

Evaluation of Bevacizumab (Avastin) Therapy for Diabetic Macular Edema

Thesis Submitted for Partial Fulfillment
of Medical Degree in Ophthalmology

BY

Tarek Mohamed Abdel Aziz

M.B., B.Ch., M.Sc.

Supervised By

Prof. Dr. Hassan Ez-Eldin El Sammaa

Professor of Ophthalmology
Faculty of Medicine
Ain Shams University

Prof. Dr. Sherif Zaki Mansour

Professor of Ophthalmology
Faculty of Medicine
Ain Shams University

Prof. Dr. Ahmed AbdAllah Darwish

Professor of Ophthalmology
Faculty of Medicine
Ain Shams University

Faculty of Medicine
Ain Shams University

Cairo, Egypt

2009

Acknowledgement

At first and foremost thanks to “Allah” who gave me the power to finish this work

*I would like to express my deepest gratitude and appreciation to **Prof. Dr. Hassan Ez-Eldin Elsamaa**, Professor of Ophthalmology, Faculty of Medicine – Ain Shams University, for his guidance, Valuable advice, and constructive remakes that added a lot to this work.*

*I owe my thanks to **Prof. Dr. Sherif Zaki**, Professor of Ophthalmology, Faculty of Medicine – Ain Shams University, for his great efforts, valuable guidance, and great concern that really supported the work.*

*I find no words by which I can express my deepest thanks and profound respect to my honored professor, **Prof. Dr. Ahmed Darwish**, Professor of ophthalmology, faculty of Medicine - Ain Shams University for the continuous kind encouragement, guidance and support he gave me throughout the whole work. .*

I’ am greatly indebted to all my staff members in the ophthalmic department and colleagues, for the great support and help offered throughout this study.

Also I would like to thank my wife, daughter, parents, all my relatives who participated in a way or another in this work; I owe my thanks and appreciation.

Last but not least, I would like to express my endless gratitude to my dear patients who were the corner stone of this 'work, wishing them a rapid and complete recovery.

Table of Contents

<i>Acknowledgement</i>	<i>i</i>
<i>Table of Contents</i>	<i>iii</i>
<i>List of Abbreviations</i>	<i>iv</i>
<i>List of Figures</i>	<i>viii</i>
<i>List of Tables</i>	<i>xiii</i>
<i>Aim of the Work</i>	<i>xiii</i>
<i>Introduction</i>	<i>1</i>
<i>Review of Literature</i>	<i>4</i>
<i>Anatomy of the Macula</i>	<i>4</i>
<i>Epidemiology and Risk Factors of Diabetic Macular Edema</i>	<i>10</i>
<i>Pathogenesis and Pathophysiology of Diabetic Macular Edema</i>	<i>14</i>
<i>Clinical Picture and Diagnosis of Diabetic Macular Edema</i>	<i>22</i>
<i>Treatment</i>	<i>43</i>
<i>Subjects and Methods</i>	<i>59</i>
<i>Results</i>	<i>72</i>
<i>Discussion</i>	<i>114</i>
<i>Summary</i>	<i>125</i>
<i>Conclusion</i>	<i>Error! Bookmark not defined.</i>
<i>References</i>	<i>129</i>
<i>Arabic Summary</i>	<i>01</i>

List of Abbreviations

ACE	:	Angiotensin Converting Enzyme
Angiotensin II	:	Angiotensin II
BCVA	:	Best Corrected Visual Acuity
BFGF	:	Basic Fibroblast Growth Factor
BRB	:	Blood-Retinal Barrier
CME	:	Cystoid Macular Edema
CSME	:	Clinically Significant Diabetic Macular Edema
DM	:	Diabetic Macular Edema
DME	:	Diabetes Mellitus
DR	:	Diabetic Retinopathy
ELM	:	External Limiting Membrane
ENOS	:	Endothelial Nitric Oxide Synthase
ETDRS	:	Early Treatment Diabetic Retinopathy Study
FA	:	Fluorescein Angiography
FAZ	:	Foveal Avascular Zone
FDA	:	Food And Drug Administration
GCL	:	Ganglion Cell Layer

HGF	:	Hepatocyte Growth Factor
ICAM	:	Intercellular Adhesion Molecule
IL	:	Interleukin
INL	:	Inner Nuclear Layer
IOP	:	Intraocular Pressure
IPL	:	Inner Plexiform Layer
MAR	:	Minimum Angle Of Resolution
ME	:	Macular Edema
MMP	:	Matrix Metalloproteinases
MRNA	:	Messenger RNA
NFL	:	Nerve Fibers Layer
NPDR	:	Non Proliferative Diabetic Retinopathy
OCT	:	Optical Coherence Tomography
ONL	:	Outer Nuclear Layer
OPL	:	Outer Plexiform Layer
PDGF	:	Platelet Derived Growth Factor
PDR	:	Proliferative Diabetic Retinopathy
PHT	:	Posterior Hyaloid Traction

PKC	:	Protein Kinase C
RPE	:	Retinal Pigmented Epithelium
RTA	:	Retinal Thickness Analyzer
SD	:	Standard of Deviation
SMDLP	:	Subthreshold Micropulse Diode Laser Photocoagulation
TA	:	Triamcinolone Acetonide
TGF-B1	:	Trasformig Growth Factor- B1
TNF-A	:	Tumour Necrosis Factor A
VA	:	Visual Acuity
VEGF	:	Vascular Endothelial Growth Factor
VEGF	:	Vascular Endothelial Growth Factor
WESDR	:	Wisconsin Epidemiologic Study Of Diabetic Retinopathy

Aim of the Work

The purpose of the study is to evaluate the use of intravitreal bevacizumab (Avastin) as an adjunctive therapy to laser photocoagulation in cases of DME as regard visual outcome, central macular thickness changes and postoperative complications.

List of Figures

Figure	Subject	Page
1	Clinical posterior pole	4
2	Foveal avascular zone	5
3	Cross section of the fovea	6
4	Optical coherence tomography of the macula	7
5	Pathways of VEGF expression and effects on vascular cells	19
6	Clinical significant diabetic macular edema	23
7	Focal macular edema	27
8	Diffuse macular edema in FA	27
9	OCT map display showing diffuse retinal thickening	28
10	OCT of Diffuse retinal thickening	29
11	petaloid pattern of fluorescein leakage in CME	31
12	Fluorescein angiography showing ischemic	32

List of Figures

	maculopathy	
13	Enhanced optical coherence tomography image of the different morphological patterns of diabetic macular oedema	38
14	OCT subtypes of DME	40
15	Focal macular photocoagulation	45
16	Grid macular photocoagulation	47
17	Scheme of micropulse mode	50
18	VEGF isoforms	54
19	VEGF antibodies	56
20	Topcon TRC 50x retinal camera and fluorescein angiography	65
21	Stratus OCT	66
22	Zeiss Visulas 532s	67
23	Prepackaged Avastin syringe	69
24	General history of laser group	70

List of Figures

25	Associated systemic disease in laser group.	71
26	Affected eye and level of retinopathy (group A)	73
27	Severity of leakage in fluorescein angiography in group A.	75
28	General history of avastin group	77
29	Associated systemic disease in avastin group.	78
30	Affected eye and level of retinopathy (group A)	80
31	Severity of leakage in fluorescein angiography in group A.	82
32	Visual outcome following laser photocoagulation.	83
33	Visual change at the end of the 3 months	85
34	Visual outcome in group B	86
35	Visual change at the end of the 3 months	88
36	Visual change in both groups during follow up	89

List of Figures

37	Severity of leakage in FA in group A	90
38	Severity of leakage in FA in group B.	91
39	Severity of leakage along follow up period in both groups	92
40	Patient 11 left eye, group B, pretreatment.	93
41	Patient 11 left eye, group B, 3 months following Avastin and laser showing reduction of leakage.	94
42	Changes in CMT during follow up (laser group).	95
43	Changes in CMT during follow up (avastin group).	96
44	Comparison between reduction in CMT in both groups at one and three months	97
45	Patient 4 group B pretreatment with central macular thickening 398 um	98
46	Same patient; thickness chart	98
47	Same patient three months following treatment	99

List of Figures

	with central macular thickness 204 um	
48	Same patient thickness chart	99
49	Changes in LogMAR visual acuity (top) and OCT central macular thickness (bottom) in cases with mild edema	101
50	Changes in LogMAR visual acuity (top) and OCT central macular thickness (bottom) in cases with moderate edema.	103
51	Changes in LogMAR visual acuity (top) and OCT central macular thickness (bottom) in cases with severe edema	105
52	Change in CMT in all groups	106

List of Tables

<i>Table</i>	<i>Subject</i>	<i>Page</i>
1	Stimulators and Endogenous inhibitors of angiogenesis	17
2	International Clinical Diabetic Macular Edema Disease Severity Scale	24
3	Techniques for Investigation of Macular Edema	35
4	LogMAR visual acuity	62
5	Demography of group A	72
6	Ocular Assessment group A	74
7	Demography of group B	79
8	Ocular Assessment group B	81
9	The mean BCVA of laser group throughout follow up period.	84
10	Visual change along follow up (group A)	85

Introduction

11	The mean BCVA of group B throughout follow up period.	87
12	Visual change along follow up(group B)	88
13	Severity of leakage in FA in group A	90
14	Severity of leakage in FA in group B	91
15	Changes in CMT during follow up (laser group).	95
16	Changes in CMT during follow up (avastin group).	96
17	Changes in IOP during follow up in both groups	107

