Benefits of ANTI-VEGF Therapy for Diabetic Macular Edema with and without Vitreomacular Adhesions

Thesis

Submitted for partial fulfillment of Master Degree in Ophthalmology

Presented by

Yasmine Salah Salem *M.B.*, *B.Ch*

Supervised by

Dr.Ahmed Abdel El Alim mohamed

Assistant Professor of Ophthalmology Faculty of Medicine, Ain Shams University

Dr. Mohamed Hanafy Hashem

Lecturer of Ophthalmology
Faculty of Medicine, Ain Shams University

Dr. Mohamed Maher El Hefni

Lecturer of Ophthalmology Research institute of ophthalmology Giza

> Faculty of Medicine Ain Shams University 2018



سورة البقرة الآية: ٣٢



First and foremost thanks to ALLAH, the Most Merciful.

I wish to express my sincere gratitude to **Dr. Ahmed Abdel El Alim mohamed,** assistant Professor of Ophthalmology, Faculty of Medicine, Ain Shams University for his kind supervision, constant support and encouragement through the progress of this work.

I would like to express my deepest gratitude to **Dr. Mohamed Hanafy Hashem,** lecturer of Ophthalmology, Faculty of Medicine, Ain Shams University for his continuous valuable advice and continuous support throughout the whole study.

I feel extremely grateful to **Dr. Mohamed Maher El Hefni**, lecturer of Ophthalmology, Research institute of ophthalmology in Giza, for his precious time and continuous assistance to me.

Yasmine Salah Salem



I dedicate my dissertation work to my family. A special feeling of gratitude to my loving parents who never left my side and encourage me a lot.

Also, I can't forget the great effort of my husband "said" who push me forward all the time.

Finally I dedicate this work to anyone helped me to complete this work.

CONTENTS

Subjects	Page
• List of Abbreviations	I
List of table	III
List of Figures	IV
• Introduction	1
Aim of the Work	3
Review of literature:	
Chapter 1: Retinal anatomy	4
Chapter 2: Diabetic macular edema	13
Chapter 3: Treatment of diabetic macular edema	26
Patients And Methods	38
Results	46
• Discussion	57
• Summary	61
• Conclusion	63
References	65
Arabic Summary	79

LIST OF ABBREVIATIONS

DME : Diabetic macular edema

ANTI-VEGF: Anti-vascular endothelial growth factor

VMA : Vitreomacular adhesion
 VMT : Vitreomacular traction
 ERM : Epi-retinal membrane
 GAGs : Glycosaminoglycans
 BRB : The blood-retinal barrier
 RPE : retinal pigment epithelium
 JAMs : junctional adhesion molecules

MAGUKs: membrane-associated guanylate kinase homologs

ZO-1 : Zonula occludens -1DR : Diabetic retinopathy

PDR : Proliferative Diabetic retinopathy

HbA1C: glycosylated hemoglobin

AGE: advanced glycation end products

PKC: protein kinase C

HIF-1 : hypoxia inducible factor 1
 mRNA : Messenger ribonucleic acid
 IGF-I : Insulin growth factor-I
 FGF : fibroblast growth factor

PDGF: platelet-derived growth factor

DM : Diabetic mellitus

PVD : Posterior vitreous detachement
OCT : Optical coherence tomography

SD-OCT: Spectral domain Optical coherence tomography

TD- OCT : ime-domain OCT : phase-variance OCT PC OCT : phase contrast OCT

ssada : split-spectrum amplitude decorrelation angiography

FA : Fluorescein angiography

CSME : Clinical significant macular edemaSRD : serous sensory detachment DME

CME : Cystoid macular edemaPRP : Pan retinal photocoagulation

NPDR : non-proliferative diabetic retinopathy

&List of Abbreviations

PDR : proliferative diabetic retinopathy

TA : Triamcinolone acetonide
Fab fragment : Fragment antigen- binding

Fragment crystallizable portion of antibody
 VEGFR-1 : vascular endothelial growth factor receptor-1
 VEGFR-2 : vascular endothelial growth factor receptor-2

IgG1 : Immunoglobulin G1PIGF : placenta growth factorPPV : Pars planavitrectomy

: Internal limiting membrane

wet AMD : wet age-related macular degeneration

CRVO : central retinal vein occlusionCNV : choroidal neovascularization

VMA+ : Patient having vitreomacular adhesions

VMA- : Patient not having vitreomacular adhesions

BCVA : Best corrected visual acuity

CMT: Central subfield macular thickness

FAZ: Foveal avascular zone

ETDRS VA Early Treatment Diabetic Retinopathy Study visual

acuity chart

SD: standard deviation

IVR : Intravitreal ranibizumab injection

iop : Intraocular pressure

NIDDM : Non-insulin dependent diabetes mellitus

: insulin dependent diabetes mellitus

LIST OF TABLE

Tab. No.	Subject	Page
Table(1)	The demographic and clinical characteristics of all	47
Table(1)	the patients.	
Table(2)	The baseline demographic data analysis between	49
Table(2)	two groups.	
Table(3)	BCVA changes after 6 month follow up.	50
Table(4)	CMT changes after 6 month of follow up.	51
Table(5)	PVD occurrence in VMA+ group after 6 month.	54
Table(6)	Focal versus broad VMA changes after 6 month.	55

LIST OF FIGURES

Fig. No.	Subject	Page	
Fig. (1)	Layers of the retina.	6	
Fig. (2)	Macula microscopic picture.	8	
Fig. (3)	Mechanisms regulating VEGF expression.	15	
Fig. (4)	Treatment strategies for DME.	26	
Fig. (5)	Anti-VEGF treatment.	31	
Fig. (6)	Main characteristics of current anti –VEGF agents.	33	
Fig. (7)	Mechanism of action of anti-VEGF agents.	35	
Fig. (Q)	Illustrates the change from baseline in CMT in the	52	
Fig. (8) 2 study groups at different time points.			
Fig. (0)	Vitreomacular adhesion status change after 6	52	
month in VMA+ group.			
Fig.(10)	Representative examples of cross-sectional optical	56	
1.1g.(10)	coherence tomography scans.		

INTRODUCTION

Diabetic macular edema (DME) is one of the most popular causes for functional visual loss. For decades DME was treated by laser photocoagulation. However, the benefit of anti-vascular endothelial growth factor (anti-VEGF) has become a turning point for the treatment of DME. (1)

The severity of DME has a direct relation to the level of Vascular endothelial growth factor, It increases the abnormal angiogenesis and the permeability of the blood retinal barrier leading to more swelling of the macula. So, anti-VEGF therapy can play an important role in treating DME via inhibition of VEGF.⁽²⁾

Ranibizumab, bevacizumab, and aflibercept are important anti-VEGF drugs with efficacy has been established in phase III clinical trials. (3)

Vitreomacular interface disease have been reported to occur in up to 7% to16% of eyes with DME, with annual incidence as high as 4.5%, these anomalies include vitreomacular traction (VMT), epiretinal membrane (ERM) and vitreomacular adhesion (VMA). (4)

A Recent study proved that patients with DME and vitreomacular adhesions have a higher chance for improvement in visual acuity and anatomical outcomes after treatment with anti-VEGF therapy so we should not