

# **Recent Updates in Treatment of Multiple Sclerosis**

*An Essay*

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in Neurology and Psychiatry

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**بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ**

(... رَبِّ أَوْزِعْنِي أَنْ أَشْكُرَ نِعْمَتَكَ  
الَّتِي أَنْعَمْتَ عَلَيَّ وَعَلَى وَالِدَيَّ  
وَأَنْ أَعْمَلَ صَالِحًا تَرْضَاهُ وَأَدْخِلْنِي  
بِرَحْمَتِكَ فِي عِبَادِكَ الصَّالِحِينَ )

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## **List of Contents**

<b>Title</b>	<b>Page</b>
List of Abbreviations.....	i
List of Figures.....	iv
List of Tables.....	vi
Introduction.....	- 1 -
Aim of the Work.....	4
Chapter (1): Pathogenesis of Multiple Sclerosis .....	5
Chapter (2): Diagnosis of Multiple Sclerosis.....	42
Chapter (3): Management of Multiple Sclerosis.....	63
Discussion.....	128
Summary .....	145
Recommendations.....	152
References.....	153

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## List of Abbreviations

Abbrev.	Full term
<b>ADCC</b>	: Antibody dependent cellular cytotoxicity
<b>APC</b>	: Antigen presenting cells
<b>ARR</b>	: Annualized relapse rate
<b>ATG</b>	: Anti-thymocyte globulin
<b>AV</b>	: Atrioventricular
<b>BBB</b>	: Blood–brain barrier
<b>BOLD</b>	: Blood-oxygenation-level-dependent
<b>CBC</b>	: Complete blood count
<b>CCSVI</b>	: Chronic cerebrospinal venous insufficiency
<b>CDC</b>	: Centers for Disease Control and Prevention
<b>CDC</b>	: Complement dependent cytotoxicity
<b>CDMS</b>	: Clinically definite MS
<b>cICAM</b>	: Cellular intercellular cell adhesion molecule
<b>CIS</b>	: Clinical isolated syndrome
<b>CLEC16A</b>	: C-type lectin domain family 16 member A
<b>CMV</b>	: Cytomegalovirus
<b>CNS</b>	: Central nervous system
<b>CNTF</b>	: Ciliary neurotrophic factor
<b>CSF</b>	: Cerebrospinal fluid
<b>DIS</b>	: Dissemination in space
<b>DIT</b>	: Dissemination in time
<b>DMDs</b>	: Disease-modifying drugs
<b>DMF</b>	: Dimethylfumarate
<b>DMT</b>	: disease-modifying therapies
<b>DNA</b>	: deoxy ribonucleic acid
<b>EAE</b>	: Experimental autoimmune encephalomyelitis
<b>EBV</b>	: Epstein-Barr virus
<b>EDSS</b>	: Expanded Disability Status Scale
<b>FAE</b>	: Fumaric acid esters

## List of Abbreviations *(Cont...)*

Abbrev.	Full term
<b>fMRI</b>	: Function MRI
<b>FREEDOMS</b>	: FTY720 Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis
<b>GA</b>	: Glatiramer acetate
<b>GFAP</b>	: Glial fibrillary acidic protein
<b>GPC5</b>	: Glypican proteoglycan 5
<b>HACA</b>	: Human anti-chimeric antibodies
<b>HHV-6</b>	: Human herpesvirus-6
<b>HLA</b>	: Human leukocyte antigen
<b>IFN</b>	: Interferon
<b>IFN-<math>\beta</math></b>	: Interferon-beta
<b>Ig</b>	: Immunoglobulin
<b>IL</b>	: Interleukin
<b>IL2R</b>	: Interleukin-2 receptor gene
<b>IM</b>	: Infectious mononucleosis
<b>KIF1b</b>	: Kinesin family member 1b
<b>LFA</b>	: Lymphocyte function-associated antigen
<b>mAb</b>	: Monoclonal antibody
<b>MBP</b>	: Myelin basic protein
<b>MBP-LM</b>	: MBP like material
<b>MHC</b>	: Major histocompatibility complex
<b>miRNAs</b>	: MicroRNAs
<b>MMF</b>	: Metabolite monomethyl fumarate
<b>MMP</b>	: Matrixmetalloproteinase
<b>MOG</b>	: Myelin oligodendrocyte glycoprotein
<b>MRI</b>	: Magnetic resonance imaging
<b>MS</b>	: Multiple sclerosis
<b>MTR</b>	: Magnetization transfer ratio
<b>NAA</b>	: N-acetyl aspartate
<b>NAbs</b>	: Neutralizing antibodies

## **List of Abbreviations** *(Cont...)*

<b>Abbrev.</b>	<b>Full term</b>
<b>N-CAM</b>	: Neuronal cell adhesion molecule
<b>NF</b>	: Neurofilaments
<b>NO</b>	: Nitric oxide
<b>Nrf-2</b>	: Nuclear factor E2
<b>NSE</b>	: Neuron-specific enolase
<b>OCP</b>	: Oligoclonal bands
<b>OPCs</b>	: Oligodendrocytes precursor cells
<b>PCR</b>	: Polymerase chain reaction
<b>PET</b>	: Positron emission tomography
<b>PLP</b>	: Proteolipid protein
<b>PML</b>	: Progressive multifocal leukoencephalopathy
<b>PP</b>	: Primary progressive
<b>PPMS</b>	: Primary progressive multiple sclerosis
<b>PR-MS</b>	: Progressive-relapsing MS
<b>RA</b>	: Rheumatoid arthritis
<b>RR</b>	: Relapsing-remitting
<b>RTL</b>	: Recombinant T cell receptor ligand
<b>S1PR</b>	: Sphingosine 1-phosphate receptor
<b>sICAM</b>	: Soluble intercellular adhesion molecule
<b>SP-MS</b>	: Secondary-progressive disease course
<b>sVCAM</b>	: Soluble vascular cell adhesion molecule
<b>TGF</b>	: Transforming growth factor
<b>TGF-<math>\beta</math></b>	: Transforming growth factor-beta
<b>TMS</b>	: Transcranial magnetic stimulation
<b>TSPO</b>	: Translocator protein 18KDa
<b>TTV</b>	: Torque teno virus
<b>UCCA</b>	: Upper cervical cord area
<b>VCAM-1</b>	: Vascular cell adhesion molecule 1
<b>VLA</b>	: Very late activation antigen
<b>VZV</b>	: Varicella-zoster virus
<b>9-HPT</b>	: Nine-hole peg test

## List of Figures

<i>Figure No.</i>	<i>Title</i>	<i>Page No.</i>
<b>Figure (1):</b>	Theorazied factors of pathogenesis in MS .....	28
<b>Figure (2):</b>	T cells subpopulation .....	29
<b>Figure (3):</b>	T cells differentiation .....	31
<b>Figure (4):</b>	Antibody-dependent and -Independent Functions of B cells in Health and Disease. ....	36
<b>Figure (5):</b>	Putative remyelination mechanisms. ....	41
<b>Figure (6):</b>	Gain or loss in brain volume, as determined from serial MRI scans using registration- based software, brain volume gain (red) or loss (blue) can be determined with sub-voxel accuracy from serial MRI scans.....	47
<b>Figure (7):</b>	Composite image showing information from several sequential MRI scans of a patient with MS .....	50
<b>Figure (8):</b>	Areas of increased activation in patients with benign MS compared with healthy controls .....	51
<b>Figure (9):</b>	Maturation of naïve T lymphocytes (ThO) into T-helper I cells (Th1) or Th2 cels. ....	54
<b>Figure (10):</b>	Immunopathogenesis of MS and therapeutic interventions in development .....	66
<b>Figure (11):</b>	Betaferon®Pivotal trial in RRMS: effect on annulaized relapse rates .....	71
<b>Figure (12):</b>	Glatiramer-acetate-mediated changes on adaptive immune system .....	75
<b>Figure (13):</b>	Structure of Mitoxantrone .....	76



## **List of Figures (Cont...)**

<i>Figure No.</i>	<i>Title</i>	<i>Page No.</i>
<b>Figure (14):</b>	Approximate incidence of PML stratified by previous immune-suppressant use and duration of natalizumab treatment .....	83
<b>Figure (15):</b>	Estimated risk of PML based on anti-JCV antibody status, previous immunosuppressant use, and duration of natalizumab treatment .....	83
<b>Figure (16):</b>	Dimethyl fumarate.....	94
<b>Figure (17):</b>	Potential disease modifying mechanisms of action of laquinimod in MS.....	98
<b>Figure (18):</b>	Laquinimod: ALLERGO Study .....	102
<b>Figure (19):</b>	Teriflunomide and TEMSO trial.....	105
<b>Figure (20):</b>	Proposed Scheme for Risk Stratification of NTZ Treatment.....	132
<b>Figure (21):</b>	Current algorithm for the management of clinically isolated syndrome at risk and active relapsing–remitting multiple sclerosis.....	143

## List of Tables

<i>Table No.</i>	<i>Title</i>	<i>Page No.</i>
<b>Table (1):</b>	MS: Immunopathologic subtypes .....	26
<b>Table (2):</b>	McDonald criteria and its modifications.....	43
<b>Table (3):</b>	2010 McDonald Criteria for Diagnosis of MS in Disease with Progression from Onset .....	45
<b>Table (4):</b>	Potential CSF biomarkers related to pathomechanisms in MS. ....	61
<b>Table (5):</b>	Different formulations of IFN- $\beta$ .....	70
<b>Table (6):</b>	Clinical features indicative of MS relapse and PML. ....	84
<b>Table (7):</b>	Precautions with fingolimod use .....	88
<b>Table (8):</b>	Effects of fumaric acid esters on immune and accessory cells .....	93
<b>Table (9):</b>	CARE-MS I: Relapse Rate and Patients Free of Relapse by Treatment." .....	107
<b>Table (10):</b>	CARE-MS I: Sustained Accumulation of Disability by Treatment.....	108
<b>Table (11):</b>	CARE-MS II: Relapse Rate and Patients Free of Relapse by Treatment." .....	109
<b>Table (12):</b>	CARE-MS II: Sustained Accumulation of Disability by Treatment." .....	109
<b>Table (13):</b>	Approved therapies in multiple sclerosis.....	123
<b>Table (14):</b>	Novel therapies in multiple sclerosis currently undergoing clinical development.....	125
<b>Table (15):</b>	Promising therapeutic approaches with putative neuroprotective effects in multiple sclerosis .....	126



# Introduction

*M*ultiple sclerosis (M.S) is a chronic inflammatory disease of the central nervous system, which results in the formation of focal demyelinated plaques in the white matter with partial axonal preservation (*Lassmann et al., 2007*). In most patients disease starts with a relapsing remitting course, which is followed by a secondary progressive phase. In patients with primary progressive disease the relapsing stage of the disease is missed and patients show disease progression from the onset (*Lublin et al., 1996*).

Multiple sclerosis affects 2.1 million people worldwide and approximately 250 000 to 400 000 people in the United States. Most patients are diagnosed between the ages of 20 and 50 years with women being affected to a greater degree than men by a ratio of 1.6 females to 1 male (*Noonan et al., 2002*). The highest prevalence of multiple sclerosis is found in Caucasian women, persons of Northern European descent, and in those who live in northern latitudes. Multiple sclerosis can cause physical, mental, and emotional disability in individuals, independent of age (*Kobelt et al., 2006*).

The principal target of the disease process in M.S is the myelin sheath and/or the cell responsible for its production and maintenance, the oligodendrocyte. The majority (85%) of M.S patients have a biphasic disease course, beginning with the primary phase termed relapsing remitting M.S (RR-MS).

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During this disease course, patients experience alternating episodes of neurological disability and recovery that can last for many years (*Noseworthy, 1999; Trapp and Nave, 2008*). Within 25 years, 90% of RR-MS patients transform into a secondary-progressive disease course (SP-MS) which is characterized by steady neurological decline (*Trapp and Nave, 2008*). About 10% of M.S patients also exhibit a disease course with steady decline in neurological function without recovery and are classified as primary progressive MS (PPMS). A small minority of MS patients (5%) suffer from a disease course with progressive neurological decline accompanied by well demarcated acute attacks with or without recovery. This disease course is classified as progressive-relapsing MS (PR-MS) (*Prineas, 2001; Trapp and Nave, 2008*).

Typically, MS lesions include breakdown of the blood–brain barrier, multifocal inflammation, demyelination, oligodendrocyte loss, reactive gliosis, and axonal degeneration (*Prineas, 2001; Trapp and Nave, 2008*). While immunemediated destruction of CNS myelin and oligodendrocytes are considered the primary pathology of MS, it is well established that progressive axonal loss is the major cause of neurological disability in M.S (*Stadelmann et al., 2008*).

Being the most common cause of neurological disability in young adults, it represents a prototypic autoimmune inflammatory disorder of the CNS. The mode of action of currently approved disease-modifying drugs (DMDs) for MS is based on

immunomodulation. They include recombinant interferons and glatiramer acetate as first-line treatment, with natalizumab and mitoxantrone as second-line therapies. Several oral drugs for MS are fingolimod, teriflunomide, oral fumarates and laquinimod. Differing in their mode of action and potential adverse events, they have been evaluated in phase III clinical trials, which seem to indicate some promising results (*Kieseier et al., 2009*).

## **Aim of the Work**

To highlight the recent updates in the pathophysiology of multiple sclerosis and its implication on recent treatments for better management of these patients