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TIME OF MAXIMUM RESOLUTION OF DIABETIC MACULAR EDEMA FOLLOWING INTRAVITREAL BEVACIZUMAB

THESIS

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LIST OF ABBREVIATIONS

A II	**Angiotensin II**
Ang-1	**Angiopoietin**
AMD	**Age Related Macular Degeneration**
ARVO	**Association for Research in Vision and Ophthalmology**
BCVA	**Best Corrected Visual Acuity**
b-FGF	**Basic Fibroblast Growth Factor**
BL	**Basal Lamina**
BRB	**Blood Retinal Barrier**
CFT	**Central Foveal Thickness**
CMT	**Central Macular Thickness**
CNV	**Choroidal Neovascularization**
CSME	**Clinically Significant Macular Edema**
DEP-1	**Density Enhanced Phosphatase 1**
DME	**Diabetic Macular Edema**
DR	**Diabetic Retinopathy**
eNOS	**Endothelial Nitric Oxide Synthase**
ET	**Endothelins**
ETDRS	**Early Treatment Diabetic Retinopathy Study**
ERMs	**Epiretinal Membranes**
FA	**Fluroscein Angiography**
FAZ	**Foveolar Avascular Zone**
FDA	**Food And Drug Administration**

LIST OF ABBREVIATIONS (cont.)

GDNF	**Glial Cell Derived Neurotropic Factor**
HDL	**High Density Lipoproteins**
IgG	**Immunoglobulin G**
ILM	**Internal Limiting Membrane**
IOP	**Intraocular Pressure**
IVB	**Intravitreal Bevacizumab**
LDL	**Low Density Lipoprotein**
Mab	**Monoclonal Antibody**
MAPK	**Mitogen Activated Protein Kinase**
MLT	**Macular Laser Treatment**
MPC	**Macular laser photocoagulation**
MMPs	**Matrix Metalloproteinases**
NPDR	**Non Proliferative Diabetic Retinopathy**
OCT	**Optical Coherence Tomography**
PDGF	**Platelet Derived Growth Factor**
PDR	**Proliferative Diabetic Retinopathy**
PEDF	**Pigment Epithelium Derived Factor**
PKC	**Protein Kinase C**
PRP	**Pan Retinal Photocoagulation**
PVD	**Posterior Vitreous Detachment**
PVR	**Proliferative Vitreo Retinopathy**
RAGE	**Receptor Of Advanced Glycation End Products**
RAS	**Renin Angiotensin System**
RPE	**Retinal Pigment Epithelium**

LIST OF ABBREVIATIONS (cont.)

RVE	**Retinal Vascular Endothelium**
SCMT	**Standardized Change In Macular Thickness**
TGF-ß	**Transforming Growth Factor Beta**
Tie	**Tyrosine Kinase Receptor**
VAMP-2	**Vesicle Associated Membrane Proein -2**
VE Cadherin	**Vascular Endothelial Cadherin**
VEGF	**Vascular Endothelium Growth Factor**
VE-PTP	**Vascular Endothelial Protein Tyrosine Phosphatase**
ZO	**Zonula Occludens**
HRT	**Heidelberg Retinal Technology**

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Introduction

Diabetic retinopathy (DR) is a major cause of visual loss in patients with diabetes mellitus. Diabetic macular edema (DME), which can occur at any stage of DR, is characterised by increased vascular permeability and the deposition of hard exudates at the central retina **(Klein et al., 1998**). Although visual loss secondary to proliferative changes is more common in patients with type 1 diabetes, visual loss in patients with type II diabetes is more commonly due to macular edema **(Wormald et al., 2004).**

It has been well established that vascular endothelial growth factor (VEGF) plays a vital role in promoting neovascularization and increased vascular permeability in diabetic eyes. Levels of ocular VEGF are correlated with both the rate of growth and permeability of new vessels **(Aiello et al., 1994).**

Hypoxia has been shown to be a major inducer of VEGF gene transcription **(Ferrara, 2004).**

Studies have shown that vitreous samples from patients with DME contain elevated VEGF levels. Furthermore, introduction of VEGF into normal primate eyes induces the same pathological processes as seen in diabetic retinopathy, namely micro aneurysm formation and increased vascular permeability **(Tolentino et al., 2002).** Also, it was found that the growth of new vessels from the retina or optic nerve was thought to occur as a result of VEGF release into the vitreous cavity as a response to ischemia **(Cunningham et al., 2005).**

Because VEGF has been shown to play a major role in macular edema and retinal neovascularization, anti-VEGF treatments have been hypothesized as an alternative adjunctive treatment for DME **(Diabetic retinopathy study, 2005).**

Bevacizumab (Avastin, Genentech Inc., San Francisco, CA) is a complete full-length humanized antibody that binds to all subtypes of VEGF and is used successfully in tumor therapy as a systemic drug **(Ferrara et al., 2004).** Recent studies have demonstrated the usefulness of an intravitreal injection of bevacizumab in the reduction of macular edema secondary to central retinal vein occlusion, vascular permeability and fibrovascular proliferation in retinal neovascularization secondary to PDR, and choroidal neovascularization secondary to age-related macular degeneration (AMD) **(Spaide et al., 2006).**

The amount of human retinal penetration for a complete full-length anti-VEGF antibody is not known. However, full-thickneess retinal penetration of intravitreal bevacizumab was observed in an animal model. **(Shahar et al., 2006).**

Optical coherence tomography (OCT) is a retinal imaging technique that has applications in the diagnosis and management of a variety of diseases of the macula and optic nerve. Optical coherence tomography produces cross-sectional images of optical reflectivity in the retina in analogy to ultrasound B-scan, but with higher resolution. In patients with DR, single measurements of central foveal thickness using OCT correlate with visual acuity and provide a means of monitoring macular thickening **(Hee et al., 1995).**

Aim Of The Work

The aim of this study is to determine the time interval for maximum reduction in macular thickness in diabetic macular edema after single intravitreal Avastin injection as monitored by OCT which will allow for best results after laser application.

Anatomy Of The Macular Blood Supply

Blood supply of the macula:

Apart from the foveolar avascular zone (FAZ) the remaining human retina is too thick to be supplied by either the retinal or the choroidal circulation alone. The reason for this dual dependence is that diffusion time increases by the square of the distance. The choroidal circulation thus supplies the outer retina, whereas the inner retina is supplied by the retinal circulation **(Saint-Geniez, 2004).**

- **Retinal circulation:**

The central retinal artery emerges from within the optic cup to give rise to the retinal circulation with its four main branches, the superior and inferior temporal and nasal retinal arteries. The retinal arteries are end arteries and travel outwards towards the peripheral retina within the nerve fiber layer. The smaller arterioles give rise to two types of capillary systems: horizontal branches supply the superficial nerve fiber layer, whilst the deep branches enter the retina to form between one (periphery and perifoveal) and four (peripapillary) horizontal capillary layers in the inner retina, depending on retinal thickness **(Oyster, 1999).** The retinal circulation thus supplies all layers of the neuroretina except the photoreceptor layer, which is avascular and dependent on the choriocapillaris.

All retinal capillary blood is returned via retinal venules into the central retinal vein, which, after exiting the optic nerve, drains either into the ophthalmic veins or into the cavernous sinus directly **(Oyster, 1999).**

- **Choroidal circulation:**

The outer retina, containing the RPE and the photoreceptors, is avascular and depends on the vascular support provided by the adjacent choroid. In the presence of cilioretinal vessels, the choroid can also supply the inner retina. The choroidal circulation is fed by the ophthalmic artery via the medial and lateral posterior ciliary arteries, each of which gives rise to one long and several short posterior ciliary arteries. Apart from minor contributions from recurrent branches of the long posterior ciliary arteries, essentially all blood in the choriocapillaris is supplied by the short posterior ciliary arteries, which enter the posterior globe close to the optic nerve **(Oyster, 1999).**

The choriocapillaris supplies both the RPE and the photoreceptor layers. The choriocapillaris also requires a healthy RPE for its own formation and maintenance **(La Cour, 2003).**

The choriocapillaris is a single layer of densely arranged capillaries separated from the RPE by Bruch's membrane. The anatomic distance between the choriocapillaris and the photoreceptors is less than 20 μm facilitating rapid diffusion **(Oyster, 1999).**

In 15-20% of population a variable portion of papillomacular bundle is supplied by one or more of cilioretinal arteries derived from ciliary circulation. Occasionally large cilioretinal artery may supply entire macular region **(Bonnet et al., 1982).**