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بسم الله الرحمن الرحيم

HANAA ALY

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Assessment of Retinal Side Effects of Fingolimod (Gilenya) Used in Treatment of Multiple Sclerosis Patients

Thesis

Submitted for Partial Fulfillment of Master Degree in Ophthalmology

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Cairo – Egypt

2021

سورة البقرة الآية: ٣٢

Acknowledgments

First and foremost, I feel

always indebted to **ALLAH,** *the Most Kind and Most Merciful.*

I'd like to express my respectful thanks and profound gratitude to **Prof. Dr. Abd El Rahman Gaber Salman,** *Professor of Ophthalmology, Faculty of Medicine - Ain Shams University for his keen guidance, kind supervision, valuable advice and continuous encouragement, which made possible the completion of this work.*

I am also delighted to express my deepest gratitude and thanks to **Prof. Dr. Thanaa Helmy Mohammed,** *Professor of Ophthalmology, Faculty of Medicine - Ain Shams University, for her kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.*

I am deeply thankful to **Prof. Dr. Dina Abdelgawad Zamzam,** *Professor of Neurology, Faculty of Medicine - Ain Shams University, for her great help, active participation and guidance.*

I wish to introduce my deep respect and thanks to **Dr. Randa Hesham Ali Abd Elgawad,** *Lecturer of Ophthalmology, Faculty of Medicine - Ain Shams University, for her kindness, supervision and cooperation in this work.*

Hala Kamal

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List of Abbreviations

Abb.	Full term
BCVA	Best Corrected Visual Acuity
BRB	Blood Retinal Barrier
CD	Cell Differentiation
CFT	Central Foveal Thickness
CIS	Clinically Isolated Syndrome
CNS	Central Nervous System
CSF	Cerebro Spinal Fluid
DMT	Disease Modifying Therapy
EBV	Epstein Barr Virus
ETDRS	Early Treatment Diabetic Retinopathy
FAME	Fingolimod Associated Macular Edema
FDA	Food and drug administration
FREEDOMS	Fingolimod Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis
GCC	Ganglion Cell Complex
HBV	Hepatitis B Virus
HHV	Human Herpes Virus
ILM	Internal Limiting Membrane
INO	Internuclear Ophthalmoplegia
IOP	Intraocular Pressure
ISCEV	International Society for Clinical Electrophysiology of Vision
LNs	Lymph Nodes
Log MAR	Logarithm of Minimal Angel of Resolution
Mac thickness	Macular Thickness
ME	Macular Edema
MfERG	Multifocal Electroretinogram
MLF	Medial Longitudinal Fasciculus
MRI	Magnetic Resonance Angiography

List of Abbreviations Cont...

Abb.	Full term
MS	Multiple Sclerosis
MT	Macular Thickness
OCT-A	Optical Coherence Tomography Angiography
OD	Right Eye
ON	Optic Neuritis
OS	Left Eye
PERG	Pattern Electroretinogram
PP	Primary Progressive
PPRF	Para Median Pontine Reticular Formation
RPE	Retinal Pigment Epithelium
RR	Relapsing Remitting
S1P	Sphingosin 1 Phosphate
SD-OCT	Spectral Domain Optical Coherence Tomography
SP	Secondary Progressive
TCM	Central Memory T Cells
TEM	Effector Memory T Cells
TMV	Total Macular Volume
TRANSFORMS	Trial Assessing Injection Interferon vs Fingolimod Oral in Relapsing Multiple Sclerosis.
UAVA	Un Aided Visual Acuity
VOR	Vestibule-Ocular Reflex
WEBINO	Wall Eyed Bilateral Internuclear Ophthalmoplegia

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Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease which targets the central nervous system in a delayed-type hypersensitivity reaction ***(Höftberger and Lassmann, 2018)***.

Although the clinical presentation and course of the disease are extremely variable, several disease types can be recognized, including relapsing remitting (RR), primary progressive (PP), secondary progressive (SP) MS and clinically isolated syndrome (CIS) ***(Lublin, 2014).***

Visual troubles are encountered in multiple sclerosis (MS), and include problems with how affected individuals see the world (afferent visual pathway symptoms) and how their eyes move together (efferent visual pathway disorders). Optic neuritis is the most common afferent visual pathway manifestation of MS, from which visual recovery is frequently incomplete. Visual field abnormalities caused by injuries in retrochiasmal or retrogeniculate areas of afferent visual pathway also occur. Efferent pathway lesions producing ocular misalignment and nystagmus may produce diplopia and oscillopsia ***(Costello, 2016).***

The modern era of multiple sclerosis (MS) treatment (disease-modifying therapies) began 25 years ago, with approval of interferon beta and glatiramer acetate for the

treatment of relapsing-remitting MS. Ten years later, the first monoclonal antibody natalizumab, followed by a third significant landmark with the introduction of oral medications, primarily fingolimod and then triflunomide, dimethyl fumarate and cladribine ***(Tintore et al., 2019).***

Fingolimod (Gilenya) is a sphingosine-1- phosphate receptor modulator which is the first US Food and Drug Administration (FDA) approved oral drug for treatment of relapsing remitting forms of multiple sclerosis, its dose is 0.25 to 0.50 mg to reduce the frequency of clinical exacerbations and delay accumulation of physical disability. It has side effects like decrease heart rate, increase blood pressure, increase risk of serious infections (leuco-encephalopathy), breathing problems, increase risk of skin cancer (basal cell carcinoma and melanoma) also cause macular edema by 3 to 4 months after starting treatment, macular edema is dose dependent and reversible ***(Schelenz et al., 2018).***

There are two recent phase 3 clinical studies TRANSFORMS (Trial Assessing injectable interferon vs. Fingolimod Oral in RRMS) and FREEDOMS (Fingolimod Research Evaluating Effects of Daily Oral Therapy in MS) demonstrated a significant decrease in the annualized relapse rate in patients with relapsing remitting MS on oral fingolimod, compared to once weekly interferon B1a and placebo ***(Cugati et al., 2014).***