Recent Updates in Treatment of Multiple Sclerosis

An Essay

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بِسْمِ اللّهِ الرّحمَنِ الرّحيمِ

[...رَبِّ أَوزِعنِي أَن أَشكُرَ نِعمَتَكَ
الّتِي أَنْعَمْتَ عَلَيَّ و عَلى والِدَيَّ
و أَنْ أَعْمَلَ صَالِحاً تَرْضَاهُ و أَدْخِلْنِي
بِرَحْمَتِكَ فِي عِبَادِكَ الصَّالِحِينَ]

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Rana Magdy Mohamad El Amin

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List of Abbreviations

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

List of Abbreviations *(Cont...)*

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

List of Abbreviations *(Cont...)*

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

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Introduction

Multiple 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 majorit\y (85%) of M.S patients have a biphasic disease course, beginning with the primary phase termed relapsing remitting M.S (RR-MS).

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