Assessment of Cyclophosphamide in Relapsing Remitting Multiple Sclerosis

Thesis

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List of Abbreviations

ACTH	:	Adrenocorticotropic hormone
AHSCT	:	Autologous Haematopoietic Stem-Cell Transplantation
APC	:	Antigen presenting cell
ARR	:	Annualized relapse rate
AZA	:	Azathioprine
BBB	:	Blood brain barrier
BENEFIT	:	Betaseron/Betaferon in newly emerging multiple sclerosis for initial treatment
BDNF	:	Brain derived neurotrophic factor
BVL	:	Brain volume loss
CBP	:	childbearing period
CCR	:	C-C chemokine receptor
CHAMPS	:	Controlled high risk Avonex multiplesclerosis trial
CIS	:	Clinically isolated syndrome
CDMS	:	Clinically definite multiple sclerosis
CMSWG	:	Canadian Multiple Sclerosis Working Group
CNS	:	Central nervous system
CSF	:	Cerebrospinal fluid
CYC	:	Cyclophosphamide
CSs	:	Corticosteroids
DMDs	:	Disease modifying drugs
DMF	:	Dimethyl Fumarate
EAE	:	Experimental autoimmune encephalomyelitis
EBV	:	Epstein Barr virus
EDSS	:	Expanded Disability Status Scale
EMA	:	European Medicine Agency
ETOMS	:	early treatment of multiple sclerosis
GA	:	Glatiramer acetate
Gd	:	Gadolinium

List of Abbreviations (Cont.)

GM-CSF	:	Granulocyte-macrophage colony-stimulating factor
GnRH	:	Gonadotropin-releasing hormone
GWAS	:	Genome wide association studies
HDC	:	High dose cyclophosphamide
HLA	:	Human leukocyte antigen
HPA	:	Hypothalamic pituitary adrenal axis
HSCT	:	Hematopoetic stem cell transplant
IFN	:	Interferon
IL	:	Interleukin
IM	:	Intramuscular
IV	:	Intravenous
IVIG	:	intravenous immunoglobulin
JCV	:	John Cunningham virus
LFA	:	lymphocyte function-associated antigen
LOC	:	Level of concern
MBP	:	Myelin basic protein
MESNA	:	Mercaptoethanesulfonate
MHC	:	Major histocompatibility complex
miR	:	microRNA
MMPs	:	Matrix metalloproteinases
MOG	:	Myelin oligodendrocyte glycoprotein
MP	:	Methylprednisolone
MS	:	Multiple sclerosis
MSDM	:	Multiple sclerosis decision model
MRI	:	Magnetic resonance imaging
MTR	:	Magnetization-transfer ratio
NAB	:	Neutralizing antibodies
NEDA	:	No evidence of disease activity
OPCs	:	oligodendrocyte precursor cells
PLP	:	Proteolipid protein
PML	:	Progressive multifocal leucoencephalopathy

List of Abbreviations (Cont.)

PreCISe	:	Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome
PRMS	:	Progressive relapsing multiple sclerosis
REFLEX	:	REbif FLEXible dosing in early MS
RIS	:	Radiologically isolated syndrome
RR	:	Relapse rate
RRMS	:	Relapsing remitting multiple sclerosis
SC	:	Subcutaneous
S1PR	:	sphingosine-1-phosphate receptor
SNP	:	Single nucleotide polymorphisms
SPMS	:	Secondary progressive multiple sclerosis
TF	:	Teriflunomide
Th	:	T-helper
TGF-β	:	Transforming growth factor
TNF	:	Tumor necrosis factor
Treg	:	T-regulatory cells
URTI	:	upper respiratory tract infection
UTI	:	Urinary tract infection
VCAM-1	:	Vascular cell adhesion molecule 1
VLA-4	:	Very late activation antigen-4
VZ	:	Varicella zoster
WBCs	:	White blood cells

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Introduction

Multiple sclerosis (MS) is an idiopathic, putatively autoimmune, chronic inflammatory demyelinating disease of the central nervous system (CNS) with genetic and environmental effects ***(Noseworthy et al., 2000a)***.

The median clinical onset of MS is approximately 29 years of age, and the female/male ratio approaches 3:1 and may be increasing ***(Orton et al., 2006)***.

MS is the second most common cause of disability in young adults, and it is one of the costliest chronic diseases, with total annual costs per affected individual exceeding US$50,000, which is similar to that of congestive heart failure ***(Adelman et al., 2013)***.

MS causes bothersome or disabling physical symptoms involving problems of mobility, vision, coordination, cognitive dysfunction, fatigue, and pain. Quality of life may be further reduced by mood disorders, limitations in employment and social functioning ***(Wu et al., 2007and Feinstein, 2011)***.

Acute inflammatory lesions are initiated by activated peripheral leukocytes that enter the CNS through a breached blood-brain barrier (BBB). The clinical correlate of this process is a clinical attack ***(Compston and Coles, 2008)***.

The natural history of MS is variable and largely unpredictable on an individual level. In relapsing remitting MS (RRMS), residual effects of clinical relapses may result in accumulating neurological impairment, typically