting effect on visual acuity if it combined with focal/grid laser treatment. The downside of using intravitreal triamcinolone is the adverse effects of treatment such as raised intraocular pressure and increased incidence of cataract formation.[25]

Sustained released formulas used in the treatment of diabetic macular oedema includes the sustained-released intravitreal dexamethasone implant Ozurdex. Besides allowing for a better controlled delivery of the drug it also has a lower rate of adverse effects.[26] A study evaluated the efficacy of Ozurdex compared to observation in patients' eyes with persistent diabetic macular oedema. It found that Ozurdex implant was well tolerated and improved the visual acuity and central retinal thickness as well as decreasing fluorescein leakage compared to observation.[27]

Anti-vascular endothelial growth factor agents used in treating diabetic macular oedema include pegaptanib, ranibizumab, aflibercept and bevacizumab.[1] They target vascular

endothelial growth factor which is known to be the most potent proponent of vascular permeability[28], and has been found to be 50000 times more potent when compared to histamine[29]. Vascular endothelial growth factor has been shown to act directly on the permeability of intact blood vessels by promoting the entry of inflammatory cells into vessels, which leads to endothelial cell proptosis in the retinal vasculature. Thus by using an anti-VEGF agent this process is halted.[30]

Pegaptinib is a pegylated aptamer that targets the VEGF165 isoform. A study by the Macugen Diabetic Retinopathy study group showed that patients treated with pegaptinib had better visual acuities, increased reduction in the central retinal thickness compared to the sham group.[31]

Ranibizumab is a humanized monoclonal antibody fragment which is directed at all forms isoforms of VEGF-A.[32] The treatment of diabetic macular oedema with ranibizumab is based on many randomized clinical trials. The RESOLVE study (Safety and efficacy of Ranibizumab in diabetic macular edema), study compared the use of bevacizumab to a sham intravitreal injection and showed at 12 months greater improvements in visual acuity and greater decrease in reduction in central retinal thickness compared to the sham.[32] The READ 2 study (Ranibizumab for oedema of the macula in Diabetes) showed that intraocular injections of ranibizumab benefited patients with diabetic macular oedema up to two years and their is a synergistic effect when combined with focal or grid laser.[33] The RESTORE study (Core study to assess the efficacy and safety of Ranibizumab intravitreal injections), showed that ranibizumab as a monotherapy or combined with laser therapy has a greater benefit in terms of visual acuity gain in patients of diabetic macular oedema compared to laser therapy alone.[34]

Aflibercept is a recombinant fusion protein which consists of a VEGF binding domains of human VEGF 1 and 2 receptors fused to the Fc domain of human immunoglobulin G1.[35] The DA VINCI (DME and VEFG Trap-Eye: Investigations of Clinical Impact) study compared aflibercept to macular laser and found significant gains in visual acuity in patients treated with aflibercept.[36] The VIVID (VEGF trap-eye in vision impairment due to DME) study and VISTA (Intravitreal administration of VEGF Trap-Eye in Patients with DME) study, both show the efficacy of Aflibercept in diabetic macula oedema.[37]

Bevacizumab is a monoclonal antibody that inhibits all forms of the VEFG family; it was initially developed for the treatment of colorectal cancer but is currently used as an intravitreal treatment for macular oedema secondary to diabetes and other aetiologies. Genentech/Roche pharmaceutical company trades it as Avastin. In the treatment of diabetic macular oedema, an intravitreal injection of 1.25mg/0.05ml of bevacizumab is injected 3.5-4 mm from the limbus under local anaesthesia. It thus reduces the vascular leak in the macula and aids in reversing the oedema in the macula.[2,3,8,21]

The studies involving the use of bevacizumab use two main parameters to measure the improvement of macular oedema. The first is best-corrected visual acuity (BCVA) expressed as a change in snellen/logMar/ETDRS chart letters or proportion of participants with more than two or three lines BCVA improvement. The second is a measure of central foveal thickness using an optical coherence tomography (OCT).[3]

Several of these studies have demonstrated significant efficacy of anti-vascular endothelial agents in not only preventing loss of vision, but also improving visual acuity as much as two to three snellen lines and significant decrease in the central macular thickness on optical coherence tomography.[2,3,8,22]

The Bevacizumab or laser therapy in the management of diabetic macular edema 'BOLT' trial elucidated this by comparing focal laser photocoagulation and bevacizumab[38]. Eighty patients with persistent DMO after macular laser therapy were assigned to receive continuous laser therapy or bevacizumab. Patients in the bevazicumab treatment arm had a mean gain of 8.6 letter versus 2.5 letters in the laser therapy arm at 24 months (P=0.005).[39]

Lam et al. demonstrated the efficacy of two different doses of bevacizumab in a six month randomized control trial. Patients received three monthly injections of either 1.25mg or 2.5mg bevacizumab. The mean logMAR decreased in both groups and there were significant reduction on the mean central foveal thickness.[40]

Ahmadieh et al. showed the effect of bevacizumab in DMO in a randomized control trial comparing intravitreal bevacizumab with or without triamcinolone. There was both a beneficial effect in visual acuity and mean foveal thickness in patients in the intravitreal arm of the study. At 24 weeks the mean foveal thickness decreased by an average of 95,7 micrometres.[41]

Arevalo at al proved the efficacy of bevacizumab in a 24 months retrospective study. They showed that in patients receiving 1.25mg bevacizumab the logMAR visual acuity improved from 0.88 to 0.57 and the mean central macular thickness decreased from 465+/-145.2 micrometres at baseline to 286.6+/- 81.5 micron at 24 months.[42]

At the CMJAH all patients with DMO with a visual acuity less than 6/12 (Snellen chart) get three loading doses of bevacizumab (one injection per month for three months). Patients are reviewed one week following each injection for clinical signs of endophthalmitis. Following these three injections, patients are reviewed every month and given treatment as needed from month four until there is resolution of the macular oedema or until there is no response to treatment.

1.3 Study Aim and Objectives

The Aim of this study is to analyse the outcomes of treatment of diabetic macular oedema using bevacizumab at Charlotte Maxeke Johannesburg academic hospital 'CMJAH'.

The objectives of this study:

- **Primary objective**: to analyse the visual outcome of bevacizumab treatment of diabetic macular oedema at Charlotte Maxeke Johannesburg academic hospital.
- **Secondary objective**: to analyse the anatomic outcome of bevacizumab treatment of diabetic macular oedema at the Charlotte Maxeke Johannesburg academic hospital

The outcome measures of this study:

- Primary outcome measure: A change in visual acuity at three months following the first bevacizumab injection
- Secondary outcome measure: A change in retinal macular thickness on optical coherence tomography at three months following the first bevacizumab injection

CHAPTER 2

2 Methodology

2.1 Research Question

In patients with diabetic macula oedema how does the use of intravitreal bevacizumab affect the visual acuity and the thickness of the macula at three months from baseline?

2.2 Research Design

This is a hospital-based, restrospective case series review of all patients treated with intravitreal bevacizumab for diabetic macular oedema from 1 January 2013 to 31 December 2015 at CMJAH.

2.3 Materials and Methods

The Human Research Ethics Committee of the University of the Witwatersrand approved this study and consent was obtained from the CEO of CMJAH.

A register of all patients treated with bevacizumab was established by the CMJAH retinal service from the year 2013. This register was analysed and patients who were treated for diabetic macular oedema were selected as study subjects from 1st January 2013 to 31 December 2013.

Study subjects were assigned a number and strict confidentially was maintained as the patients name and hospital number was kept separate from the data sheet number.

The study subjects' files were retrieved from the records departments at CMJAH and a data collection sheet was completed as shown in Appendix 7.1. Data regarding OCT numerical

values and qualitative information was collected from the OCT at the CMJAH. Data regarding the patients HbAlc, renal function and lipid profile was collected by tracing the patients' hospital number on the CMJAH hospital results computer services.

2.4 Sample

The study population are all patients receiving intravitreal injections for diabetic macular oedema at CMJAH and recorded in the intravitreal injections register.

Inclusion criteria:

- Patients who are receiving intravitreal bevacizumab for diabetic macular oedema and recorded in the register of intravitreal injections.
- Patients whose clinical records of the first injection are available

Exclusion criteria:

- Patients receiving intravitreal bevacizumab for other causes of macular oedema
- Patients with inadequate records

2.5 Data Collection

A data collection sheet containing the subject number and relevant clinical information was completed from the hospital records, OCT machine and results computer at the CMJAH. The patients' name and hospital number was kept separate from the data sheet. All information was then captured on a Microsoft Excel spreadsheet.

2.6 Data Analysis

Descriptive data such as the patients age, gender, co-morbidities was analysed from an excel spreadsheet. The visual acuities from a snellen chart notation were converted to LogMAR prior to being analysed. Paired t-tests were used to compare visual acuity and optical OCT measurements before and after injections. Four groups of patients were found in the study, namely those who had one, two, three and those who went on to having more than three injections of bevacizumab. The four groups were compared using Kruskal-Wallis ANOVA from baseline values of visual acuity at baseline and at three months. GraphPad Prism version 5 was used for statistical analysis.

2.7 Limitations

A major limitation of this retrospective study was the missing patient records and incompleteness of data within available patient's records.

CHAPTER 3

3 Results

3.1 Total

A total of 454 patients received intravitreal bevacizumab injections. 167 patients were treated for diabetic macular oedema and 287 were treated for other causes of macular oedema. From the 167 patients treated for diabetic macular oedema, 16 had inadequate records or their files could not be retrieved. Hence, a total of 151 patients were collected for this study after the inclusion and exclusion criteria were applied. From these 151 patients, 178 eyes were treated for diabetic macular oedema during the period of 1 January 2013 to 31 December 2015. From the 178 eyes treated for diabetic macular oedema, 88 were left eyes (49.4%) and 90 were right eyes (50.6%).

3.2 Demographics

The mean age of the patients in this study is 63.8 years with standard deviation of 9.9 years. The majority of patients in the study were females, accounting for 58.3%.

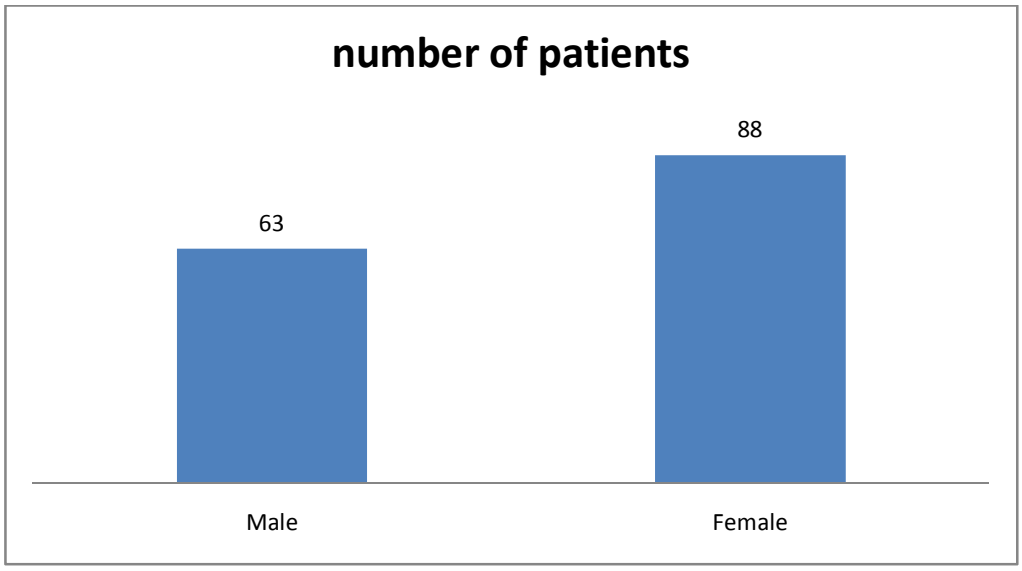


Figure 3.1 Gender of patients

The race of the patients in the study were as follows: 50% of patients were African (89 patients), 19.10% of patients were Caucasian (34 patients), 16.1% of patients were Indian (24 patients), 0.01% of patients were Coloured and 16.29% (29 patients) had a non-specified race.

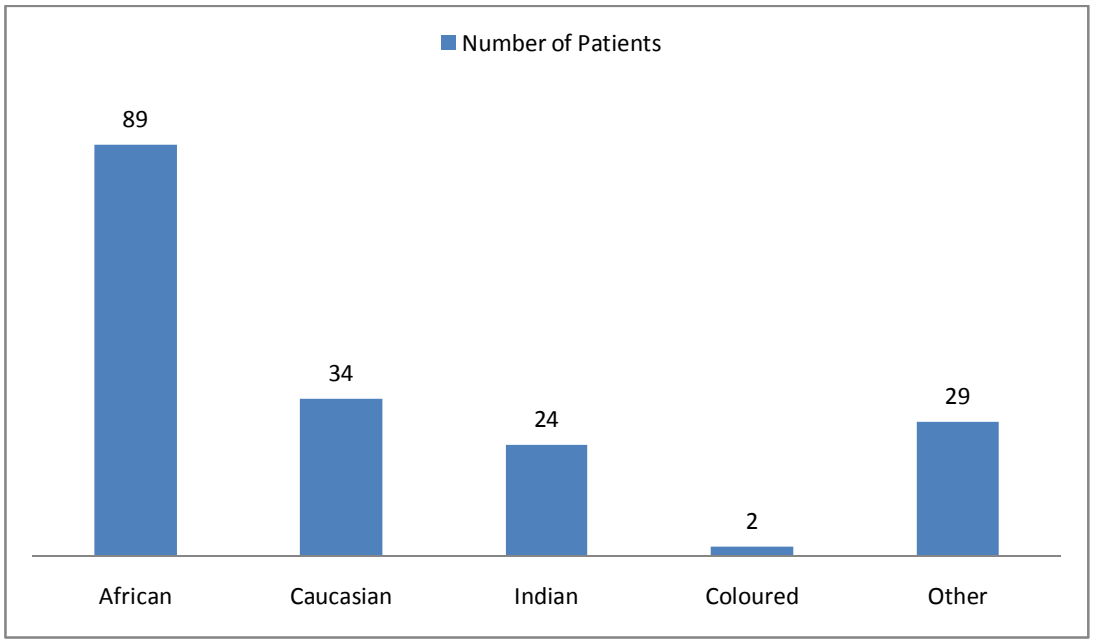


Figure 3.2 Race of patients

3.3 Co-morbidities of patients

3.3.1 Diabetes

From the 151 patients, 3.3% (5 patients) were type 1 and 96,7% (146 patients) were type 2 diabetic.

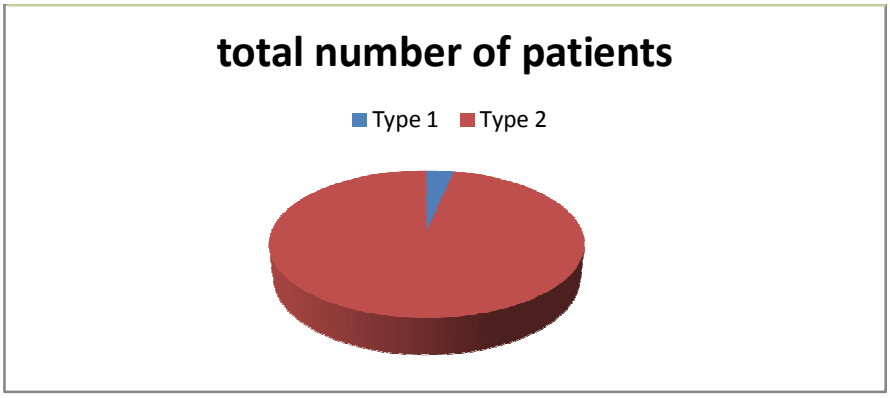


Figure 3.3 Type of Diabetes in study patients

HbA1c was found in the records of 72 patients. The mean HbA1c was 9.11 with a standard deviation of 1.96.

3.3.2 Hypertension

70.2% of the 151 patients were hypertensive, with a mean systolic blood pressure of 162.3mm Hg (SD 16.4) and mean diastolic blood pressure of 83.5mmHg (SD 11.9)

3.3.3 Lipid function

Lipid function was found in the records of 68 patients. 32.1% of these patients (25 patients) had lipid dysfunction. The lipid total median was 4.42 mmol/L with and IQR of 3.76- 5.3 (normal value: <5.2mmol/L). The triglycerides median was 1.77 with and IQR of 1.3-2.2 (normal value: 0.45-1.71mmol/L). High Density lipoprotein median was 1.145 with an IQR of 0.9-1.34 (normal value: >0.91 mmol/L). Low-density lipoprotein mean was 2.5 standard deviation of 2.5 (normal value: <3.4mmol/L).

3.3.4 Renal function

Renal function was found in the records of 81 patients. 50.6% of these patients (41 patients) had renal dysfunction. The Urea median of 81 patients with records was 7.6mmol/L with an IQR of 5.55-10.8 (normal value: 4.0-8.2 mmol/L). The Creatine median was 95.5umol/L with an IQR of 71.3–134 (normal value 50-110umol/L).

Urine albumin:creatine ratio was only found in the records of 9 patients with a median value of 1.4mg/mmol and an IQR of (0.6 – 25.7mg/mmol).

3.4 Baseline Values

3.4.1 Baseline Visual Acuity

The baseline visual acuity of the patients in our study was found in all 178 patients eyes (100% of eyes) and are expressed in terms of a snellen chart notation in the table below:

Baseline V/A	N=178
6/9	0.6% (1)
6/12	3.9% (7)
6/18	14.6 %(26)
6/24	20.8% (37)
6/36	21.9% (39)
6/60	12.9% (23)
CF	22.5% (40)
HM	2.8% (5)

Table 3.1 Baseline Visual Acuities of eyes

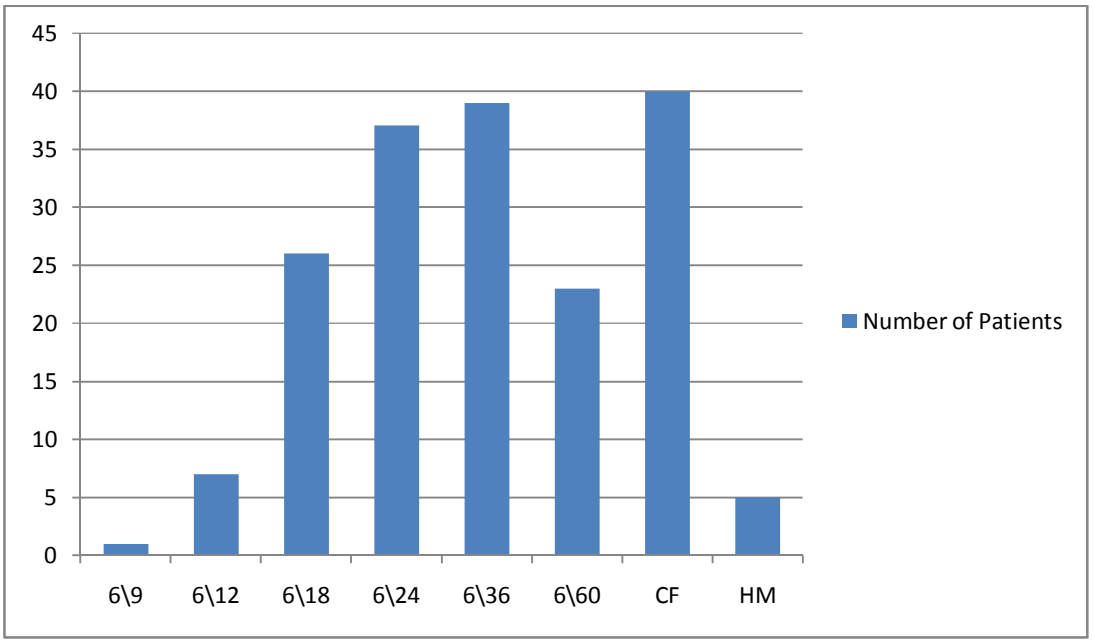


Figure 3.4 Visual acuity of eyes in snellen notation

3.4.2 Baseline OCT

The baseline OCT values were found in 167 eyes treated for DMO. The median OCT thickness was 378 micrometres.

The baseline OCT qualitative assessment of the diabetic macular oedema on 167 eyes (93.8% of total eyes) can be seen in the graph below:

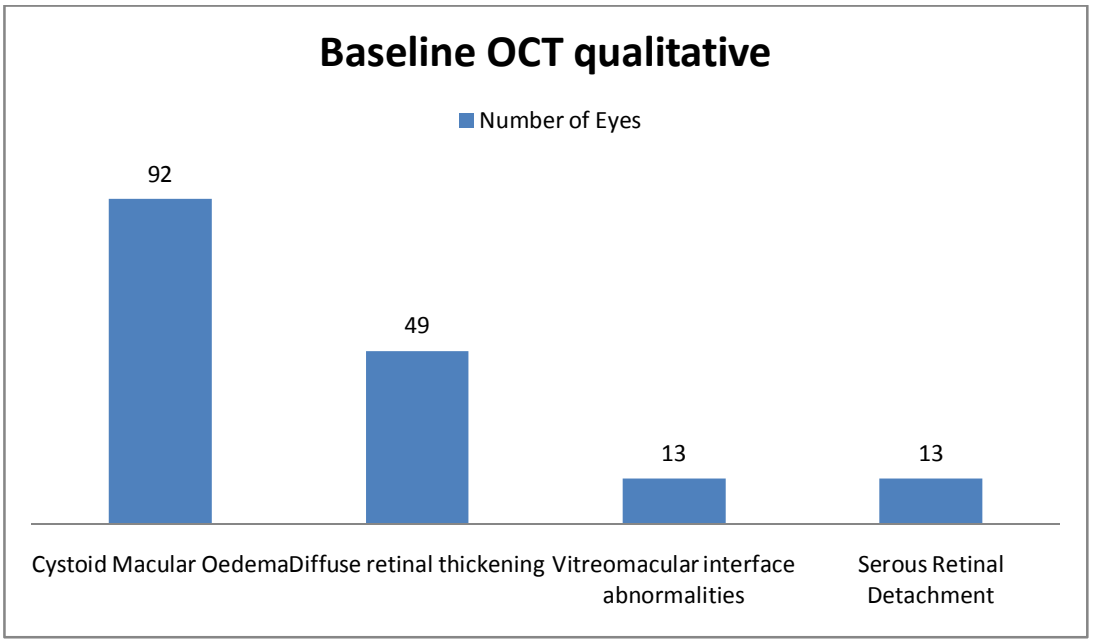


Figure 3.5 Baseline OCT qualitative

Cystoid macular oedema accounted for 92 eyes, diffuse retinal thickening 49 eyes, vitreomacular interface abnormatlites accounted for 13 eyes and 13 had serous retinal detachment

3.5 Total number of injections at 3 months from baseline

From the 178 eyes treated with bevacizumab for DMO, 17 eyes were treated with 1 injection, 33 with 2 injections and 128 eyes were treated with 3 injections

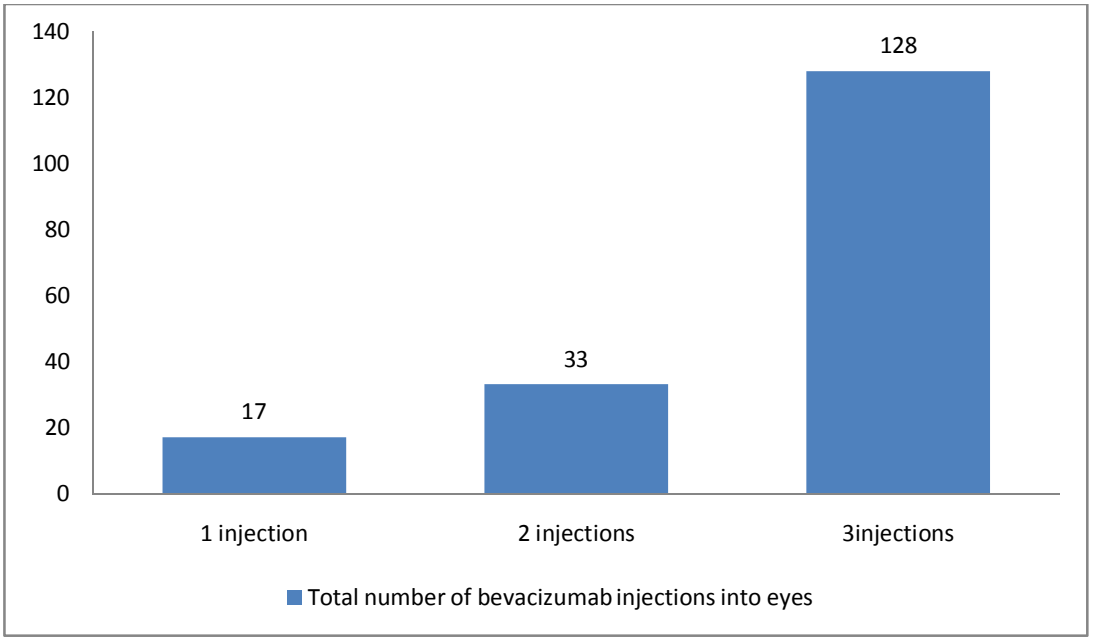


Figure 3.6 Total number of injections in 3 months from baseline

The patients eyes who received 3 intravitreal bevacizumab injections, can be divided into two groups, those who stopped treatment at 3 injections and those who went on to receive further intravitreal injections (more than 3). 80 eyes were treated with 3 injections, and 48 went on to receive more than 3 injections.

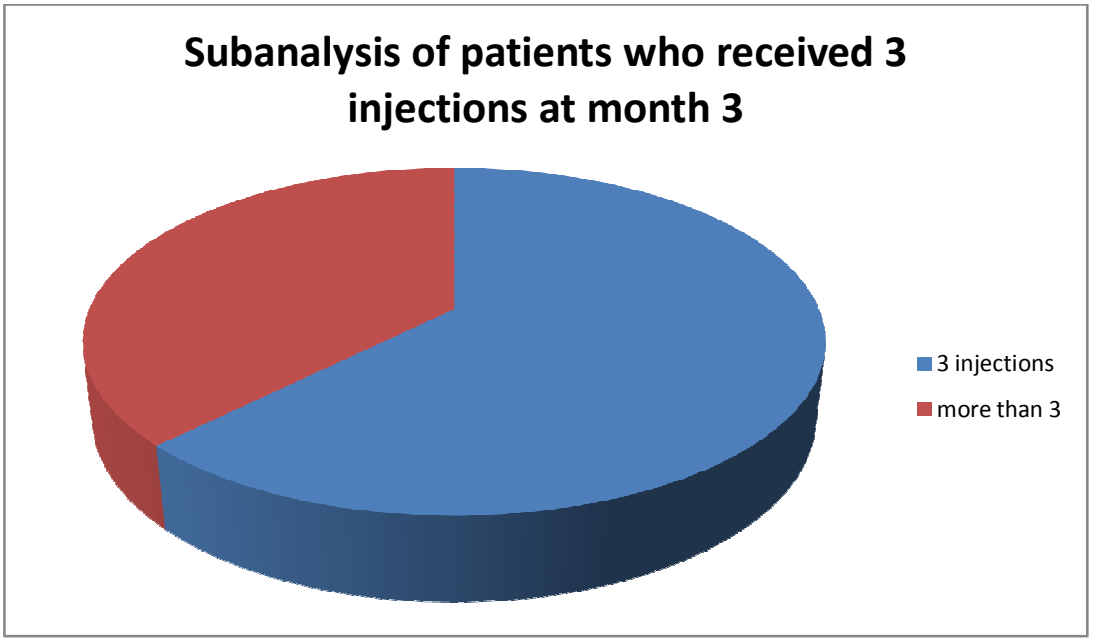


Figure 3.7 Sub-analysis of patients who received injections at month 3

3.6 Analysis of change in visual acuity and OCT thickness

The visual acuity of patients was converted to a logMar value prior to analysis being conducted.N= number of eyes, n = number of injections. The values mentioned in the table below are in medians and the values in brackets reflect the inter quartile ranges:

No of injections	**1 (n=17)**	**2 (n=33)**	**3 (n=80)**	**More than 3 (n=48)**	**P value for ANOVA[3]**
Log MAR	N = 17	N = 33	N = 80	N = 48	
Baseline	1.0 (0.6;2.00)	0.77 (0.6;2.00)	0.77 (0.6;1.00)	0.77 (0.6;1.00)	0.1209
	N = 12	N = 20	N = 77	N = 46	
1 month	0.685 (0.48;2.00)	0.77 (0.55;1.75)	0.60 (0.48;1.00)	0.60 (0.48;1.00)	0.4099
	N = 7	N = 29	N = 79	N = 47	
3 month	1.0 (0.48;2.00)	0.77 (0.6;1.00)	0.60 (0.48;0.77)	0.60 (0.48;1.00)	**0.0110[4]**
P values[1]	0.8084	0.8614	0.0733	0.1438	
OCT thickness(CFT)	N = 17	N = 31	N = 72	N = 47	
Baseline	323 (231;437)	320 (259;444)	313 (256;419)	398 (328;452)	**0.0362[5]**
	N = 4	N = 3	N = 36	N = 37	
1 month	245 (197;289)	310 (182;477)	300 (225;430)	341 (258;429)	0.4187
	N = 7	N = 22	N = 73	N = 38	
3 month	296 (248;389)	287 (253;384)	266 (219;364)	321 (262;387)	0.2647
P values [2]	0.2878	0.6370	**0.018[6]**	**0.0061[7]**	

Table 3.2 Table showing analysis of change in visual acuity and OCT thickness

P values for [1] : These show a difference between the log MAR values before (baseline) and after injections(3months) for each group divided by the number of injections

P values for [2]: these show a difference between OCT thickness values before (baseline) and after the injections (3months) for each group divided by the number of injections

P values for [3]: this is a comparison of a difference at each time point between the number of groups with different number of injections. This Analysis of variance "ANOVA' was done using the Kruskal-Wallis for non-parametric data.

[4]: there is a significant p value between the four groups at the 3 month comparison. Theres is a significant decrease in logMar between the group who had less than 3 and those who had 3 or more injections.

[5]: there is a significant P value for baseline OCT thickness. The difference ($P<0.05$) between three and greater than 3 injections means that patients who received more than 3 injections started with a higher OCT thickness (398) compared to those who only received 3 injections (313).

[6]: There is a significant p-value ($P<0.05$) for 3 injections. The baseline value (313) is significantly higher than at three months(266)

[7]: There is a significant p-value ($P<0.05$) for patients who received more than 3 intravitreal bevacizumab injections.

CHAPTER 4

4 Discussion

It was shown that from the 151 patients, 3.3% (5 patients) were type 1 and 96,7% (146 patients) were type 2 diabetic. DMO has been shown to be more prevalent in patients with type 1 diabetes. Ding et al has reported that 14% of people with type 1 diabetes have DMO and 6% of people with type 2 diabetes have DMO.[10] However type 2 diabetes is much more common than type 1 diabetes. It has been shown that 1 in 11 adults in the world has diabetes mellitus, 90% of these adults have type 2 diabetes mellitus.[43] This explains the reason for 96,7% of the patients having type 2 diabetes in this study.

In the study it was found that the mean HbA1c was 9.11. Patients with HbA1c levels greater than 8 have been shown to have an increased risk for DMO, which is consistent with this study. In a restrospective cohort study by Chou et al. of 102 patients, an HbA1c level greater than 8 ($p=0.005$) was significantly associated with an increased risk for DMO.[44]

The majority (70.2%) of the patients in the study were hypertensive. Concomitant hypertension with diabetes has been shown to increase the risk for the development of DMO. This has been shown in Wisconson epidemiologic study of diabetic retinopathy.[14] Another study involving 112 patients with DMO by Lopes de Faria et al found a higher risk of developing DMO with hypertension and higher prevalence of hypertension in patients with DMO. It was shown in their study that each increase of 10mmHg increase in systolic blood pressure above 160mmHg increased the risk of DMO by 23%. [45]

Records of Lipid function were found in the records of 68 of the 151 patients in the study. 32.1% of these patients (25 patients) had lipid dysfunction. An association between total cholesterol, LDL cholesterol and non-HDL cholesterol with DMO has been shown in an epidemiology study by Rema et al. [46]

Records of renal function were found in the records of 81 patients. 50.6% (41 patients) had renal dysfunction. Diabetic nephropathy has been shown to be a risk factor for DMO.[11]

Urine albumin:creatine ratio was only found in the records of 9 patients with a median value of 1.4mg/mmol and an Inter quartile range of (0.6 – 25.7mg/mmol). Urine microalbuminuria has been shown to be an independant risk factor for DMO.[14]

Baseline OCT measurements were found in a total of 167 eyes (93.8% of total eyes in the study). From the 167 eyes with macular oedema, the qualitative measurement patterns revealed that 92 had cystoid macular oedema (55% of measured patients), 49 has diffuse retinal thickening (29% of measured patients), 13 had serous retinal detachments (8% of measured patients) and 13 had vitreomacular interface abnormalities (8% of measured patients). The results of baseline OCT measurements are similar to those found in a study by Wu et al. In their study of 31 eyes they found that 32,3%(10 eyes) had cystoid macular oedema, 32,3% of eyes had diffuse retinal thickening (10 eyes), 6.5%(2 eyes) had serous retinal detachment and 25.8%(8 eyes) had vitreomacular interface abnormalities.[19]

OCT patterns of diabetic macular oedema can predict the outcome of treatment of anti-Vegf in diabetic macular oedema, this was however beyond the objectives of this study. In the study by Wu et al. it was shown that patients with cystoids macular oedema had greater improvements in vision and macular thickness after bevacizumab was used as the primary treatment of diabetic macular oedema.[19] In another study patients with 2 patterns of diabetic macular oedema were treated with bevacizumab, the patterns of diabetic macular oedema treated were diffuse retinal thickening and cystoid macular oedema. They found that in 56 eyes of patients, those with cystoids macular oedema had greater improvements in visual acuity and macular thickness after intravitreal bevacizumab.[47]

Ideally at our institution, Charlotte Maxeke Johannannesburg academic hospital, the patients' involved eyes should receive three injections in total in the first three-month from the diagnosis of diabetic macular oedema. However it can be seen that only 128 out of 178 (72%) patients' eyes received three injections in the first three months. The reason from this is multifactorial and because of the restropective nature of this study, the exact reason cannot be determined. Reasons could include the fact that the patients had uncontrolled diabetes at the

times of injection, which would put them at risk of endophthalmitis hence their intravitreal injection for that specific visit was cancelled. Diabetic patients have been shown to have a change in ocular flora and have been shown in studies to have a higher percentage of developing endophthalmitis post operatively in many studies.[48,49]

Other reasons could include lost or incomplete patient records and poor patient compliance to follow up visits. A study in Germany by Weiss et al. looked at the adherence and compliance of patients with diabetic macular oedema to intravitreal anti-VEGF therapy. They found that 51% of patients had an average delay of 33.4 days for intravitreal injections in their first year of therapy. They also found that 21% of patients had at least 1 therapy break off (defined as an absence of more than 100 days of therapy) within the first year of study. Only 35% of patients had never been late by more than 14 days. The main reason given by patients as to the abstaining was illness. They have mentioned strategies to improve compliance which include: to train staff to teach compliance and to support and not to blame patients and to increase doctor to patient communication.[50] An Australian study has shown that text messages can also greatly reduce the amount of missed appointments by patients.[51]

As seen in table 2, the visual acuity and central foveal thickness on OCT of our patients varied according to the amount of injections they had over the three month period. In patients receiving 1 and 2 injections in the three month period, their median logMar value remained similar with no median gain in visual acuity. The P-values of the difference in log MAR in patients receiving 1 injection and 2 injections from baseline to 3 month was P=0.8084 and P=0.8614. There was however a change in thickness in the central foveal thickness on OCT measurements. In patients receiving only 1 injection the median central foveal OCT thickness decreased by 27micrometres, with a p-value P=0.2878. In patients receiving 2 injections in three month the median central foveal OCT thickness decreased by 33micrometres with a p-value P=0.6370.

In patients receiving 3 intravitreal bevacizumab injections in a three month period (both in patients who stopped treatment at three months and those who went on to receive further injections), there was median gain in visual acuity.It was a decrease in LogMar by 0.17, which can be converted to an approximate increase in 8.5 letters.[52] In patients who stopped treatment at three intravitreal injections of bevacizumab at three months the median central foveal thickness decreased by 47 micrometres and a significant P-value of P=0.018 was

found in the difference between OCT central foveal thickness before and after the three injections. In patients who went on to receiving further treatment after the initial three injections, their central foveal thickness decreased by 77 from baseline to three months after three additional injections. A significant P-value of P=0.0061 was found in the difference between OCT central foveal thickness before and after the three injections. It should be noted that they had a higher median central foveal thickness.

When comparing the four groups in table 2, by using the non-parametric one-Way ANOVA (Kruskal-Wallis) at baseline there is no significant difference between the groups P=0.1209. However there is a significant p value between the four groups at the 3 month comparison. There is a significant decrease in logMar between the groups who had less than 3 and those who had 3 or more injections. This shows that 3 injections in 3 months are more effective than 1 or 2 injections.

In the BOLT study[38], patients who received intravitreal bevacizumab 6 weekly with a minimum of 3 injections and a maximum of 9 injections in a period of 12 months gained an median of 8 letters at 12 months[38]. This is very similar to the result in our study where patients who received three injections in three months had a median gain of 8.5 letters. The patients in the BOLT study however did have a larger decrease in central foveal thickness, which can be attributed to more intravitreal bevacizumab injections.

In the Diabetic Retinopathy Clinical Research Network study[1], patients who were treated with bevacizumab had mean improvement of 11.8 letters. In our study the patients who received three injections, had a lower visual improvement of visual acuity (8.5 letters). This could be attributed to the fact that our patients starting visual acuity was worse (LogMAR 0,77) compared to their starting visual acuity and their study was over a period of 1 year compared to ours of 3 months.

A study by Faghihi et al. compared intravitreal bevacizumab versus bevacizumab-triamcinolone versus macular laser photocoagulation[53]. In their study, the patients who were in the bevacizumab arm of the study only received a single intravitreal injection of bevacizumab, and were assessed at 4 weeks and 16 weeks. This can be compared to the patients in our study who received only 1 injection in the three month period. In their study the baseline VA improved at 4 weeks by a decrease a logMARof 0.12 and returned back to the baseline at 16 weeks. In our study the median VA improved by a decrease in of

LogMAR0.31 but returned to baseline at 3 months. In their study the mean CFT decreased by 27 from baseline and in our study the median CFT decreased by 27 from baseline.

In a randomized clinical trial by Lam et al. Patients were randomized to receive three intravitreal monthly bevacizumab injections at a dose of 1.25mg or 2.5mg. The mean logMAR in the 1.25 mg bevacizumab group improved from 0.63log MAR to 0.50log MAR at three months (a decrease of 0.13 Log MAR) and there were significant reductions on the mean central foveal thickness of 142micrometres from baseline to three months. These trials' results are comparable to our studies results.

4.1 Recommendations

It can thus be seen that for the treatment of diabetic macular oedema, three intravitreal bevacizumab injections prove efficacious. Only 72% of eyes received three intravitreal injections, and due to the restrospective nature of this study, it can only be extrapolated that one of the reasons is poor patient compliance. It would however still be worthwhile to increase patient counselling to follow up regularly for their monthly injections and to implement a system to remind patients about their follow up visits.

CHAPTER 5

5 Conclusion

In this retrospective study of 178 eyes, it can be shown that patients who receive bevacizumab monthly for diabetic macular oedema have an increase in visual acuity at three months following their first intravitreal bevacizumab injection, provided they have monthly injections.

Patients who have monthly intravitreal injections also have the greatest decrease in thickness as measured by retinal macular optical tomography.

Intravitreal bevacizumab is useful for the treatment of diabetic macular oedema in our setting provided patients have monthly injections for the first three months.

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7 Appendices

7.1 Data Collection Form

DATA COLLECTION SHEET: The Outcome of Bevacizumab treatment for diabetic macular oedema at the Charlotte Maxeke Johannesburg academic hospital

Subject Number	.....

Age	.....				
Gender	Male		Female		
Race	Black	White	Coloured	Indian	Other

Diabetes Mellitus	Type 1	Type 2	Unknown	HbA1C:
Hypertension	Yes	No	Unknown	BP
Lipid dysfunction	Yes	No	Unknown	Total: Trigs: HDL: LDL:
Renal Dysfunction	Yes	No	Unknown	Urea: Creatinine:
				P:Cr Alb:Creat

	Right Eye	**Left Eye**	
Diabetic Retinopathy grade			Unknown
Foveal Exudates			Unknown
Prior Focal Laser			Unknown

	Right Eye	**Left Eye**	
Baseline VA			Unknown
Month 1 VA			Unknown
Month 3 VA			Unknown
Month 6 VA			Unknown

	Right Eye	**Left Eye**	
Baseline OCT thickness			Unknown
Baseline OCT Quantitative			Unknown
Month 1 OCT			Unknown
Month 3 OCT			Unknown
Month 6 OCT			Unknown

Avastin	**Right Eye**			**Left Eye**		
Month 1	Yes	No	Unknown	Yes	No	Unknown
Month 2	Yes	No	Unknown	Yes	No	Unknown
Month 3	Yes	No	Unknown	Yes	No	Unknown
Month 4	Yes	No	Unknown	Yes	No	Unknown
Month 5	Yes	No	Unknown	Yes	No	Unknown
Month 6	Yes	No	Unknown	Yes	No	Unknown

	Right Eye	**Left Eye**	
Other Diabetic Macular Oedema treatment(Specify/Number)			Unknown
Focal/Grid Laser			Unknown
PRP			Unknown

7.2 HREC Ethics Clearance

R14/49 Dr Irfaan Hasrod

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160222

NAME: (Principal Investigator)	Dr Irfaan Hasrodi
DEPARTMENT:	Neurosciences Division of Ophthalmology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	The Outcome of Bevacizumab Treatment in Diabetic Macula Oedema at Charlotte Maxeke Johannesburg Academic Hospital
DATE CONSIDERED:	26/02/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Aubrey Makgotloe

APPROVED BY: Professor P Cleaton-Jones,Chairperson, HREC (Medical)

DATE OF APPROVAL: 04/03/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10C04, 10th floor, Senate House/2nd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.**

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

7.3 Plagiarism Declaration to be signed by all higher degree students

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Irfaan Hasrod (Student number: 0402908N) am a student registered for the degree of MMed Ophthalmology in the academic year 2018 .

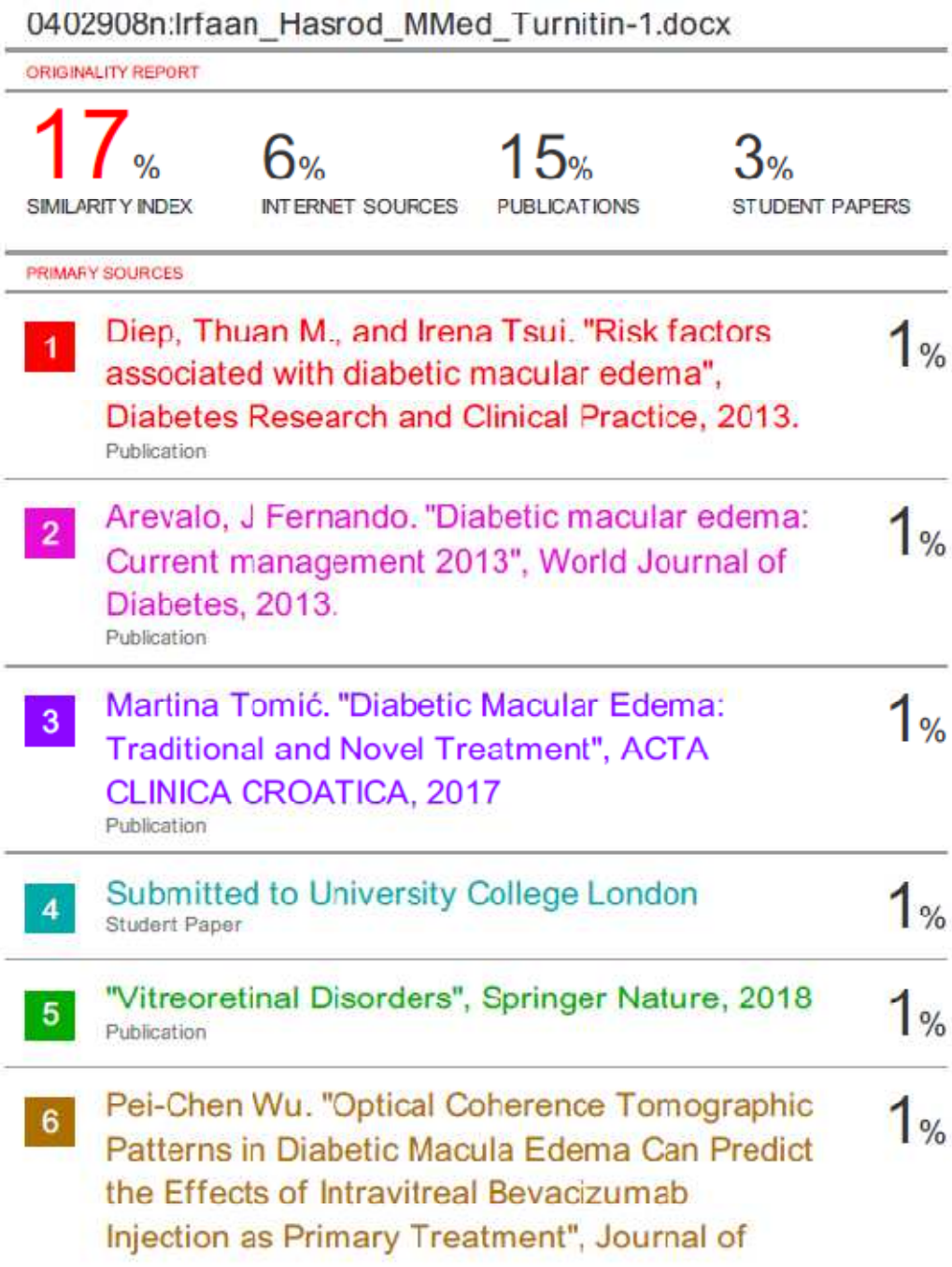
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I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.

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