بسم الله الرحمن الرحيم

∞∞∞∞

تم رفع هذه الرسالة بواسطة / سلوي محمود عقل

بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

ملاحظات:
.....
.....
.....
.....
.....

Assessment of laboratory side effects of disease modifying drugs in a sample of multiple sclerosis patients in Ain Shams University Hospitals

Thesis

Submitted for Partial Fulfillment of Master Degree
In Neuropsychiatry

By

Somaia Hamdy Ismail Zidan
(M.B.,B.Ch.)

Supervised by

Prof. Dr. Azza Abdel Nasser Abdel Aziz
Professor of Neurology
Faculty of Medicine - Ain Shams University

Prof. Lobna Mohamed El-nabil Elsayed
Professor of Neurology
Faculty of Medicine - Ain shams University

Dr. Mohamed Aly Abd El-hafeez
Lecturer of Neurology
Faculty of Medicine - Ain shams University

Faculty of Medicine
Ain Shams University
2021

List of Contents

List of Abbreviations

Abb.	Full term
2-CdATP	2 – Chlorodesoxy – Adenosine -5'-Triphosphate
ADCC	Antibody-dependent cellular cytotoxicity
ALT	Alanine Aminotransferase
ARR	Annualized Relapse Rate
ARR	Annualized Relapse Rates
AST	Aspartate Aminotransferase
ASU	Ain Shams University
BAFF	B-cell-activating factor
CBC	Complete Blood Count
CDC	Centers for Disease Control
CDP	Confirmed Disability Progression
CIS	Clinically Isolated Syndrome
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome
CYP2R1	Cytochrome P450 Family 2 Subfamily R Member 1
DIS	Dissemination in Space
DIT	Dissemination in Time
DM	Diabetes Mellitus
DMDs	Disease Modifying Drugs
DMF	Dimethyl fumarate
DMF	Dimethyl Fumarate
DMTs	Disease-Modifying Therapies

List of Abbreviations (Continued)

Abb.	Full term
DNA	Deoxyribonucleic Acid
EAE	Experimental Autoimmune Encephalomyelitis
EBV	Epstein–Barr virus
EDSS	Expanded Disability Status Scale
EU	European Union
F	Female
FDA	Food and Drug Administration
FH	Family History
GA	Glatiramer Acetate
Gd	Gadolinium
HB	Hemoglobin
HBsAg	hepatitis B surface antigen
HBV	Hepatitis B virus
HLA	Human Leukocyte Antigen
HS	Highly Significant
HTN	Hypertension
IFNβ	Interferon Beta
IL2RA	Interleukin 2 Receptor Subunit Alpha
IL7R	Interleukin 7 Receptor
IM	Intramuscular
IRRs	Infusion-Related Reactions
IVIG	Intravenous Immunoglobulin
IVMP	IV Methylprednisolone
JCV	John Cunningham Virus

List of Abbreviations (Continued)

Abb.	Full term
LON	Late-Onset Neutropenia
M	Male
MAb	Monoclonal Antibody
MBP	Myelin Basic Protein
MHC	Major Histocompatibility Complex
MRI	Magnetic resonant imaging
MS	Multiple sclerosis
MSFC	MS Functional Composite
Nabs	Neutralizing Abs
NEDA	No Evidence of Disease Activity
NK	Natural Killer
NS	Non-Significant
NTZ	Natalizumab
OCR	Ocrelizumab
PE	Plasma Exchange
Plts	Platelets
PML	Progressive Multifocal Leuko-encephalopathy
PPMS	Primary Progressive Multiple Sclerosis
RRMS	Relapsing Remitting Multiple Sclerosis
RTX	Rituximab
S	Significant
SC	Subcutaneous
SD	Standard Deviation
SPMS	Secondary Progressive Multiple Sclerosis
TB	Tuberculosis

List of Abbreviations (Continued)

Abb.	Full term
TCR	T cell Receptors
TH	T helper
TNFR1	Tumor necrosis factor receptor 1
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
URTI	Upper Respiratory Tract Infection
USA	United States of America
UTI	Urinary Tract Infection
UVB	Ultraviolet B light
VLA-4	Very Late Antigen 4
WBCs	White Blood Cells

List of Tables

List of Tables (Continued)

List of Figures

List of Figures (Continued)

List of Figures (Continued)

ABSTRACT

Background: Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS) of presumed autoimmune etiology, characterized by localized areas of inflammation, demyelination, axonal loss and gliosis in the brain and spinal cord. Treatment options for patients with MS have broadened tremendously, however, several potentially serious safety concerns have been raised, necessitating regular assessment and laboratory monitoring. All agents that are currently approved for clinical use have potential side effects, and a careful risk–benefit evaluation is part of a decision algorithm to identify the optimal treatment choice for MS patients.

Aim of the Work: To assess the effect of different disease modifying drugs (DMDs) on complete blood count (CBC), liver enzymes and thyroid profile in a sample of Egyptian Multiple Sclerosis patients.

Patients and Methods: The current study enrolled 105 MS patients attending ASU MS unit, within a period Starting from November 2020 till May 2021, Age above 18 years old, with diagnosis of MS according to the revised McDonald criteria with exclusion Patients with other medical conditions that may affect laboratory results. Clinical, medication and laboratory data including CBC, liver enzymes (AST, ALT) and TSH were collected at baseline and after 6 months of starting DMD**s.**

Results: The mean age of MS patients was 32.15 ± 8.53 years, ranging from 18 to 58 years. Ninety-eight (73.7%) were females while 35 (26.3%) were males, Thirty (28.6%) patients received interferon beta A1, 28 (26.7%) patients received Fingolimod, 15 (14.3%) patients received Dimethyl fumarate, 11 (10.5%) patients received Rituximab, 10 (9.5%) patients received Ocrelizumab, 10 (9.5%) patients received Teriflunomide, and 1 (1.0%) received Cladribine, Regarding comparison of laboratory changes before, 3ms and 6ms after starting medications in MS patients, there was a significant decrease in lymphocytes in patients receiving Fingolimod and significant elevation of AST & ALT & TSH in patients receiving interferon.

Conclusions: Treatment options in MS patients have expanded tremendously in recent years. Each of the drugs has a different side effects profile. Routine laboratory examinations allow identification of some of these side effects. Understanding the side effects of MS therapies is highly relevant, as it will guide the clinician and the patient in choosing the right agent for their disease.

Keywords: Multiple Sclerosis, DMDs, Laboratory side effects of DMDs, Patient safety.

INTRODUCTION

Multiple sclerosis is the commonest non-traumatic disabling disease to affect young adults ***(Kobelt et al., 2017).*** There is increasing incidence and prevalence of MS in both developed and developing countries ***(Browne et al., 2014).***

The underlying cause of which remains uncertain. MS is a complex disease; many genes modestly increase disease susceptibility in addition to several well-defined environmental factors, in particular vitamin D or ultraviolet B light (UVB) exposure, Epstein-Barr virus (EBV) infection, obesity and smoking ***(Ascherio, 2013).***

The treatment of MS can be divided into disease-modifying therapies that tend to be MS-specific and symptomatic therapies that are often used in different disease areas to treat symptoms resulting from neurological dysfunction ***(Dobsona and Giovannonib, 2019).*** The selection of the first DMT is important given the benefits of early treatment in patients with multiple sclerosis ***(Cerqueira et al., 2018).***

The 2017 revisions of the McDonald diagnostic criteria for multiple sclerosis ***(Thompson et al., 2018)*** enable earlier diagnosis in individuals with perhaps less inflammatory activity than for the clinical trial populations

who were diagnosed with the 2010 McDonald criteria ***(Zhang et al., 2018)*** several have shown that commencing DMTs after a first clinical attack with lesions shown by MRI suggestive of multiple sclerosis, even with modestly effective DMT, improves long-term clinical outcomes ***(Armoiry et al., 2018)***.

Since the number and efficacy of disease-modifying therapies has increased, interest in early treatment of MS in order to prevent long-term disability has grown. Historically, treatments have included immune suppressant (including Fingolimod, Natalizumab, Ocrelizumab) or immunomodulatory (such as Interferon beta, Glatiramer acetate, Teriflunomide), meaning that ongoing treatment is required to maintain suppression of inflammation and disease activity. Immune reconstitution therapies (including Alemtuzumab and Cladribine) can be given as short courses with the aim of producing enduring immunological actions, this is at present the closest to a potential cure for MS ***(Dobsona and Giovannonib, 2019).***

The common treatment-related adverse events of multiple sclerosis DMTs tended to be mild to moderate, with a few notable exceptions: bradycardia and atrioventricular block with Fingolimod ***(Calabresi et al., 2014)***, gastroenteritis with Dimethyl fumarate ***(Gold et al., 2012)*** and lymphopenia with Cladribine ***(Leist et al., 2014).***