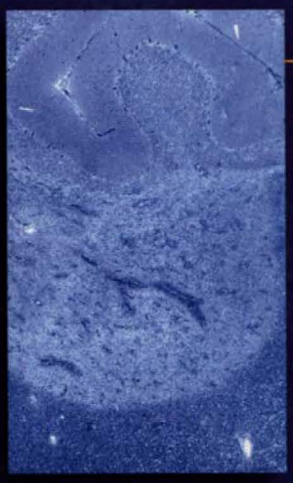
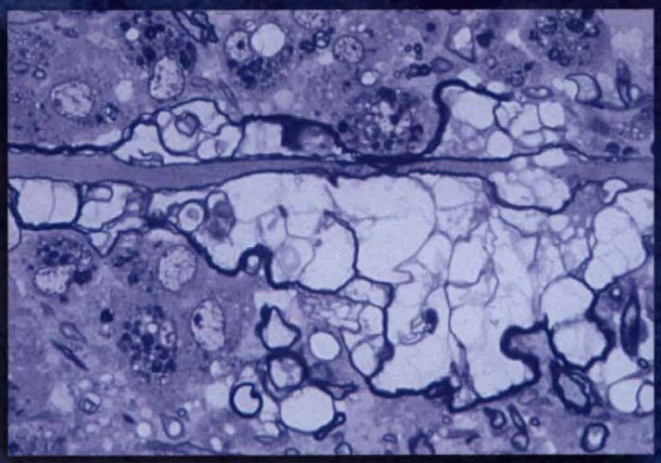


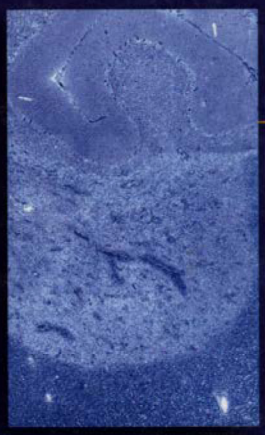
Multiple Sclerosis

A COMPREHENSIVE TEXT

Edited by
CEDRIC S. RAINE
HENRY F. McFARLAND
REINHARD HOHLFELD

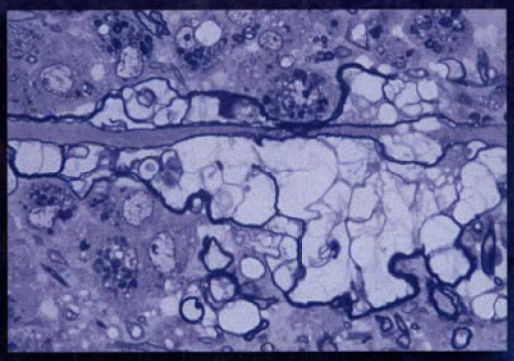


SAUNDERS
ELSEVIER



Multiple Sclerosis

A COMPREHENSIVE TEXT



SAUNDERS
ELSEVIER
www.elsevierhealth.com

ISBN 978-0-7020-2811-3
9780702028113

Multiple Sclerosis:
A Comprehensive Text

Edited by

Cedric S. Raine PhD DSc FRCPath

Professor, Departments of Pathology (Neuropathology),
Neurology and Neuroscience,
Albert Einstein College of Medicine,
New York, USA

Henry F. McFarland MD

Chief, Neuroimmunology Branch, and Clinical Director,
National Institute of Neurological Disorders and Stroke,
National Institutes of Health, Bethesda,
Maryland, USA

Reinhard Hohlfeld MD

Professor and Director of the Institute for Clinical Neuroimmunology,
Ludwig-Maximilians University, Klinikum Grosshadern,
Institute for Clinical Neuroimmunology,
Munich, Germany

EDINBURGH LONDON NEW YORK OXFORD PHILADELPHIA ST LOUIS SYDNEY TORONTO 2008

SAUNDERS
ELSEVIER
An imprint of Elsevier Limited

ISBN 978-0-7020-2811-3

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging in Publication Data
A catalogue record for this book is available from the Library of Congress

Note
Knowledge and best practice in this field are constantly changing. As new research and experience broaden our knowledge, changes in practice, treatment and drug therapy may become necessary or appropriate. Readers are advised to check the most current information provided (i) on procedures featured or (ii) by the manufacturer of each product to be administered, to verify the recommended dose or formula, the method and duration of administration, and contraindications. It is the responsibility of the practitioner, relying on their own experience and knowledge of the patient, to make diagnoses, to determine dosages and the best treatment for each individual patient, and to take all appropriate safety precautions. To the fullest extent of the law, neither the Publisher nor the Editors assume any liability for any injury and/or damage to persons or property arising out of or related to any use of the material contained in this book.

The Publisher

Printed in China

Preface

Why another book on multiple sclerosis? To us, the reason was obvious – the terrain of multiple sclerosis (MS) is vast and ever-changing. So much is happening that concepts forged just 2 years ago are already passé. Whether viewed from the platform of the health professional responsible for the day-to-day care of the patient or the scientist working to unravel what makes this a unique disease, MS has over the last decade evolved into a condition necessitating multidisciplinary approaches to both its management and understanding. One needs only to peruse the profiles of the personnel associated with an MS care center (particularly one located in an academic setting) to appreciate the enormous array of skills and treatments now available to the patient. For the scientific investigator, the rapidity of developments in recent years has been quite intimidating as genetics, immunology and molecular biology have assumed center stage, a fact reflected daily in our language, tools and techniques. In short, MS is a moving target and, as a consequence, we need to keep adjusting our sights. This book is the latest adjustment.

Why a 'comprehensive' textbook? In the past, authors of texts on MS have shied away from broad-fronted coverage, with the preface of one renowned 1985 tome announcing 'it is no longer possible even to attempt a comprehensive work on multiple sclerosis'. If that were the case 20-plus years ago when the number of treatments for the MS patient was virtually zero and the diagnostic tools and research options were limited (to say the least), imagine the scope of the endeavor today! We have for certain come a long way since the 1980s – just look how much is out there now for the patient! With more than half-a-dozen approved and effective drugs specifically designed for MS, and dozens in advanced stages of clinical trials and/or awaiting approval, there is a wealth of new information to report. Thus, because the horizon is brighter than ever before for those affected with or involved in the condition, we think the time is ripe for a fresh look at the status of MS as a clinical problem, for the latest coverage on expanding prospects for the patient, and for a state-of-the-art re-evaluation of changes occurring within the nervous system. Since any approach to MS, scientific or care-related, is almost guaranteed to embrace the combined skills of several disciplines, for an individual to embark single-handed upon the preparation of a text on the subject might understandably be deemed over-ambitious. Therefore, fully cognizant of the challenge and somewhat intimidated by recently published excellent works on the subject, the present Anglo-American-German editorial alliance was assembled, each editor having one foot firmly planted in MS and the other in a

Cedric S. Raine,
New York City, NY, USA

Henry F. McFarland,
Washington, DC, USA

Reinhard Hohlfeld,
Munich, Germany

field different from the other two. Our principal task was to compile a comprehensive Table of Contents replete with outstanding contributors, with long track records in both basic and clinical research. We have invested heavily in the project and are highly satisfied with the result, which is not a dogmatic, subjective treatise reflecting personal viewpoints but rather a series of succinct and interlocking contributions (actually 31 chapters) from a unique team of clinicians and investigators never before assembled whose collective skills traverse the entire landscape of MS.

What will the book achieve? Considering that MS can still be difficult to define both clinically and pathologically, and that not too long ago (to some of us, at least), diagnosis was regarded as proven only after autopsy or biopsy (McDonald & Halliday 1977), we feel that the present coverage more than does justice to the field since it portrays MS as a definable entity and sets what we hope is a new gold-standard for its characterization. Parenthetically, after a long dormancy, it took a lay person (Sylvia Lawry), not a neurologist or a scientist, to bring MS into the limelight and to give it the prominence it deserves. Sylvia was seeking guidance in 1945 to help her brother afflicted with MS when she ran a short announcement in the *New York Times* asking people with MS to contact her, a venture that culminated with the recognition of this as an important disease and the establishment of Multiple Sclerosis Societies around the world. Her efforts were also pivotal in the formation in the USA of what is now known as the National Institute of Neurological Diseases and Stroke. It is largely as a result of her energy and insight that we are where we are today and for this we owe her a debt of gratitude. Thanks in part to work supported by agencies like those Sylvia created, we no longer doubt that the quality of life for the MS patient can be improved, that the clinical course can be beneficially modified, that the immunological assault on the nervous system can be assuaged, that axonal damage can be reduced, and that myelin repair is feasible – the challenge is to correct these anomalies simultaneously in the MS patient. True, many issues still need to be resolved (like whether MS is a single disease or a collection of variants), and we recognize that no book on MS will ever be really complete since, like the canvas of the master painter, details can always be added.

For helping us bring the most recent advances in MS together in one volume, we thank the contributors, each of whom has striven to provide a didactic narrative that is both comprehensive and current. We feel that any reader entering into a dialogue with this book will emerge refreshed, fulfilled and brimming with anticipation about issues such as what the next clinical trial will bring, what triggers this devastating disease and whether more able symptomatic treatments will be uncovered. We are not unaware that this will not be the last word on MS and that it will be the latest for a brief window of time only, but we are confident that it will remain a major source of knowledge for many years to come.

Contributors

Oluf Andersen MD PhD
Professor of Neurology, Institute of Neuroscience and Physiology, University of Gothenburg, Gothenburg, Sweden

Brenda L. Banwell MD FRCPC
Assistant Professor of Pediatrics (Neurology) and Associate Scientist, Research Institute, The Hospital for Sick Children, University of Toronto, Canada

Ralph H. B. Benedict PhD
Associate Professor of Neurology, Erie County Medical Center, Buffalo, USA

Jeffrey L. Bennett MD PhD
Associate Professor of Neurology and Ophthalmology, Departments of Neurology and Ophthalmology, University of Colorado, Health Sciences Center, Denver, Colorado, USA

Monika Bradl PhD
Head of Cellular Neuroimmunology Group, Medical University Vienna, Center for Brain Research, Division of Neuroimmunology, Vienna, Austria

Mark P. Burgoon PhD
Assistant Professor, Department of Neurology, University of Colorado, Health Sciences Center, Denver, Colorado, USA

Fredric K. Cantor MD
Adjunct Investigator, Neuroimmunology Branch, NINDS, NIH, Bethesda, Maryland, USA

Stacey S. Cofield PhD
Assistant Professor of Biostatistics, Department of Biostatistics, University of Alabama at Birmingham, Alabama, USA

Gary R. Cutter PhD
Professor of Biostatistics, Department of Biostatistics, University of Alabama at Birmingham, Alabama, USA

Klaus Dornmair PHD
Head of Research Group, Ludwig-Maximilians University, Klinikum Grosshadern, Institute for Clinical Neuroimmunology, Munich, Germany

Monique Dubois-Dalcq MD
Honorary Professor, Pasteur Institute, Paris, France; Guest at National Institute of Neurological Disorders and Stroke Porter Neuroscience Research Center, Bethesda, Maryland, USA

Halima El-Moslimany MD
Post-doctoral Fellow in Multiple Sclerosis, The Corinne Goldsmith Dickinson Center for Multiple Sclerosis, Mount Sinai School of Medicine, New York, USA

Clare J. Fowler FRCP
Professor, Institute of Neurology; Consultant in Uro-Neurology, National Hospital for Neurology and Neurosurgery, University College London Hospitals, London, UK

Claude Genain MD
Associate Professor, California Pacific Medical Center Research Institute (Neurosciences), San Francisco, California, USA

Donald H. Gilden MD
Louise Baum Professor and Chairman, Departments of Neurology and Microbiology, University of Colorado, Health Sciences Center, Denver, Colorado, USA

Gavin Giovannoni MB ChB PhD FCP FRCP FCPath
Professor of Neurology, Institute of Cell and Molecular Science, Barts and The London Queen Mary's School of Medicine and Dentistry, London, UK

Ralf Gold MD
Professor and Chair, Department of Neurology, St Josef-Hospital, Ruhr-University Bochum, Germany

Douglas S. Goodin MD
Director of the Multiple Sclerosis Center, Department of Neurology, University of California, San Francisco, California, USA

Stephen L. Hauser MD PHD
Chair and Robert A. Fishman Distinguished Professor, Department of Neurology, University of California, San Francisco, California, USA

Reinhard Hohlfeld MD
Professor and Director of the Institute for Clinical Neuroimmunology, Ludwig-Maximilians University, Klinikum Grosshadern, Institute for Clinical Neuroimmunology, Munich, Germany

Vinay Kalsi MRCS
Registrar in Uro-Neurology, National Hospital for Neurology and Neurosurgery, University College London Hospitals, London, UK

Ludwig Kappos MD
Professor of Neurology, Department of Neurology, Universitätsspital Basel, Basel, Switzerland

Jürg Kesselring MD
Professor of Neurology and Neurorehabilitation, Universities of Bern and Zürich, Switzerland; Chair of Neurorehabilitation, Università Vita e Salute, San Raffaele, Milano, Italy

Jeffery D. Kocsis PhD
Professor of Neurology, Department of Neurology, Yale University School of Medicine; Associate Director, Center for Neuroscience and Regeneration Research, VA Medical Center, West Haven Connecticut, USA

Tanya J. Lehky MD
Director, Clinical EMG Laboratory, EMG Branch, NINDS, NIH, Bethesda, Maryland, USA

Catherine Lubetzki MD DSci
Professor of Neurology, Université Pierre et Marie Curie, Faculté de Médecine, Paris; Assistance Publique-Hôpitaux de Paris, Hôpital de la Salpêtrière, Paris, France

Fred D. Lublin MD
Saunders Family Professor of Neurology; Director, The Corinne Goldsmith Dickinson Center for Multiple Sclerosis, Mount Sinai Medical Center, Mount Sinai School of Medicine, New York, USA

Samuel K. Ludwin MB ChB FRCP(C)
Professor of Pathology, Department of Pathology and Molecular Medicine, Queens University and Kingston General Hospital, Kingston, Ontario, Canada

Henry F. McFarland MD
Chief, Neuroimmunology Branch, and Clinical Director, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland, USA

Roland Martin MD
Research Professor, Institute for Neuroimmunology and Clinical MS Research, Center for Molecular Neurobiology Hamburg (ZMNH), University Medical Center Eppendorf, Hamburg, Germany

Aaron E. Miller MD
Medical Director, Corinne Goldsmith Dickinson Center for Multiple Sclerosis; Professor of Neurology, Mount Sinai School of Medicine, New York, USA

David H. Miller MB ChB MD FRACP FRCP
Professor of Clinical Neurology, Department of Neuroinflammation, Institute of Neurology, University College London, London, UK

John H. Noseworthy MD FRCPC
Professor and Chair, Department of Neurology, Mayo Clinic College of Medicine, Rochester, Minnesota, USA

Jorge R. Oksenberg PhD
Professor, Department of Neurology, School of Medicine, University of California at San Francisco, California, USA

Gregory P. Owens PhD
Associate Professor, Department of Neurology, University of Colorado, Health Sciences Center, Denver, Colorado, USA

Trevor Owens PhD
Professor, Medical Biotechnology Centre, Center for Medical Biotechnology, Syddansk Universitet, Odense, Denmark

Chris H. Polman MD PhD
Professor of Neurology, VU Medical Center, Amsterdam, The Netherlands

Maura Pugliatti MD
Research Assistant in Neurology, Institute of Clinical Neurology, Medical Faculty, University of Sassari, Sassari, Italy

Michael K. Racke MD
Professor of Neurology, Department of Neurology, Department of Molecular Virology, Immunology and Medical Genetics, The Ohio State University Medical Center, Columbus, Ohio, USA

Cedric S. Raine PhD DSc FRCPath
Departments of Pathology (Neuropathology), Neurology and Neuroscience, Albert Einstein College of Medicine, New York, USA

Stephen M. Rao PhD
Professor of Neurology, Department of Neurology, Cell Biology, Neurobiology and Anatomy, Medical College of Wisconsin, Milwaukee, Wisconsin, USA

Stephen C. Reingold PhD
Research Counsellor, National Multiple Sclerosis Society, New York City, New York; President Scientific and Clinical Review Associates LLC, Salisbury, Connecticut and New York City, USA

Giulio Rosati MD
Professor of Neurology and Head of Institute of Clinical Neurology; Dean of Medical Faculty, University of Sassari, Sassari, Italy

Randall T. Schapiro MD
Director, The Schapiro Center for Multiple Sclerosis, Minneapolis Clinic of Neurology, Minneapolis; Clinical Professor of Neurology, University of Minnesota, Minneapolis, Minnesota, USA

Neil J. Scolding FRCP PhD
Burden Professor of Clinical Neurosciences, Department of Neurology, University of Bristol, Institute of Clinical Neurosciences, Frenchay Hospital, Bristol, UK

Mireia Sospedra MD
Research Associate Institute for Neuroimmunology and Clinical MS Research, Center for Molecular Neurobiology Hamburg (ZMNH), University Medical Center Eppendorf, Hamburg, Germany

Alan J. Thompson MD FRCP FRCPI
Garfield Weston Professor of Clinical Neurology and Neurorehabilitation, Department of Brain Repair and Rehabilitation, Institute of Neurology, University College London, London, UK

Edward J. Thompson PhD MD DSc FRCPath FRCP
Emeritus Professor of Neurochemistry and Honorary Consultant at the National Hospital for Neurology and Neurosurgery, The Institute of Neurology, London, UK

Bob W. van Oosten MD PhD
Neurologist, VU University Medical Center, Amsterdam, The Netherlands

Stephen G. Waxman MD PhD
Professor and Chairman, Department of Neurology, Yale University Medical School, New Haven, USA; Director, Center for Neuroscience and Regeneration Research, VA Medical Center, West Haven, CT, USA

Brian G. Weinshenker MD FRCP(C)
Consultant in Neurology, Mayo Clinic; Professor of Neurology, Mayo Clinic College of Medicine, Rochester, USA

Dean M. Wingerchuk MD FRCP(C)
Consultant in Neurology, Mayo Clinic; Assistant Professor of Neurology, Mayo Clinic College of Medicine, Scottsdale, USA

Heather A. Wishart PhD
Associate Professor of Psychiatry, Dartmouth Medical School, Lebanon, New Hampshire, USA

Xiaoli Yu PhD
Instructor, Department of Neurology, University of Colorado, Health Sciences Center, Denver, Colorado, USA

Bernard Zalc MD DSci
Directeur de Recherche, Institut National de la Santé et de la Recherche Médicale, and Universîté Pierre et Marie Curie Unit 711, Hôpital de la Salpêtrière, Paris, France

Simone P. Zehntner PHD
Director, Small Animal Imaging Laboratory, Brain Imaging Center, Montreal Neurological Institute, Montreal, Quebec, Canada

Contents

CHAPTER 22

Escape therapies and management of multiple sclerosis

H. El-Moslimany and A. E. Miller

INTRODUCTION

Based on the conviction that multiple sclerosis (MS) is an autoimmune disease, primarily cell-mediated, nonspecific immunosuppressants have long been used in an attempt to halt or slow disease progression. Because current disease-modifying agents are only moderately successful at preventing further exacerbations and persistent neurological deterioration, neurologists continue to resort to the use of nonspecific immunosuppressants while seeking newer more effective agents. Currently, class I evidence of benefit exists only for interferon (IFN)β,[1–3] glatiramer acetate,[4] natalizumab, and mitoxantrone.[5] Although some other agents, particularly the nonspecific immunosuppressants, have been the subject of extensive research, none has been clearly determined to provide benefit in double-blinded, randomized, placebo-controlled trials. The newer agents still require study for safety as well as efficacy, a concern intensified after the occurrence of progressive multifocal leukoencephalopathy associated with natalizumab.[6] This chapter will review a variety of drugs or procedures that have been studied for the treatment of MS and suggest a context for their use. Before the agents are discussed individually, however, one must consider the circumstances that would prompt their use.

TREATMENT FAILURE

Multiple sclerosis is a chronic inflammatory disease of the central nervous system (CNS) in which immune-mediated events result in demyelination and also probably lead to axon damage, ultimately causing neurological disability. Inflammatory events are recognized more frequently in the early stages both as clinical attacks and MRI disease activity. Often, over time, inflammatory events diminish in frequency. Progressive neurological disability may also result from neurodegeneration. Controversy exists over whether inflammation or neurodegeneration is the primary pathological process in MS[7] but most investigators agree that inflammation plays an important role in the eventual development of neurological disability. Trapp et al found that axon destruction occurs in active lesions.[8] IFNβ treatment has decreased clinical disease activity and, more strikingly, lesions that are evident on magnetic resonance imaging (MRI).[1,2,9–12] Hence, reduction of inflammation may potentially limit subsequent disability, as has been demonstrated, for example, in some of the trials of IFNβ.[1,3]

The clinical trials of various immunomodulatory drugs for the treatment of MS have demonstrated a modest reduction in the relapse rate and limited effects on disability. Relatively few patients were completely free of disease activity in each study ranging in duration from 24 weeks to 6 years. Thus, for most patients the treatment was only partially effective in controlling the clinical expressions of disease.

Establishing precise definitions of treatment failure is difficult. Rio et al[13] examined different criteria for treatment failure in a cohort of relapsing–remitting MS (RRMS) patients treated with IFNβ. They noted that determinations of progression that rely on a certain degree of deterioration on clinical rating scales sustained for 3 or 6 months may include a significant proportion of erroneously categorized treatment failures because of delayed improvement after exacerbations. In an extension of their work, Rio et al[14] concluded, after applying various criteria for nonresponsiveness after 2 years of IFN treatment, that the development of disability (confirmed after 6 months) was more sensitive, specific and accurate in predicting progression to considerable disability (median Expanded Disability Status Scale (EDSS) 6.5) after 6 years than measures that relied totally or in part on relapses.[14] The Multiple Sclerosis Therapy Consensus Group determined that no recommendations regarding the optimal total duration of treatment with any

immunomodulatory regimen in MS can be considered to be evidence-based.[15] Patients should be evaluated every 3–6 months using the EDSS and the Multiple Sclerosis Functional Composite score (MSFC). If worsening is apparent on clinical examination, as determined by the EDSS and MSFC, the patient should undergo an MRI of the brain with gadolinium. If clinical worsening is present, escalation of treatment with either a different disease-modifying agent or a nonspecific immunosuppressant for the management of disease may be considered at this stage.

Clearly, clinical relapses often produce a sustained effect on disability. Lublin et al found residual deficit months after the first in-study relapse among placebo-treated patients who participated in the trials of the disease-modifying agents.[16] Also, evidence suggests that inflammation contributes to cumulative neurological impairment,[17,18] e.g. the observation by Weinshenker et al that patients who have an increased frequency of relapses in the first years of MS have a higher risk of later disability.[17] In the CHAMPS trial of patients who had a positive MRI at the time of their initial neurological event, the best predictors of the development of clinically definite MS over a short interval were the presence of gadolinium-enhancing lesions and satisfaction of the Barkhof MRI criteria[19] for dissemination in space.[20]

Recent functional MRI studies have suggested that relapse recovery involves adaptive recruitment of networks of additional brain regions to restore function.[21–23] Therefore, multiple attacks may gradually erode the reserve available for recruitment and, consequently, some might consider that any attack is an indication of suboptimal treatment response. Most neurologists would agree that patients who are still having frequent attacks on disease-modifying therapy are suboptimal responders, especially if serial examinations demonstrate progression of neurological impairment. Insidious progression also indicates a suboptimal treatment response but, in the absence of signs of active inflammation, has negative implications for a response to any immunosuppressive agent. An important issue is whether to use MRI findings alone to determine suboptimal response. New enhancing lesions are associated with increased relapse rates and increased T2 lesion burden, and may be associated with progression of disability in the short term in patients with RRMS.[24–28] Since the disease-modifying agents, particularly the IFNs, reduce the number of new T2 lesions, an increasing T2 lesion burden in a patient on therapy might be considered indicative of a suboptimal response.[28–30] However, because existing US Food and Drug Administration (FDA)-approved disease-modifying therapies are only moderately effective in reducing MRI activity and because the correlation of T2 disease burden on brain MRI with clinical activity is weak, using change in MRI alone as a basis for changing treatment is problematic.

A task force of MS specialists convened by the National Multiple Sclerosis Society of the USA recently recommended criteria for determining suboptimal response to therapy and changing treatment. The task force advised that patients remain on a medication for at least a year before a judgment of suboptimal response is made.[31] Suboptimal responders would then be patients who had experienced more than one attack per year or had failed to show a reduction from the pretreatment relapse rate. The patient can also be considered a suboptimal responder if there has been an increase in the EDSS of 1 point from a baseline score of 3.0–5.5 or a 0.5 point increase from a baseline score of 6.0 or greater. The task force cautioned, however, about basing a decision to change treatment on deterioration in EDSS score that was associated with an acute exacerbation, because of the potential for recovery.

Although new activity on the MRI is a cause for concern, the task force opposed switching therapy on the basis of changes on regularly scheduled or periodic MRIs alone, in the absence of clinical activity. However, ongoing MRI activity after an attack has occurred could support a decision to change treatment. While a significant increase of T2 disease burden is a cause for concern, the extent of change that is considered significant was not established. While current agents do not completely suppress new lesion activity, Cohen et al stated that brainstem and spinal cord lesions are more worrisome and that the presence of new lesions in those regions is sufficient reason to alter therapy.[32]

The frequency at which the physician should obtain MRIs also remains controversial. The Multiple Sclerosis Treatment Consensus Group advises obtaining MRI scans only if there is any change in EDSS or MSFC.[15] Cohen et al suggest that MRIs should be obtained when treatment is changed, in order to provide an updated baseline to determine the effectiveness of the new therapy.[32] If surveillance scans are to be done, the studies are helpful only in the first few years of disease and not after 5 years if there is little change clinically.[32] According to the NMSS task force, all patients should have a baseline brain MRI, and spinal cord MRI if the patient has myelopathic symptoms.[31] The patients should report any suspected relapse, which would then require prompt neurological examination.[31] MRI scans should be obtained in suspected suboptimal responders to support decisions to change therapy and should be obtained to establish a new baseline if change of therapy occurs.[31] If patients are developing progressive impairment, with subtle relapse activity, a follow-up MRI is needed.

Subtle symptoms affecting activities of daily living, even in the absence of a change on examination, can also be indicative of a suboptimal response to treatment if the symptom accumulation is stepwise.[32] However, potential effects of medications, sedation, increased spasticity, sleep disturbances and comorbid medical conditions must be excluded before attributing changes to a suboptimal response. Cohen et al[32] also suggested that patients developing multifocal disease affecting multiple neurological systems while on therapy could be considered suboptimal responders. A patient who experiences progressive motor or cognitive impairment sufficient to disrupt daily activities could be regarded as a suboptimal responder.

Río and his group re-examined in 2006 the question of suboptimal response to IFNβ.[33] They followed 393 patients with RRMS who were treated with IFNβ. Various criteria were examined in an attempt to define nonresponse to IFNβ, including number of relapses, disability progression or both. They found that the most clinically relevant criterion of response to IFNβ is disability progression. Disability progression was defined as an increase in the EDSS of 1.5 points for patients with a baseline EDSS of 0; an increase of 1 point for scores from 1.0–5.0, and an increase of 0.5 points for scores equal to or higher than 5.5.

Natalizumab, which is discussed in Chapter 21, was reintroduced to the market in July 2005 with a risk management program, known as TOUCH®, to minimize the potential of harm from the development of PML. Two cases of that opportunistic viral infection of the brain had occurred in patients who had received a combination of natalizumab and weekly interferon β-1a for more than 2 years.[34,35] Now, natalizumab, which reduced relapse rate by 68% and slowed EDSS progression in the monotherapy AFFIRM trial,[36] is a reasonable option for patients who are having an inadequate response to interferon or glatiramer and are willing to accept the uncertain level of risk associated with the use of that monoclonal antibody against the adhesion molecule, α4β1 integrin (VLA-4).

Irrespective of the specific criteria applied, the physician who decides a patient is failing currently approved disease-modifying therapy faces a bewildering number of agents that might be potentially beneficial. The rest of this chapter will focus on the individual drugs and procedures that are currently available. These drugs can be classified in a variety of ways, including their route of administration (Table 22.1), whether they are used alone or in combination (Table 22.2), or by their class (Table 22.3).

TABLE 22.1 Drugs for the management of multiple sclerosis, by route of administration

Drugs taken orally	Drugs taken by injection	Nonpharmacological approaches
Azathioprine	Mitoxantrone	Plasma exchange
Cyclophosphamide	Cyclophosphamide	Bone marrow transplantation
Mycophenolate mofetil	Steroids	
Methotrexate	Intravenous immunoglobulin	
Cladribine	Alemtuzumab	
Tacrolimus	Rituximab	
Ciclosporin	Daclizumab	
Sulfasalazine		

TABLE 22.2 Therapies for the management of multiple sclerosis, by method of use

Therapies used by themselves	Therapies used in combination with interferon-β
Azathioprine	Azathioprine
Ciclosporin	Ciclosporin
Mitoxantrone	Methotrexate
Methotrexate	Mycophenolate mofetil
Mycophenolate mofetil	Alemtuzumab
Intravenous immunoglobulin	Daclizumab
Plasma exchange	
Tacrolimus	
Ciclosporin	
Sulfasalazine	
Alemtuzumab	
Rituximab	
Daclizumab	
Bone marrow transplantation	

TABLE 22.3 Classes of drug studied in the management of multiple sclerosis

Antineoplastic agents	Immunosuppressants
Mitoxantrone	Cyclophosphamide
Methotrexate	Azathioprine
Rituximab	Steroids
	Mycophenolate mofetil
	Cladribine
	Intravenous immunoglobulin
	Tacrolimus
	Ciclosporin
	Alemtuzumab
	Daclizumab

MITOXANTRONE

Mitoxantrone (Novantrone) was the first drug approved by the FDA for treatment of patients with secondary progressive MS (SPMS) or with a worsening relapsing disease course.[37] This approval was based on the results of a multicenter, randomized, placebo-controlled phase III trial.[5] Like Adriamycin and daunorubicin, mitoxantrone is an anthracenedione, which is used as an antineoplastic agent alone or in combination therapy for the treatment of prostate cancer, non-Hodgkin's lymphoma and acute nonlymphocytic leukemia.[38–40]

Mitoxantrone intercalates into DNA through hydrogen bonding, causing crosslinks and strand breaks.[38] It also interferes with DNA topoisomerase II.[38] When DNA is replicated or transcribed, the topological formation of DNA is altered, resulting in a DNA molecule that is not in the correct formation, making it impossible to undergo further transcription or replication.[41] DNA topoisomerase II is an enzyme that helps in the separation of two intertwined daughter DNA molecules after DNA replication by the transient formation of double-strand breaks.[42] The transient breaks allow the DNA molecules to separate and then rewind into the correct topological formation prior to ligation. Mitoxantrone affects replication by inhibiting topoisomerase II in dividing and nondividing cells. Most pharmacokinetic data in humans were generated through its use in cancer patients receiving daily doses of this drug.[43,44]

Mitoxantrone is 80% plasma-protein-bound and its half-life is approximately 1–3 hours. The drug is extensively distributed in various tissues and metabolized primarily in the liver. In MS, some of its beneficial clinical effects are believed to be attributable to the suppression of replication of autoreactive T cells, B cells and macrophages.[42] In vitro studies demonstrated that mitoxantrone impairs antigen presentation and the secretion of inflammatory cytokines, including IFNγ, tumor necrosis factor (TNF)α, and interleukin (IL)-2.[45,46]

Mitoxantrone can cause cardiotoxicity, which may manifest as tachycardia and arrhythmia, asymptomatic decrease in measures of left ventricular ejection fraction, or symptomatic congestive heart failure.[47] An increased risk of cardiotoxicity is also associated with higher cumulative doses of mitoxantrone, prior treatment with anthracyclines, prior mediastinal radiotherapy and pre-existing cardiovascular disease. It is therefore mandatory that patients undergo evaluation of their cardiac output before initiation of therapy, if they develop signs and symptoms of congestive heart failure, and before each dose when the drug is administered every 3 months, as currently recommended.[48] MS patients with a left ventricular ejection fraction of less than 50% or signs of congestive heart failure should not be treated with this drug.[47] Patients should also be asked if they have ever been treated with mitoxantrone or one of the anthracyclines. Factors resulting in mitoxantrone-induced cardiotoxicity are not entirely understood but may include formation of reactive oxygen intermediates that lead to damage of myocardial tissue. Another explanation for cardiotoxicity is that the impairment

of DNA repair by mitoxantrone's inhibition of topoisomerase II may exert a cytocidal effect on myocardial cells by chelating with iron and forming complexes. The myocardial damage is due to intracellular generation of reactive oxygen intermediates via iron- or enzyme-mediated oxidation–reduction reactions.[49] Myocytes appear to be selectively susceptible to the formation of reactive oxygen intermediates because of their relative lack of defense mechanisms such as catalase and superoxide dismutase.[49] Dexrazoxane is an iron chelator that can prevent iron–mitoxantrone complex formation, potentially inhibiting the generation of reactive oxygen intermediates.[50] It may be a potential cardioprotectant, but more investigation is necessary.[51] A study analyzing the long-term safety and tolerability of mitoxantrone in MS patients is expected to be completed in 2007.[49]

Leukemia, albeit rare, is another serious adverse effect of mitoxantrone.[49] Topoisomerase II inhibitors are associated with characteristic toxic acute myelogenous leukemias (AMLs) that differ from those reported with alkylating agents.[49] Topoisomerase-II-related AMLs exhibit shorter latency (median 2 years), absence of a myelodysplastic phase and characteristic chromosomal aberrations.[49] An increased risk for leukemia has been observed in breast cancer patients when mitoxantrone was used in combination with other alkylating agents and radiotherapy.[52] In a series of breast cancer patients, the prognosis for toxic AML was poorer than for those with de novo cases of AML.[52,53] At least seven cases of toxic AML and two cases of promyelocytic leukemia have been reported in association with mitoxantrone therapy for MS.[52–60] In contrast to the experience with breast cancer patients, most of the MS cases had a favorable response to therapy for leukemia.[61] Previous exposure to alkylating agents may increase the risk for mitoxantrone-associated leukemia and may account for some of the difference in the two populations. The cancer patients may also have received higher doses. Mitoxantrone should be used with caution in patients who have received previous cytotoxic therapy (e.g. cyclophosphamide). Because the total number of MS patients treated with mitoxantrone is unknown, it is difficult to determine an accurate incidence rate.[62] Ongoing registries will help to further determine the frequency of toxic leukemias in association with mitoxantrone monotherapy for MS. An estimate of 0.07% has been reported based on a review of three series comprising over 1300 patients.[49]

Patients treated with mitoxantrone usually develop transitory leukopenia and neutropenia, with the nadir typically occurring 10–14 days postinfusion.[49] Mitoxantrone should not be used in patients who are otherwise immunosuppressed.[58] Treatment with mitoxantrone can cause uremia and may lead to acute attacks of gout.[49,63] Thrombocytopenia may also occur.[49,63] Other less serious adverse effects include reversible alopecia, temporary discoloration of sclera and urine, sinus congestion, constipation, diarrhea, nausea, vomiting, headaches, dysmenorrhea and cervical lymphadenopathy.[49]

Mitoxantrone may cause birth defects if either the female or the male partner was being treated at the time of conception or during pregnancy.[49] Sterility, sometimes permanent, has been reported when the drug was used alone or in combination with other antineoplastic agents.[63] Permanent amenorrhea occurs in about 14% of women over the age of 35.[49] Female patients should not breast-feed.

The FDA has approved the use of mitoxantrone in SPMS and worsening relapsing MS when administered at 12 mg/m^2 once every 3 months until the lifetime cumulative dose of 140 mg/m^2 is met, based on the phase II safety trial[64,65] and the phase III randomized, placebo-controlled, double blind trial (MIMS trial).[5] The phase II trial included 42 MS patients with very active disease by clinical and MRI criteria who were randomized to receive monthly intravenous pulse doses of either 20 mg mitoxantrone plus 1 g methylprednisolone or 1 g methylprednisolone alone for 6 months. In the methylprednisolone alone group, five patients dropped out because of severe clinical exacerbations.[65] Blinded analysis of MRI data showed significantly fewer new enhancing lesions in the mitoxantrone group.[65] Unblinded clinical assessments showed a significant improvement in clinical disability and a significant reduction in the number of relapses at months 2–6 in the mitoxantrone-treated group.[65]

The MIMS trial included 194 patients who had relapsing–progressive MS (i.e. relapsing disease with incomplete recovery between relapses) or SPMS.[5] Patients were randomized to receive either placebo, low-dose intravenous mitoxantrone (5 mg/m^2), or high-dose mitoxantrone (12 mg/m^2) every 3 months for 24 months. The total follow-up time was 36 months. The primary efficacy outcome consisted of five clinical measures tested in one composite of stochastic ordered alternatives: change from baseline EDSS at 24 months, change from baseline ambulation index at 24 months, number of relapses treated with corticosteroids, time to first treated relapse, and change from baseline standardized neurological status at 24 months.[5] Secondary endpoints included the proportion of patients with deterioration of at least 1 EDSS point, proportion of patients with such EDSS deterioration confirmed after 3 months and 6 months, time to first sustained EDSS deterioration, time to first relapse, number and annual rate of relapses, proportion of patients without relapse, number of days in hospital, use of wheelchair assistance, and quality of life assessed by the Stanford Health Assessment Questionnaire.[5] The high-dose (12 mg/m^2) mitoxantrone-treated group showed a 64% reduction in sustained disease progression and a 69% reduction in the number of treated relapses compared with the placebo control group.[5] Blinded evaluations of brain MRI scans from a subgroup of patients showed a decrease of gadolinium-enhancing lesions and T2-weighted lesion load in the high-dose mitoxantrone-treated group compared with the placebo treatment group.[5] The correlation of improvement in the clinical outcome measures with diminished CNS inflammation as measured by brain MRI suggests that broad-spectrum immunosuppression is of some benefit in patients with progressive MS.[5]

Gonsette noted that an induction phase with 3-monthly administrations of 12 mg/m^2 of mitoxantrone followed by a maintenance phase every 3 months seems to be a good compromise, allowing treatment for at least 2 years with an acceptable lifetime dose. An induction phase may be helpful in the control of rapidly progressive disease, but then a rapid switch to maintenance therapy would allow a longer period of treatment for a chronic disease.[66] Mitoxantrone has been shown to be effective in patients with active inflammatory disease in a randomized, double blind trial comparing it to methylprednisolone.[67] Despite Gonsette's suggestion, opinion differs about the dose regimen and whether to use mitoxantrone alone or with methylprednisolone. However, practice recommendations for the use of mitoxantrone state that the medication should be used in patients with rapidly advancing disease who have failed other therapies, and that patients can receive a dose every 3 months. Cardiac, liver and kidney function should be regularly monitored in patients taking mitoxantrone.[68]

SUMMARY

Mitoxantrone is the only medication approved by the FDA for severe relapsing disease (both RRMS and SPMS). Side effects, particularly cardiotoxicity, limit the lifetime dosage of the medication, thereby limiting the length of time during which a patient can be treated with it. Issues such as optimal dosage and frequency of administration still need to be resolved.

AZATHIOPRINE

Azathioprine is cleaved to 6-mercaptopurine, which in turn is converted to additional metabolites that inhibit de novo purine synthesis.[69,70] The metabolite is incorporated into DNA and gene translation is inhibited.[69,71] Azathioprine may reduce levels of TNFα and increase suppressor–inducer lymphocytes.[72] The side effects include bone marrow suppression with leukopenia, thrombocytopenia and/or anemia.[72] An increased susceptibility to infections, hepatotoxicity, alopecia, gastrointestinal toxicity, pancreatitis and increased risk of neoplasia may occur.[73] Patients who take azathioprine may also develop an idiosyncratic hypersensitivity reaction.[74] This reaction has been reported in about 2% of patients with inflammatory bowel disease[75] and ranges in occurrence from 11–15% in rheumatoid arthritis[76] and myasthenia gravis.[77] In one report of azathioprine intolerance in MS, many patients had nausea, myalgia and arthralgia, which manifests early in the course of therapy, with most of the patients withdrawing from therapy within 2 months of initiation.[75] Patients could also have vomiting, diarrhea, rash, purpura, fever, dermatitis and malaise.[78] The symptoms disappear upon withdrawal of the drug and re-emerge when the patient is rechallenged.[78]

In a British and Dutch prospective, double-blind, placebo-controlled, randomized trial, patients with RRMS and SPMS[79] were treated for 3 years with either azathioprine 2.5 mg/kg/d or placebo. No difference between the treatment and placebo groups was seen in the first 3 years after the start of the trial, so follow-up was continued up to 4.5 years. After the first year, the EDSS score had worsened slightly more in the azathioprine group compared to placebo but the ambulation index was better in the azathioprine group. In subsequent years, the patients in the azathioprine group deteriorated slightly less than the patients taking placebo. The only statistically significant difference was a reduction in the deterioration of the ambulation index of the patients taking azathioprine compared to those taking placebo after 3 years of study.

At the last follow-up, in July 2002, of the 149 patients who had received active drug, 34 had died and 12 had diagnosed cancers.[80] In the placebo group, 40 had died and seven had diagnosed cancers. The increase in cancer and deaths in patients with a diagnosis of cancer in those taking azathioprine was not statistically significant.[80] However, another study examining the risk of cancer in patients treated with azathioprine showed an increased risk of cancer after 10 years of continuous therapy.[81]

Another prospective, double-blind, placebo-controlled trial randomized 59 patients who had experienced at least two exacerbations in the 18 months prior to the beginning of the study to receive either 3 mg/kg/day of azathioprine or placebo for 2 years.[82] Results suggested that azathioprine may reduce rates of relapse in patients with relapsing forms of MS. However, side effects are common, particularly gastrointestinal disorders and hematological disorders, which may affect drug adherence.[82]

A meta-analysis of published blinded, placebo-controlled trials showed that azathioprine significantly increases the likelihood of remaining relapse-free and marginally decreases progression of disability after 2–3 years of treatment, but not after the first year.[83,84] However, whether the slight clinical benefits of azathioprine outweigh the risks is debatable.

COMBINATION WITH INTERFERON

The combination of azathioprine with IFNβ-1b was evaluated in an open-label pilot study of six RRMS patients with continuing disease activity despite IFNβ-1b treatment.[85] The addition of azathioprine to IFNβ-1b decreased the number of contrast-enhancing lesions by 69% after a period of 15 months compared to the IFNβ-1b only group. Azathioprine with IFNβ-1a was evaluated in another open-label study in RRMS patients who were not responsive to either IFNβ-1a or azathioprine as monotherapy, or who had never been previously treated.[86]

The dose of azathioprine was adjusted to reduce lymphocyte count to 1000/μl in association with IFNβ-1a at a dose of 6 MIU every other day. The number of new lesions was decreased on MRI and the number of relapses and change in EDSS was less on the combined therapy when compared to the observations in the same patients prior to combined therapy.

SUMMARY

In the blinded, placebo-controlled trials for the treatment of MS with azathioprine, one trial showed a possible benefit of azathioprine in the reduction of relapses in MS while the other trial showed no benefit for the treatment of MS. These studies, as well as published meta-analysis, suggest that azathioprine as monotherapy has, at best, marginal benefit in MS. The combination of azathioprine with IFNβ has only been evaluated in open-label studies, which showed some benefit, but until the combination is studied in rigorous, double-blinded trials, the results are not very helpful. Consideration of the use of azathioprine should be further tempered by its adverse effect profile, including a probable increased risk of cancer with long-term use.

CYCLOPHOSPHAMIDE

Cyclophosphamide is an alkylating agent that is chemically related to the nitrogen mustards. The drug undergoes metabolic activation (hydroxylation) by the cytochrome P450 system, with transport of the activated intermediate to sites of action,[87] where it forms covalent linkages by alkylation of various nucleophilic moieties. The cytotoxic effects are directly related to the alkylation of DNA. Cyclophosphamide is used for the treatment of many autoimmune disorders, including Wegener's granulomatosis, polyarteritis nodosa, polymyositis, peripheral neuropathies[88] and lupus nephritis.[89,90] Toxicity includes myelosuppression with platelet sparing, alopecia, nausea, vomiting, mucosal ulcerations, interstitial pulmonary fibrosis, sterile hemorrhagic cystitis (reduced by MESNA[90]), the syndrome of inappropriate antidiuresis, amenorrhea and gonadal failure.[91]

IMMUNOLOGIC EFFECTS OF CYCLOPHOSPHAMIDE

Cyclophosphamide suppresses experimental autoimmune encephalomyelitis (EAE).[92] In humans, it enters the CNS and reduces cerebrospinal fluid (CSF) myelin basic protein (MBP) and IgG.[93–96] The drug causes lymphopenia involving T and B cells, with a more pronounced effect on $CD4^+$ cells,[97–99] which usually resolves 4 months after treatment is stopped. It increases the anti-inflammatory cytokines IL-4, IL-5, IL-10 and transforming growth factor (TGF)β and is associated with eosinophilia.[100–102] Cyclophosphamide also decreases IL-12, which has been linked to its therapeutic response.[103] The levels of IL-12 pretreatment may have predictive value, as patients who have higher levels of IL-12 pretreatment do not respond as well.[104] Cyclophosphamide preferentially induces antigen Th2 responses to myelin autoantigens[102] and shifts immune responses from T helper (Th)1 towards Th2.[103]

USE IN MULTIPLE SCLEROSIS

Cyclophosphamide has been used for the treatment of MS since 1966.[90] Open-label studies of short duration demonstrated

positive effects in small populations of both RRMS and progressive patients.[105–107] Hommes[108] studied a group of 32 progressive patients who were treated in an uncontrolled open-label trial with 100 mg oral cyclophosphamide four times daily and 50 mg prednisone twice daily.[108] The patients received a total of 8 g cyclophosphamide over 20 days. The authors reported stabilization in 69% of patients over a period of 1–5 years. Hommes[109] studied 39 patients with chronic progressive disease in another open-label, uncontrolled trial, which also showed stabilization in 69% of the patients over a period of 1–5 years.[109] Factors that predicted a good response to therapy included disease onset before 28 years of age, short duration of disease prior to treatment, rapid progression of disease, low initial disability and HLA-DRw2 positivity.[102] Hommes[110] also reported six patients with chronic progressive MS who had been treated with oral cyclophosphamide plus prednisone in order to induce leukopenia below 2000/mm^3.[110] The authors found that CSF and serum levels of cyclophosphamide were in the same range, indicating that cyclophosphamide crosses the blood–brain barrier and, perhaps, is effective in the CNS.

In a retrospective study, Theys and colleagues, on the other hand, reported that patients with moderately advanced MS experienced no benefit from treatment with 6–8 g of cyclophosphamide given over 3–4 weeks compared to patients with similar disability scores who were not treated with cyclophosphamide.[111] Gonsette and colleagues reported on 110 patients in an open-label study, with follow up for 2–6 years.[112] Patients were treated with 1–2 g intravenous cyclophosphamide without corticosteroids over a 1–2-week period, with dosage adjusted to maintain a leukopenia of 2000 and lymphopenia of 1000 for 2–3 weeks. The annual relapse rate decreased by 75% compared to the relapse rate 1–2 years prior to treatment in 70% of patients. The most pronounced effects occurred in those patients with the shortest duration of disease. Patients who were already severely handicapped experienced no benefit. Some 30% of patients failed to respond to cyclophosphamide.

Open-label studies with cyclophosphamide have shown positive results in patients refractory to currently approved disease-modifying therapies.[113,114] Weinstock-Guttman reported 75% improved or stable at 12 months following induction therapy with intravenous cyclophosphamide followed by maintenance therapy with cyclophosphamide and either methotrexate, methylprednisolone or IFNβ-1b in an open-label study involving 17 patients.[115] Of these, 13 either improved or were stable at 12 months, and nine of the 13 remained stable at 24 months. Khan reported clinical improvement or stability in an open-label study of 14 consecutive patients with clinically definite MS who had severe clinical deterioration during the 12 months prior to treatment with cyclophosphamide.[116] The patients received monthly cyclophosphamide pulses for 6 months with doses adjusted to achieve a leukocyte nadir of 2000–2200 cells/mm^3 followed by resumption of one of the approved disease-modifying therapies. All patients were followed for at least 18 months after the first dose of cyclophosphamide.

Gobbini and colleagues treated five patients with RRMS not responsive to immunomodulatory therapies with monthly pulses of cyclophosphamide (1000 mg/m^2), in an open-label study.[113] Patients were followed with monthly MRI and clinical evaluation for a mean of 28 months. All patients showed a rapid reduction in contrast-enhancing lesion frequency and three patients experienced a decrease in T2 lesion load within 5 months of starting therapy.

A randomized double-blind placebo-controlled trial evaluated 14 RRMS patients, six of whom were treated with monthly pulses of 750 mg/m^2 intravenous cyclophosphamide for 1 year.[117] Although fewer relapses occurred in the treated patients than in the placebo patients after 1 year of treatment, the results were not statistically significant. A Canadian study evaluating cyclophosphamide and plasma exchange in 168 patients with progressive disease in a randomized, double-blind, placebo-controlled study found no difference between the treatment and the placebo groups.[118] Patients with progressive MS received either active drug treatment consisting of 1 g of cyclophosphamide on alternate days until the leukocyte count fell below 4.5 or until 9 g had been administered plus 40 mg prednisone orally for 10 days, placebo, or plasma exchange. Of the cyclophosphamide-treated patients, 60% were classified as chronic–progressive whereas 40% were relapsing–progressive. Although a positive trend early in the study favored the cyclophosphamide-treated patients, subsequently the cyclophosphamide group fared worse than the placebo group. Notably, though, the Canadian study reported stable disease in two-thirds of their placebo patients. The study results suggest that cyclophosphamide is not effective in later stages of progressive MS, when inflammation is probably playing a lesser role in the disease process.[102]

In a randomized, single-blind, placebo-controlled study in 22 progressive patients, Likosky and colleagues found no difference between cyclophosphamide-treated patients and the placebo group over a 24-month treatment period.[119]

In a multicenter study of 489 patients, Zephir and colleagues found that, after 12 months of pulse cyclophosphamide, 78.6% of the SPMS and 73.5% of the primary progressive MS (PPMS) patients had stabilized or had an improved EDSS.[120] In this study, for patients with an EDSS score of 5 or less, improvement or worsening was defined as at least a 1 point variation on EDSS. For patients with an EDSS score of 5.5, improvement was defined as at least a one point improvement, and worsening was at least 0.5 point worsening. For patients with an EDSS of 6 or over, improvement or worsening corresponded to at least a 0.5 point variation. There was no difference in treatment response among the groups. The apparent beneficial response to cyclophosphamide in SPMS patients was linked to the presence of superimposed relapses during the year prior to treatment, supporting the hypothesis that cyclophosphamide is most effective when there is an inflammatory component to the disease. Perini and colleagues reported development of fewer T2 lesions and gadolinium-enhancing lesions on MRI in 26 secondary progressive patients given monthly intravenous cyclophosphamide at 800–1250 mg/m^2 for 1 year and then every 8 weeks the second year.[121]

The safety and tolerability of cyclophosphamide pulse therapy was further evaluated by Portaccio et al in primary progressive or SPMS patients who had experienced deterioration of at least 0.5 points on the EDSS in the year prior to treatment and in RRMS patients who had a high relapse rate with incomplete remission.[122] A total of 112 patients received monthly pulses of 700 mg/m^2 of cyclophosphamide for 12 months followed by a bimonthly administration at the same dosage for an additional 12 months. Side effects included urinary tract infections (56.3%), nausea and vomiting (38.4%), amenorrhea (33.3%), lymphopenia (15%), increase of hepatic enzymes (10.8%), hypogammaglobulinemia 6.3%, respiratory tract infections (6%), alopecia, hemorrhagic cystitis, macroscopic hematuria, microscopic hematuria, hypersensitivity reaction and leukopenia. Four patients (3.6%) had developed malignancies but three of these had previously been treated with azathioprine.

TREATMENT REGIMENS

A variety of regimens for intravenous cyclophosphamide for the treatment of MS have been suggested (Table 22.4).[102] In one 8-day induction protocol, 600 mg/m^2 of cyclophosphamide is given on days 1, 2, 4, 6 and 8 along with daily methylprednisolone. In another protocol, 1 g of methylprednisolone is

TABLE 22.4 Regimens for intravenous cyclophosphamide for the treatment of multiple sclerosis

Protocol	Administration route	Dosage	Frequency	Duration	Adjuvant therapy
1	Intravenous	600 mg/m^2	Day 1, 2, 4, 6, 8	8 d	i.v. methylprednisolone
2	Intravenous	800 mg/m^2*	q.4weeks	12 cycles	i.v. methylprednisolone†
3	Intravenous	800 mg/m^2*	q.6 weeks	12 cycles	i.v. methylprednisolone†
4	Intravenous	800 mg/m^2*	q.8 weeks	12 cycles	i.v. methylprednisolone†
5	Intravenous	800–1000 mg/m^2	q.4–8 weeks	12–24 months	None

*Variable dosage to maintain a leucopenia of 2000/mm^3, maximum dosage 1600 mg/mm^3. †Initially 5 days of 1 g of i.v. methylprednisolone, then 1 g of i.v. methylprednisolone administered at the same time as the cyclophosphamide.
Source: Adapted from reference 102.

administered daily for 5 days, followed by intravenous pulses of cyclophosphamide with 1 g of methylprednisolone. The cyclophosphamide pulses begin at 800 mg/m^2 and the dose is escalated to produce a leukopenia of 2000/mm^3. The cyclophosphamide and methylprednisolone can be given every 4 weeks for 12 cycles, every 6 weeks for 12 cycles or every 2 months for 12 cycles. The maximum cyclophosphamide dose for this protocol is 1600 mg/m^2.

If one does not want to deal with variable doses of cyclophosphamide, one can give intravenous pulse therapy of cyclophosphamide, either with or without methylprednisolone, at a fixed dose of 800–1000 mg/m^2 every 4–8 weeks for 12–24 months. If patients are not responding well to IFNβ or glatiramer acetate, some authors suggest the use of intravenous pulse cyclophosphamide therapy using one of the above protocols, in combination with an approved disease-modifying agent.

COMBINATION WITH INTERFERON

The addition of a cyclophosphamide regimen to IFNβ treatment has been reported to show benefit in small open-label studies of patients with rapidly 'transitional' MS,[123–125] a stage during which a RRMS patient may be converting to a secondary progressive course. In some, this transition is associated with rapidly progressive deterioration unresponsive to steroid therapy.[123] In one open-label, unblinded trial of consecutive patients with clinically definite MS that became rapidly progressive following an initial relapsing–remitting course, 10 patients were treated with cyclophosphamide and methylprednisolone followed by IFNβ maintenance therapy.[123] Two of the 10 patients had become rapidly progressive while taking IFN therapy for 1 year or more. Treatment consisted of cyclophosphamide 500 mg/m^2 and 1000 mg daily methylprednisolone by intravenous infusion for 5 days. Then 6 weeks after cyclophosphamide/methylprednisolone induction, patients were started on either IFNβ-1b or IFNβ-1a. At 3 months, seven patients were improved by 1.0 EDSS and three remained stable. At 12 months, five of seven remained improved and two of seven were stable. No serious complications of treatment occurred.

Patti and colleagues reported on the effectiveness of a combination of cyclophosphamide and IFNβ in patients with rapidly progressive or 'transitional' MS characterized by frequent and severe attacks plus worsening on the disability status scale.[124] A total of 10 patients underwent monthly pulses of intravenous cyclophosphamide to obtain a lymphopenia of between 600 and 900/mm^3 for 12 consecutive months and then at 2-month intervals for a further 6 months. The authors reported a significant reduction of the number of relapses, progression, disability and T2 MRI burden of disease. Leukopenia and nausea were the most frequent side effects.

Patti and colleagues reported 36-month clinical and MRI follow-up on the patients reported in their 2001 study who had received 18 months of combination therapy with IFNβ and cyclophosphamide.[125] The patients were found to have stable relapse rates, EDSS, T2 MRI burden and lesion number. No gadolinium-enhancing lesions had appeared.

Patti's group looked at another ten patients with rapidly transitional MS (extremely active with very frequent and severe attacks, which produced a dramatic increase on the EDSS), who were treated with IFNβ without benefit (six on intramuscular IFNβ-1a, four on IFNβ-1b).[126] Monthly treatment with intravenous cyclophosphamide from 500–1500 mg/m^2 was titrated to produce a chronic lymphocytopenia. Patients experienced a marked and significant reduction in the number of relapses, disability accumulated and T2 MRI lesion burden. The EDSS was stable in all patients 1 year after the treatment course and relapses occurred with very low frequency. Side effects, including leukopenia and nausea, were mild. One patient developed a peripheral neuropathy. Weiner and colleagues analyzed the data from multiple trials involving cyclophosphamide and concluded that its use can be effective in MS during the active inflammatory component of the disease.[102]

SUMMARY

Many, but not all, unblinded studies of cyclophosphamide appear to show a benefit of the drug, used alone or in combination with IFN. Unfortunately, double-blind studies have generally failed to prove a benefit. Cyclophosphamide tends to show an effect in patients who are earlier in their disease process, with a recent history of multiple relapses and multiple gadolinium enhancing lesions on MRI.[127–129] Once the disease enters the later, progressive stages, with less accumulation of T2 lesions, the drug is not effective.[102,127] The use of cyclophosphamide is worth considering for patients with very aggressive disease or rapidly progressive disease with a high frequency of relapses and a rapid accumulation of disability, particularly after a suboptimal response to high dose IFNβ therapy. Patients should be informed of the absence of convincing blinded, placebo-controlled data substantiating its benefit, and adequately educated about its risks.

MYCOPHENOLATE MOFETIL

Mycophenolate mofetil is a prodrug rapidly hydrolyzed to the active drug, mycophenolic acid, which is a selective, uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase, an important enzyme in the de novo pathway of guanine nucleotide synthesis.[130] B or T lymphocytes are highly dependent on the inosine monophosphate dehydrogenase pathway for cell proliferation, whereas other cell types use salvage pathways. Thus, mycophenolate mofetil inhibits lymphocyte proliferation and functions. The addition of guanosine

or deoxyguanosine to the cells can reverse the effects of mycophenolic acid on lymphocytes. Side effects of mycophenolate mofetil include leukopenia, diarrhea, vomiting and increased incidence of some infections, especially cytomegalovirus.[131,132]

IMMUNOLOGICAL EFFECTS OF MYCOPHENOLATE MOFETIL

Mycophenolate mofetil almost completely inhibits antibody formation and inhibits superantigen induction of IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-10, TNFα, TGFβ and granulocyte–macrophage colony-stimulating factor (GM-CSF) but not mitogen induction.[133] Mycophenolate also impairs the synthesis of adhesion molecules, which facilitate the attachment of leukocytes to endothelial cells and target cells.[134] Its use in MS is based on studies in experimental allergic encephalomyelitis, where treatment with mycophenolate at the onset of clinical symptoms resulted in a more rapid recovery than in control or ciclosporin-treated mice.[135] Oral treatment with mycophenolate mofetil from the day of immunization for 2 weeks both significantly delayed the development of active experimental allergic encephalomyelitis in Lewis rats and reduced the antibody response to MBP. Rats treated with mycophenolate mofetil had less infiltration of T cells, B cells, macrophages and dendritic cells into brainstems than either the control or ciclosporin-treated rats. The brainstems of mycophenolate-mofetil-treated rats also had lower levels of mRNA for Th1 (IL-2, IL-12Rβ2, IFNγ), Th2 (IL-4, IL-10) cytokines and TNFα and TGFβ than ciclosporin-treated and control groups.

Frohman et al[133] reviewed their experience with the use of mycophenolate mofetil in 79 patients (14 with RRMS, 61 with SPMS, four with PPMS) who were not responsive to currently approved disease-modifying therapy.[136] Patients were started on mycophenolate mofetil at 250 mg b.i.d. for 1 week, then 500 mg b.i.d. for 1 week, then 750 mg b.i.d. for 1 week and 1000 mg b.i.d. thereafter. Of the patients, 15 used mycophenolate as monotherapy while the rest took it as an adjunctive treatment with glatiramer acetate or IFNβ. A total of 70% of the patients continued mycophenolate mofetil for an average of 12 months. Eight patients discontinued therapy because of side effects, most commonly diarrhea, one of which was secondary to cytomegalovirus. One stopped because of abnormal liver function studies that resolved upon drug discontinuation. Seven patients discontinued mycophenolate because of clinical deterioration. Subjective clinical improvement was experienced by 12 patients, characterized by reduction or absence of relapse, stabilization or improvements in activities of daily living, marked reductions in daily chronic fatigue, improved ambulation, less dependency on assistive devices and greater exercise tolerance.

SUMMARY AND RECOMMENDATIONS

There are few data on the management of MS with mycophenolate mofetil. Available data are unblinded and without placebo control. However, because of its substantial immunosuppressant activity, its strong benefit in other clinical situations such as organ transplantation, its oral route of administration and its relatively good tolerability, mycophenolate mofetil seems worth trying in MS patients who are failing conventional disease-modifying therapy and may not be candidates for intravenous immunosuppressant agents such as mitoxantrone or cyclophosphamide.

METHOTREXATE

Methotrexate, an inhibitor of dihydrofolate reductase, directly interferes with the folate-dependent enzymes of de novo purine and thymidylate synthesis, and inhibits cell mediated immune reactions.[87] Methotrexate affects all rapidly dividing cells, so toxicity includes mucositis, myelosuppression and thrombocytopenia. Pneumonitis characterized by patchy inflammatory infiltrates, which rapidly regresses upon discontinuation of the drug, may occur, as well as hepatic fibrosis and cirrhosis.[87]

Methotrexate was considered to be a potential treatment for MS because of its success in the treatment of rheumatoid arthritis, a disorder that has some immunological similarities with MS (e.g. reduced number of suppressor–inducer cells, increased ratio of helper–inducer to suppressor–inducer cells in blood).[137,138] Additionally, methotrexate inhibits the development of experimental allergic encephalomyelitis.[139]

An early trial suggested a reduction in exacerbation rates for RRMS patients treated with methotrexate but not for chronic progressive MS.[140] Goodkin et al treated clinically definite chronic progressive patients with weekly, oral, low-dose (7.5 mg) methotrexate for 2 years, followed by observation for an additional year, in a placebo controlled, randomized, double-blinded clinical trial.[141] The improvement in the EDSS scale was not statistically significant; however, the improvement in upper extremity function as evaluated with the nine-hole peg test (16.1% failing with methotrexate treatment vs 48% failing with placebo: $n=31$) and the box and block test (12.9% failing with methotrexate vs 34.5% failing with placebo: $n=29$) was statistically significant. Analysis of serial MRIs revealed a slight drop in the number of enlarging and active lesions in the methotrexate-treated group compared to the placebo group.[142] The change in the lesion load was related significantly to sustained change in the nine-hole peg test. Side effects, including upper respiratory tract infection, urinary tract infection, nausea, headache, fever, mucocutaneous herpes, sore muscles, back ache, indigestion and diarrhea), were similarly distributed between the treatment and placebo group. Only three of the 31 patients in the study had to stop therapy.

COMBINATION WITH INTERFERONS

In an open-label pilot study, 21 patients who had continued to experience exacerbations while taking weekly IFNβ-1a were treated with methotrexate in addition to IFN.[143] The combination was safe and well tolerated, with nausea as the major side effect (12 of 15 patients). There was a 44% reduction in the number of gadolinium-enhancing lesions (done with triple-dose gadolinium) in patients treated with methotrexate and IFN compared to those noted during treatment with IFN alone.

In another open-label study, 15 patients with relapsing MS who were worsening while on once-weekly IFNβ-1a therapy were treated with high dose intravenous methotrexate at 2 g/m^2 followed by leucovorin rescue.[144] Treatment was administered every 2 months for a total of six treatments. Once-weekly IFNβ-1a therapy was continued throughout the study. MSFC scores and MRIs were determined at baseline and every 4 months. Among the four patients who completed six treatments, three had an improved MSFC score and one was unchanged. Among the four patients who completed three treatments, all had positive changes in MSFC. No significant hematological, renal or other toxicity occurred.

SUMMARY AND RECOMMENDATIONS

The very limited available studies on methotrexate provide little basis for enthusiasm about the use of this medication for management of MS. In particular, one double-blind, placebo-controlled study in progressive MS showed only marginal benefit.[141] Use of the drug should probably be reserved for circumstances in which other alternatives have either failed or cannot be used.

CLADRIBINE

Cladribine, an adenosine-deaminase-resistant purine analog, is converted to cladribine triphosphate and incorporated into DNA. It causes DNA strand breaks and NAD and ATP depletion, as well as apoptosis in some cell lines.[145,146] Although its mechanism of action is not entirely understood, the drug does not require cell division to be cytotoxic.[87] Cladribine's toxicity includes myelosuppression, thrombocytopenia, infections including opportunistic infections associated with low $CD4^+$ cell counts, nausea, high fever, headache, fatigue and skin rashes.

In one study, 51 patients with MS (mostly secondary progressive) were randomized to cladribine treatment consisting of four monthly, 7-day infusions (0.1 mg/kg/d) or placebo.[147] During the second year, blinding was maintained but patients who had received placebo were given active drug at half the total dose given the drug-treated patients in the first year. In the first year of the study, the average EDSS scores and Scripps Neurologic Rating Scale (Scripps NRS) scores of patients on cladribine improved modestly while patients on placebo continued to deteriorate. Differences at 1 year were significant using both the EDSS scores and the Scripps NRS. The scores were at their best level about 18 months after beginning treatment. The patients were able to maintain their improved EDSS and SNRS scores for the 24 months of follow-up.

After 2 years, unblinded observations revealed a decline in the average scores. This suggested a dose–response effect with cladribine and a wearing off of improvement, with resumption of progressive MS symptoms in some patients 2 years after discontinuation of treatment. The number of enhancing lesions was much less in the cladribine group. Toxicity observed in this study included thrombocytopenia, leukopenia and mild dermatomal herpes zoster.

In a subsequent multicenter, double blind, placebo-controlled trial done to evaluate the safety and efficacy of cladribine in progressive MS,[148] no significant treatment effects were found for cladribine, using the Expanded Disability Status Scale scores. In this study, 159 patients, with a median Expanded Disability Status Scale of 6.0, were randomly assigned to receive either cladribine or placebo. The patients who received cladribine took 0.07 mg/kg/d for 5 consecutive days every 4 weeks for either two or six cycles (total dose 7 mg/kg or 2.1 mg/kg), followed by placebo for 8 weeks. Of these patients, 30% had PPMS while 70% had SPMS. The EDSS scores and the Scripps NRS scores were assessed bimonthly. MRIs were performed every 6 months. Even though no difference was achieved in the primary outcome measure of disability change, fewer patients receiving cladribine at either dose developed gadolinium-enhancing lesions. Patients in the cladribine group had a reduction in the number and volume of gadolinium-enhancing T1 lesions when compared to the placebo group, which was statistically significant at 6 months through month 18. The T2 burden of disease improved in the cladribine-treated group and worsened in the placebo group. Patients in the cladribine-treated group were more likely to have upper respiratory tract infections, muscle weakness, purpura, injection site reactions, hypertonia, back pain, urinary tract infections, depression, arthralgias, rhinitis, ataxia and pharyngitis. None of the side effects were treatment-limiting.

SUMMARY AND RECOMMENDATIONS

Initial trials with cladribine showed promise in the treatment of SPMS but these results were not seen in the subsequent blinded, randomized, placebo-controlled trial. Furthermore, studies of cladribine continue to show an enigmatic dissociation between positive effects on MRI and unconvincing clinical benefit. Another drawback to the use of cladribine is the profound and very long-lasting lymphopenia induced by the drug. This may preclude the use of other immunosuppressant agents and administration of cladribine almost invariably disqualifies a patient from consideration for other clinical trials. At this point, it seems prudent to await the results of a prospective, randomized, blinded trial of oral cladribine before recommending its use in patients with MS.

STEROIDS

Glucocorticoids affect the immune system by inhibiting or increasing transcription of selected genes by acting through the glucocorticoid receptor.[149] The binding of the hormone to the receptor causes it to activate and translocate to the nucleus. Glucocorticoids increase the transcription of specific genes either by stabilizing the transcription preinitiation complexes at the TATA box of gene promoters or by distorting chromatin structure and unmasking binding sites for factors that facilitate initiation of transcription. They also cause repression of genes for certain inflammatory cytokines, including IL-1, IL-2–6, IL-8 and IFNγ.[150] Glucocorticoids have also been shown to inhibit mRNA translation of IL-1b.[151]

In MS, steroids decrease E selectin and ICAM-1 expression in vitro.[152] They inhibit inflammatory edema by reducing capillary permeability, resulting in a reduction of gadolinium enhancement on MR imaging.[153–155] They also inhibit metalloproteases.[156]

Steroids decrease the number of circulating $CD4^+$ T cells and B lymphocytes, but not $CD8^+$ cells, within 4 hours by redistribution.[157] They decrease lymphocyte proliferation to lectins and antigen, mixed lymphocyte responses and cytokine release, including IFNγ.[158] Steroids also upregulate expression of IL-10 and TGFβ.[159,160] Glucocorticoid administration leads to apoptosis of T cells activated against MBP and protects oligodendrocytes from cytokine-induced death.[161]

The Optic Neuritis Treatment Trial studied the effects of steroid treatment in monosymptomatic optic neuritis.[162,163] Patients treated with intravenous methylprednisolone had greater recovery of visual acuity, visual fields, contrast sensitivity and color vision by 2 weeks. The treatment effect on visual acuity was no longer evident at 6 months, at which time 94% of the study subjects had recovered visual acuity to 20/40 or better. Surprisingly, patients who received oral prednisone at a dose of 1 mg/kg had a higher rate of recurrence of optic neuritis.

Chronic use of corticosteroids has not been convincingly demonstrated to slow progression of disability. However, rigorously controlled phase III clinical trials have not addressed the question.[164] In a double blind, dose comparison phase II study in SPMS, Goodkin et al gave intravenous methylprednisolone every other month for up to 2 years to 109 patients.[165] Patients were randomly assigned to receive intravenous pulses of either 500 mg or 10 mg methylprednisolone in lieu of placebo, on 3 consecutive days, every 8 weeks for 2 years. Each bimonthly pulse was followed by a tapering course of methylprednisolone administered orally, starting on day 4 and concluding on day 14. The primary outcome measure for the study was a comparison of the proportion of sustained treatment failures in each treatment arm during the 2-year treatment phase.

Patients were considered to be at risk for sustained treatment failure if any of the components of the primary composite outcome were satisfied. The primary composite outcome included worsening of the entry EDSS score by 1.0 or more points for patients with an entry score of 4.0–5.0, or by 0.5 or more points for patients with an entry score of 5.5–6.5; worsening of the entry ambulation index score by 1.0 or more points;

worsening of 20% or more from the baseline value on the best performance of two box and block tests or nine-hole peg tests obtained with either hand; or two exacerbations treated with unscheduled doses of methylprednisolone within 11 successive months.

Patients who experienced worsening of any of the components of the primary composite outcome and sustained the worsening for 5 or more months or experienced three exacerbations treated with unscheduled doses of methylprednisolone during 12 successive months met criteria for sustained treatment failure. Patients were evaluated within a 1-month window of scheduled 6-month visits or upon report of clinical deterioration by an examining neurologist, who was blinded to treatment assignment and treating neurologist.

No significant difference in efficacy was demonstrated between groups receiving high- or low-dose intravenous methylprednisolone on sustained progression of disability at the end of 2 years; however, patients who were treated with high doses had a delay in the onset of sustained treatment failure.[165,166]

In a randomized, controlled, single-blind phase II clinical trial, 126 patients with clinically definite RRMS were randomly assigned to receive either regular pulses of intravenous methylprednisolone (1 g/d for 5 d) with an oral prednisone taper as well as steroid treatment for relapses, or steroid treatment for relapses only, using the same treatment regimen of 1 g/d for 5 d with an oral prednisone taper.[167] Treatment was administered every 4 months for 3 years and then every 6 months for the next 2 years. The primary outcome measure was the treatment effect on quantitative MRI parameters (T2 and T1 lesion volume) and brain parenchymal volume changes. There were no significant differences in T2 lesion volume between the two treatment arms at the 5-year follow up. Although both groups demonstrated significant increases in T1 lesion volumes over the course of the study, the increase in lesion volume was less in the pulsed methylprednisolone group. Patients in the pulsed methylprednisolone arm did not develop brain atrophy during the study, whereas patients in the control group had significant brain atrophy by the end of the study. The patients treated with the pulse steroids had lower disability scores compared to patients receiving steroids only for relapses.

SUMMARY AND RECOMMENDATIONS

At this point, intravenous steroids have shown proven benefit in the management of acute exacerbations by achieving clinical benefit faster than if the patient was left untreated. Administration of regularly scheduled intermittent doses of pulse steroids has not been established as effective therapy for the prevention of clinical worsening in MS. Nonetheless, perhaps because the regimen is inexpensive and generally well tolerated, the practice continues to be fairly widespread among clinicians dealing with patients with worsening MS. Suggestion of possible benefit comes from the 5-year study by Zivadinov and colleagues[167] and a hint of at least transient success in the earlier study by Goodkin et al.[165] Physicians who consider the use of intermittent pulse steroid regimens should recognize the fact that no data support the use of monthly single-day high doses of intravenous methylprednisolone and should perhaps opt instead for multiday regimens similar to those cited above.

INTRAVENOUS IMMUNOGLOBULIN

Although the mechanism of action of polyclonal immunoglobulin is unknown, its beneficial effects in the treatment of neurological disease may include inhibition of complement binding and prevention of membrane attack complex formation, neutralization of certain pathogenic cytokines, downregulation of antibody production and modulation of Fc-receptor-mediated phagocytosis.[168] Additional actions include an effect on superantigens, modulation of T-cell function and antigen recognition, and enhancement of remyelination.

In experimental allergic encephalomyelitis, prophylactic treatment with intravenous immunoglobulin (IVIg) is effective if it is administered at the time of induction. When given in this manner, immunoglobulin significantly reduces the symptoms of disease as well as the underlying CNS pathology.[169] Therapeutic IVIg treatment of established experimental allergic encephalomyelitis did not prove effective.

Fazekas et al conducted a randomized, double-blind, placebo-controlled study in which 75 patients with RRMS received 1 g/kg IVIg once a month for 2 years and were compared with 73 patients receiving placebo.[170] The IVIg group experienced 62 relapses compared to 116 in the placebo group. A total of 40 IVIg patients remained relapse-free during the 2-year study compared to 26 in the placebo group. The annual relapse rate reduction was similar during year 1 and year 2 in the IVIg-treated group, whereas in the placebo group some reduction was noted only in year 2. The time from baseline to first relapse did not differ significantly between the groups. However, the interval between relapses during the study period was significantly longer among patients in the IVIg group than among those in the placebo group. The severity of relapses during the study, as measured by the change in EDSS, did not differ significantly between the groups. A slight improvement in clinical disability occurred in the IVIg group, compared to no significant change in clinical disability in the placebo group. Adverse events were reported by three IVIg-treated patients and four patients in the placebo group. Cutaneous reactions were reported by two IVIg-treated patients; symptoms consisted of a short-lived rash, which developed a few days after the infusion but was not seen by the treating physician.

In the first year of an open-label trial with IVIg in a small number of RRMS patients, the exacerbation rate dropped post-treatment when compared to pretreatment exacerbation rates in the same patients.[171] In another small, open-label trial, IVIg patients showed a greater drop in the mean annual exacerbation rate after being on treatment both for 2 years and for 3 years, compared to their exacerbation rates in the years prior to being treated with immunoglobulin.[172] The adverse event rate inversely correlated with duration of IVIg treatment. Also, the severity of acute exacerbations was favorably influenced by treatment. The majority of exacerbations in the IVIg group were mild to moderate, while in untreated controls most of the acute exacerbations were moderate to severe. The mean change in neurological disability was significantly different after 3 years.

In another study by Sorensen et al, 20 RRMS patients and five SPMS patients were randomly assigned to receive either infusions of IVIg at 1.0 g/kg/d for 2 consecutive days at intervals of 4 weeks or placebo, for 2 years.[173] A total of 17 patients (11 treated, six placebo) completed the study. The relapse rate was lower in the treated group than in the placebo group. The total number of acute exacerbations in the IVIg treatment group was 11 compared to 15 in the placebo group. Severe acute exacerbations requiring treatment with intravenous methylprednisolone occurred in four cases during IVIg treatment and in six cases on placebo. However, neurological disability did not change significantly from baseline in either group. Adverse effects included eczema (most common), urticaria, headache, hepatitis C (the most severe), fever and nausea. The urticaria and headaches were mild and subsided within hours or a few days. Two patients withdrew because of severe eczema; one died from a pulmonary embolism occurring 2 weeks after infusion.

A recent European study evaluated IVIg in SPMS (ESIMS).[174] A total of 318 patients with clinically definite SPMS were

randomly assigned to receive IVIg 1 g/kg per month or an equivalent volume of placebo for 27 months. Patients were assessed clinically every 3 months and with MRI every 12 months. No difference between the IVIg- and placebo-treated groups occurred for the primary outcome of confirmed worsening of disability, as defined by the time to first confirmed progression on EDSS. Similarly no significant differences occurred for the secondary outcome measures of the annual relapse rate and change in lesion load on T2-weighted MRI.[175]

SUMMARY AND RECOMMENDATIONS

The ESIMS study has clearly demonstrated a lack of benefit in SPMS[174] and no justification exists for use of this treatment in such patients. While one might consider that 'the jury is still out' on the question of the efficacy of IVIg in RRMS, the answer may come when the results of a prospective, randomized clinical trial sponsored by Bayer Pharmaceuticals are revealed.

PLASMA EXCHANGE

Plasma exchange has been used to treat many neuroimmunological diseases. In the process of removing a patient's plasma by continuous flow centrifugation and replacing it with saline and albumin, antibodies are eliminated, presumably thereby mitigating the immunological attack against the nervous system.[176] Plasmapheresis has been used successfully in myasthenia gravis,[177] Guillain–Barré syndrome[176] and chronic inflammatory demyelinating polyneuropathy.

Weinshenker et al treated 22 patients who had experienced a severe inflammatory attack (not all patients had MS).[178] Patients chosen for this study had either clinically definite or laboratory-supported definite MS by the Poser criteria, or other idiopathic inflammatory demyelinating diseases, which had caused an acute severe neurological deficit affecting consciousness, language, brainstem function or spinal cord function.[180] Patients had previously been treated with high-dose intravenous corticosteroids for a minimum of 5 days with minimal improvement at most. The deficit must have been present for at least 21 days from onset of symptoms and 14 days from onset of treatment with intravenous methylprednisolone. If the deficit had continued to worsen after 5 days of intravenous corticosteroid treatment, plasma exchange could be initiated 12 days after the onset of symptoms. Half the patients initially received active exchange while half received sham exchange, for a total of seven treatments. Then the groups were crossed over to the other treatment. After the first cycle, five of the actively treated patients improved to a marked or moderate degree compared to only one who received sham treatment. When the patients were crossed over to the other group, three who received active treatment in the second treatment period improved moderately to markedly, compared with none who received sham. Responders tended to be male and younger. Nonresponders tended to have a worse baseline deficit. However, neither the type of demyelinating disease nor the interval from onset to enrollment was significantly associated with outcome. Plasma exchange was tolerated well, although anemia occurred in most patients. Improvement during treatment was sustained during follow-up, whereas moderate improvement occurred over the course of follow-up in only two of 12 patients who were treatment failures.

In a follow-up to the previous study, Keegan et al looked at predictors of response to plasma exchange treatment for severe attacks of CNS demyelination.[176] Male sex, preserved reflexes and early initiation of treatment were associated with moderate or marked improvement. Successfully treated patients improved rapidly following plasma exchange and improvement was sustained for at least 1 year post treatment. Even though early initiation of treatment was associated with greater improvement, some patients who were treated as long as 60 days after the onset of symptoms also experienced a favorable response. The authors suggest that such patients should not be excluded from treatment if the onset of the neurological event was acute.

Keegan and colleagues studied treatment success and failure with plasmapheresis, in the four immunopathological patterns of demyelination.[180] Looking at 19 patients treated with therapeutic plasma exchange, only patients with pattern II MS pathology, characterized by immunoglobulin deposition and complement activation, responded. This selective response caused the authors to theorize that the mechanism of action of plasma exchange in the successful treatment of patients with pattern II MS pathology is the removal of pathogenic humoral and plasma factors. The authors also theorized that cellular components probably do not account for the recorded differences in response to plasma exchange.

SUMMARY AND RECOMMENDATIONS

At the present time, plasmapheresis should be reserved for patients with poor recovery from severe attacks. No evidence currently exists to support the use of plasma exchange in chronic treatment of MS.

TACROLIMUS

Tacrolimus, a macrolide antibiotic produced by *Streptomyces tsukubaensis*,[181] inhibits T-cell activation by inhibiting calcineurin.[182] The drug binds to an intracellular protein, FK506-binding protein (FKBP)-12, an immunophilin structurally related to cyclophilin. A complex of tacrolimus-FKBP-12, calcium, calmodulin and calcineurin then forms, and calcineurin phosphatase activity is inhibited, leading to inhibition of T-cell activation.[69]

Tacrolimus has been tested in MS because it markedly protects against demyelination and axonal loss in an EAE animal model.[183] Treatment failed to modify either acute or chronic disease activity and its use was limited by the side effects of nephrotoxicity, hypertension and hyperlipidemia.[184]

SUMMARY AND RECOMMENDATION

Data do not support the use of tacrolimus for the treatment of MS at this time, especially in view of the occurrence of potentially serious adverse events.

CICLOSPORIN

Ciclosporin suppresses humoral immunity to some extent but is more effective against T-cell-dependent immune mechanisms such as those underlying transplant rejection and some forms of autoimmunity.[185] It preferentially inhibits antigen-triggered signal transduction in T lymphocytes, blunting expression of many lymphokines, including IL-2, as well as expression of antiapoptotic proteins. Ciclosporin forms a complex with cyclophilin, a cytoplasmic receptor protein present in target cells. Calcineurin enzymatic activity is inhibited following physical interaction with the ciclosporin/cyclophilin complex. This results in the blockade of nuclear factor of activated T cells(NFAT) dephosphorylation; thus, the cytoplasmic component of NFAT does not enter the nucleus, gene transcription is not activated and the T lymphocyte fails to respond to specific antigenic stimulation.[69] Ciclosporin also increases expression of TGFβ, a potent inhibitor of IL-2-stimulated T-cell proliferation and generation of cytotoxic T lymphocytes.[186]

The drug has been compared with azathioprine as a long-term immunosuppressive treatment for patients with MS in a randomized drug comparison study.[187] A total of 31 patients were randomized to complete 12 months' treatment with either ciclosporin (5 mg/kg/d)[17] or azathioprine (2 mg/kg/d). The ciclosporin treatment group improved in the mean EDSS score and remained more or less stable for the remaining 9 months, while no change could be observed in the azathioprine treatment group. There was no significant difference between the treatment groups in terms of the disability status score or Ambulation Index, although the azathioprine group scored slightly higher throughout the 12-month study on both scores.

The frequencies of concomitant corticosteroid treatment were not significantly different between the two treatment groups. The total frequency of clinical side effects was significantly higher in the ciclosporin treatment group, mainly because of hypertrichosis and headache. There was no significant difference for the CD4 inducer/CD8suppressor, cytotoxic mean ratio. This study suggested a trend for improvement in MS by ciclosporin but the effect was by no means as dramatic as that in reported studies in kidney transplant or type I diabetes. Because of its narrow risk:therapeutic ratio, due to its dose-dependent nephrotoxicity, long-term administration of larger doses of ciclosporin would be unsafe.

A large randomized, double-blind, placebo-controlled trial evaluated the use of ciclosporin in chronic progressive MS. A total of 577 patients were randomized to receive either ciclosporin (273) or placebo (274).[188] Ciclosporin dosage was adjusted for toxicity. The primary combined outcome measure included time to become wheelchair-bound, time to sustained progression and effect on activities of daily living. Ciclosporin delayed the time to becoming wheelchair-bound, but the effects seen in the time to sustained progression and effect on activities of daily living were not statistically significant. A large number of patients from the ciclosporin arm had to drop out of the study because of nephrotoxicity or hypertension.

SUMMARY AND RECOMMENDATIONS

Given its success in the therapy of other autoimmune disorders, ciclosporin seemed a promising candidate for the treatment of MS. However, a large prospective trial in chronic progressive MS showed little, if any, benefit and certainly not enough to warrant its use considering the significant risks of hypertension or renal damage. Other studies have not emerged to justify reconsideration of this verdict. At this point, ciclosporin should not be considered part of the therapeutic armamentarium for the treatment of MS.

SULFASALAZINE

Sulfasalazine, widely used in the treatment of inflammatory bowel disease, is metabolized to its active components, sulfapyridine and mesalamine, by bacteria in the colon.[189] When given as sulfasalazine, a larger quantity of sulfapyridine and mesalamine reach the colon than when these agents are administered as single agents. Once sulfapyridine and mesalamine reach the colon, the beneficial effects result primarily from the anti-inflammatory properties of mesalamine. The anti-inflammatory mechanism of mesalamine is believed to occur, at least in part, through the inhibition of arachidonic acid metabolism in the bowel mucosa by inhibition of cyclooxygenase. This effectively diminishes the production of prostaglandins, thereby reducing colonic inflammation. Production of arachidonic metabolites appears to be increased in patients with inflammatory bowel disease. Mesalamine also inhibits leukotriene synthesis, possibly through the inhibition of lipoxygenase. This action has been suggested as a major component of the drug's anti-inflammatory effects. Inhibition of colonic mucosal sulfidopeptide leukotriene synthesis and chemotactic stimuli for polymorphonuclear leukocytes may also occur.[189]

Side effects of sulfasalazine are common.[189] Several of these are dependent on plasma levels of sulfapyridine and are therefore related to both dose and acetylation status of the patient. They include fever and malaise, nausea, vomiting, headaches, epigastric discomfort and diarrhea and may be partially overcome by gradual increments of the dose. Megaloblastic anemia and low sperm counts, believed to be due to impaired folic acid absorption, can also occur, and some physicians advocate the routine coadministration of folate supplements. Allergic reactions (not related to plasma levels) can include arthralgias, hemolysis, agranulocytosis, thrombocytopenia, red cell aplasia and a variety of skin manifestations such as rash, urticaria and a bluish discoloration. Most serious, but rare, are toxic epidermal necrolysis and Stevens–Johnson syndrome, pancreatitis, eosinophilic pneumonia, bronchospasm, fibrosing alveolitis, drug-induced lupus and neurotoxicity.

Noseworthy et al conducted a placebo-controlled, randomized, double-blind phase III trial of sulfasalazine in MS.[190] A total of 199 patients with RRMS (151) and progressive (48) MS were evaluated at 3-month intervals for a minimum of 3 years. MRI studies were performed at 6-month intervals on a subset of 89 patients.

By the end of the study, sulfasalazine had failed to slow or prevent disability progression as measured on EDSS. However, during the first 18 months of the trial, the annualized relapse rate, proportion of relapse-free patients, rate of EDSS progression at 1 and 2 years in the progressive subgroup only, and median time to EDSS progression were all better in the treatment group compared to placebo. The positive findings observed in the first half of the trial were not sustained, however.

SUMMARY AND RECOMMENDATIONS

The major prospective trial of sulfasalazine emphasizes the important point that short-term results can be misleading in this chronic disease. At the present time, this drug should not be considered a useful agent for the treatment of MS.

ALEMTUZUMAB

The monoclonal antibody alemtuzumab targets the CD52 antigen, present on T and B cells and macrophages.[191] It causes a sustained depletion of T-cells.[192] Alemtuzumab was first used in patients with MS in 1991 with the hope that the T-cell repertoire regenerated after lymphocyte depletion by the antibody would no longer exert the aberrant autoimmune responses characteristic of MS.[192] By 1999, 36 patients had been treated; all had SPMS with an EDSS of 6.0 or less.[193] Enhancing lesions were present on an MRI done 3 months prior to treatment in all patients. Alemtuzumab was administered as an intravenous infusion of 100 mg over 5 consecutive days as a daily 20 mg infusion over 4 h, every 12 months. Treated patients experienced a systemic response accompanied by a transient, often severe but reversible reactivation of neurological disease activity that lasted for a few hours. This was thought to be due to the release of mediators that impede conduction at previously demyelinated sites. The reaction could be prevented by pretreatment with methylprednisolone. Radiological markers of cerebral inflammation persisted for several weeks after treatment but thereafter radiological markers of cerebral inflammation were suppressed for at least 18 months during which patients remained asymptomatic. Some 6 years after treatment a subgroup of patients underwent MRI, which showed no

appreciable increase in the T1-hypointense, or T2-lesion volume in these patients. However, approximately half the patients continued to experience progressive disability and increasing brain atrophy, thought to be secondary to axonal degeneration, which correlated with the extent of cerebral inflammation in the pretreatment phase. Because of the observations in SPMS, the emphasis was switched to studying patients with active RRMS. Some 22 patients with active RRMS whose disease was not controlled by currently approved DMAs or in whom a high relapse rate was seen early in the disease were treated with alemtuzumab. The patients who received the monoclonal antibody had a 94% reduction in relapse rate. However, accumulation of disability continued despite suppression of inflammation. There was a reduction in new lesion incidence rates.[184] Use of alemtuzumab is also characterized by a markedly increased risk for autoimmune thyroiditis.[184,194]

A recent trial of alemtuzumab in comparison to IFN β-1a (subcutaneous) intended for 3 years, showed a 75% relapse rate reduction for the monoclonal antibody compared to IFNβ at the end of 2 years. However, six cases (one fatal) of idiopathic thrombocytopenic purpura developed in the alemtuzumab group, so the trial was stopped prematurely.[195] A Phase III trial will include a risk management plan with very close surveillance to reduce the risk of severe ITP.

SUMMARY AND RECOMMENDATIONS

Although alemtuzumab appears to be a drug of continuing interest for MS, the occurrence of thrombocytopenic purpura requires further clarification.

RITUXIMAB

Rituximab, the first monoclonal antibody approved by the FDA,[196] is a genetically engineered, chimeric murine/human monoclonal antibody containing IgG_1 heavy-chain and κ light-chain constant region sequences and murine variable region sequences.[197] It binds specifically to the CD20 antigen, a 35 kDa transmembrane protein that is involved in cell cycle progression and differentiation.[198,199] The CD20 is expressed on normal B lymphocytes, from pre-B cells to activated B cells, but not on differentiated plasma cells, T cells, hematopoietic stem cells or nonhematopoietic normal tissues.[200] Rituximab causes rapid depletion of $CD20^+$ B cells in the peripheral blood.[201] However, antibody production is still maintained by plasma cells, and normal peripheral B cells are subsequently replenished by hematopoietic stem cells in most patients 3–12 months after therapy.[200] Mechanisms of action may include inhibition of antibody-dependent cellular cytotoxicity, complement-mediated cell lysis, induction of apoptosis, inhibition of cell growth and sensitization to chemotherapy.[197,202,203]

Use of rituximab was initially reported in neuromyelitis optica and rapidly worsening MS.[204] Four patients with progressive relapsing myelitis each received 4-weekly intravenous infusions of rituximab (375 mg/m^2) and were followed for lymphocyte subset counts, adverse events and neurological disability. B-cell counts dropped to zero and remained undetectable 6 months after the infusions ended. Two of the four MS patients experienced an improvement in ambulation and fatigue following treatment. All four patients remained relapse-free for the duration of follow-up, which was an average of 6 months.[204] Other lymphocyte subsets were not affected, except for a transient drop in $CD4^+$ T cells in some patients.

A phase II trial in relapsing-remitting MS was recently completed. The results showed statistically significant benefit on both new gadolinium-enhanced lesions and relapse rate. Phase III trials in both RRMS and PPMS are planned.

Pender[205] proposed two different hypotheses to explain how progression of neurological impairment in PPMS could occur.[205] The first hypothesis postulates that neurological impairment is due to a rapid and relentless immune attack on CNS myelin and axons by T cells and antibody. The alternative is by prolonged slow immune attack on myelin and axons without CNS repair. This is more likely to occur when antibodies constitute the main mechanism of attack because of circulating antigen-specific T cells. A failure of CNS repair could be due to immune attack preventing remyelination or because of immune-medicated destruction of axons, which cannot regenerate in the human CNS. Antibodies are effective inhibitors of remyelination because of their persistence and ability to spread diffusely through the CNS parenchyma. Progressive MS could be due to a predominantly antibody-mediated immune attack that causes demyelination and inhibits remyelination or that causes axonal destruction. Relapses, on the other hand, may be due to T-cell immune attack on the CNS. Because of the possibility of antibody-mediated attack on the CNS in PPMS, an agent such as rituximab, which can cause depletion of B cells, might be beneficial in this form of the disease.

For the most part, the side effects of rituximab are mild, such as fever, chills and nausea, but hypersensitivity reactions can occasionally be severe or even fatal. Patients who receive this therapy must be monitored very carefully during infusion, particularly the second infusion.[206] Patients may need to be pretreated with diphenhydramine and steroids.[207] The infusion may need to run very slowly or even be stopped to prevent the occurrence of the hypersensitivity reaction.

SUMMARY AND RECOMMENDATIONS

Rituximab is a monoclonal antibody that remains of significant interest for its potential use in MS. It is currently undergoing randomized, placebo-controlled trials in both RRMS and PPMS. Pending results of these studies, very few data exist to support its use in worsening MS, although uncontrolled studies suggest a benefit in neuromyelitis optica. Since no controlled studies exist for treatment of neuromyelitis optica, rituximab may be a reasonable choice for this often devastating condition.

DACLIZUMAB

Daclizumab is a monoclonal antibody directed against the α chain (CD25), a component of the high-affinity IL-2 receptor. After demonstration that the drug inhibits experimental autoimmune encephalomyelitis models,[208–210] 10 patients with RRMS or SPMS were treated with the combination of daclizumab and IFNβ after suboptimal response to the latter alone.[211] The patients had experienced at least one exacerbation or progression of disability by at least 1 point on the EDSS during the preceding 18 months on therapy. Patients were treated with intravenous daclizumab at 1 mg/kg/dose 2 weeks apart for the first two doses and once every 4 weeks thereafter for a total of seven infusions (6 months). Patients were followed with monthly clinical and MRI examinations. Primary outcome measures were new contrast-enhancing lesions and total number of contrast-enhancing lesions on IFNβ versus combination therapy of IFNβ and daclizumab. The 10 patients with relapsing forms of MS treated with the combination of IFNβ and daclizumab had a 78% reduction in new contrast-enhancing lesions and a significant improvement in the nine-hole peg test, Scripps NRS and the exacerbation rate. There were also positive trends for EDSS, the timed 25-foot walk, changes in T2 lesion volume and black hole volume, and the ambulation index.

The reduction in contrast-enhancing lesions occurred gradually over 1.5–2 months, unlike that seen with IFN[212] or

natalizumab.[213] The authors postulate that, instead of targeting the blood–brain barrier, daclizumab induces a gradual immunomodulatory change that is responsible for the observed decrease in brain inflammation.

In another open-label study, 19 patients with relapsing forms of MS were treated.[214] Of these patients, 17 had not responded well to conventional therapy. Most of the patients received daclizumab as monotherapy but two received both IFN and daclizumab and then were switched to daclizumab monotherapy. Clinical improvement occurred in 10 patients and the other nine had stabilization of disease and reduction of MRI activity during the mean treatment period of 14 months. Patients experienced minimal adverse events. A recently completed Phase II trial, in which daclizumab or placebo was added in patients taking weekly intramuscular IFNB-1a, showed a statistically significant benefit for the monoclonal antibody on the primary endpoint of new MRI activity. A reduction in relapse rate did not reach statistical significance.[215]

SUMMARY AND RECOMMENDATIONS

Daclizumab is another monoclonal antibody of substantial interest as a potential treatment for MS. Additional randomized clinical trials are planned or in progress, but, pending their conclusion, use of this agent off label (as it is approved for other purposes) seems unwarranted because of the limited data on efficacy and safety in MS, as well as its very high cost.

BONE MARROW TRANSPLANTATION

Autologous hematopoietic stem cell transplantation was introduced as a treatment for patients with MS after animal studies showed that the course of experimental allergic encephalomyelitis could be modified by high-dose immunosuppression causing hematolymphatic ablation, and subsequent bone marrow transplantation.[216–219] Further support for the idea resulted from the observations that some patients who were treated with hematopoietic stem cell transplantation for concurrent malignancies were found to have prolonged remissions of their MS.[220–222]

European studies of hematopoietic stem cell transplantation have been conducted in all types of MS.[223] In the largest European study, seven of 85 treated patients died.[218] The patients who died had high EDSS scores, were older and had received intensely T-cell-purged grafts. Still, the authors reported 74% progression-free survival for all patients after 3 years, 78% for SPMS. Clinical improvement was noted in 21%.

Originally conducted as single-center trials, the study of bone marrow transplantation in MS expanded to multicenter safety clinical trials. In one such trial the median EDSS was 4.5–8.[218,224] All patients had failed a number of standard therapies and had progressing disease, with a worsening EDSS over the past year. Patients were treated with immunosuppression, and peripheral blood stem cells were mobilized using cyclophosphamide and granulocyte colony-stimulating factor (G-CSF). Transient neurological deterioration often occurred after patients had received G-CSF.[225] Progression-free survival was 81% for SP and RRMS and 67% for PPMS. Pathological MRI activity was suppressed but brain atrophy continued to occur.[226]

Wolinsky outlined the obstacles to the use of hematopoietic stem cell therapy for patients with MS at a conference on the subject in 2001.[227] He felt that this treatment modality would need to effect a reduction in the level of morbidity and mortality, a drop in attack frequency of at least 70% and a drop in sustained EDSS score progression of 1.0 point to 8% of patients at 2 years and 17% at 3 years after therapy in order to demonstrate effectiveness comparable to that of mitoxantrone. Also, hematopoietic stem cell therapy must have a durable response lasting beyond 3 years in order to warrant its use instead of mitoxantrone.

Stem cell transplantation can be used to treat MS in two different manners. The first method is to suppress disease activity with immunosuppressive agents without killing all immune cells.[228] The stem cells would then act as a rescue to overcome immunodeficiency. The other way is to cause total immune ablation, with the infusion of stem cells intended to completely renew the immune system. Hintzen noted that unsatisfactory results with the use of conventional immunosuppressants in autoimmune disease could be secondary to the incomplete removal of autoreactive lymphocytes.[228] However, he also acknowledged that increasing the intensity of immunosuppression will lead to higher morbidity.

Many obstacles must be overcome to develop a randomized clinical trial with bone marrow transplantation, and so far none have been done. Multiple variables are involved in the implementation of hematopoietic stem cell therapy, including the choices of tissue source of the graft, donor source of the graft and mobilization procedures, as well as different graft manipulations and the different methods of myeloablation. Patients selected for the procedure should have rapidly progressive disease without diffuse irreversible white matter disease. There must be a standardized protocol in order to conduct a controlled trial. Issues with the selection of an appropriate placebo therapy and with the establishment of effective blinding are also important. It would also be difficult to match the patients in both arms of the study. Nonetheless, Hintzen suggested that these obstacles could all be overcome, allowing the conduct of a blinded, placebo-controlled, randomized clinical trial.

SUMMARY AND RECOMMENDATIONS

Hematopoietic stem cell transplantation continues to garner much attention and patients frequently ask their clinicians about it. The treatment remains an interesting but very risky procedure the efficacy of which has not been clearly established. Patients who seek this treatment are generally unaware of the number of deaths, as well as other serious morbidity, that have been reported with the treatment. The barriers to the successful design of a properly controlled clinical trial have so far been formidable and have prevented such a much-needed study. In the interim, performance of this procedure should be restricted to centers with a high degree of experience, where investigators using well defined research protocols enroll only those patients who have failed more conventional therapy and fully understand the significant risks and lack of established benefit.

WHAT TO DO IF THE PATIENT DOES NOT RESPOND TO STANDARD THERAPY: A SYSTEMATIC APPROACH

Currently approved immunomodulatory medications are, at best, only moderately effective in preventing relapses. Furthermore, all currently available agents, including those immunosuppressive agents used 'off-label' for the treatment of MS, apparently target the inflammatory process. It is not clear that any currently available drug significantly affects the neurodegenerative process that seems to characterize most progressive cases.

No specific approach has yet been widely accepted for a patient who is failing conventional therapy. However, it is possible for clinicians to develop a strategy with which they are comfortable to deal with such situations. This will at least allow for consistency and the avoidance of agonizing indecision each time one confronts the issue.

In most RRMS patients who are continuing to experience attacks, logic suggests (and insurance often mandates) that the currently approved treatments remain the primary option. If a patient has been treated with weekly IFNβ-1a, a reasonable first approach would be to switch to an IFN preparation administered multiple times per week. The physician may wish to verify the absence of neutralizing antibodies before undertaking this option. If a patient has already been taking multiple weekly doses of IFN, a trial of glatiramer acetate might be considered next. Conversely, if glatiramer acetate had been the first agent prescribed, a switch to IFN would be appropriate. Today, many MS specialists might instead switch from the initial immunomodulatory agent to natalizumab.

In patients for whom the FDA-approved immunomodulatory drugs have failed and natalizumab is not going to be used, two potential approaches are available. The first would be to try a combination of IFN plus glatiramer. However, it must be emphasized that, while some data suggest that the combination of glatiramer acetate and IFNβ-1a (Avonex) is safe, no useful information is currently available to indicate added efficacy with the combination. Furthermore, cost considerations may be prohibitive for many patients, and third-party payers may be very reluctant to cover both drugs. The alternative approach of initiating therapy with immunosuppressive medication probably conveys a greater risk of potentially serious toxicity. Nonetheless, an evidence-based medicine paradigm would dictate the use of mitoxantrone, currently the only FDA-approved drug for SPMS (with the exception of IFNβ-1b, which has an indication in SPMS patients who are continuing to experience relapses). Mitoxantrone is also approved for the treatment of worsening forms of relapsing MS. Some experts consider the use of intravenous cyclophosphamide as equal or preferable to mitoxantrone but the evidence remains controversial.

For patients who are unwilling to use these intravenous immunosuppressive medications or are deemed by their physicians to be inappropriate candidates, the oral immunosuppressive agents may be considered. Many MS specialists currently consider mycophenolate mofetil as the first choice. This preference is probably based more on the positive effects of the drug in the prevention of organ rejection and on the general lack of enthusiasm for azathioprine (at least in the USA) and methotrexate than on currently available data supporting its benefit in MS. Rituximab and daclizumab are other options, but costs are much higher and definitive evidence of benefit is not yet available.

Patients who are failing approved therapy should be offered the opportunity to participate in properly designed clinical trials, if such are available. Clinicians should take ample time to explain the potential risks and benefits of unproved therapies, always offering hope while establishing realistic expectations for patients and their families.

REFERENCES

1. PRISMS Study Group. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Lancet 1998; 352: 1498–1504.
2. IFN Beta Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group. Neurology 1993; 43: 655–661.
3. Jacobs LD, Cookfair DL, Rudick RA et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. Ann Neurol 1996; 39: 285–294.
4. Johnson KP, Brooks BR, Cohen JA et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology 1995; 45: 1268–1276.
5. Hartung H-P, Gonsette R, Konig N et al. Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. Lancet 2002; 360: 2018–2025.
6. Kleinschmidt-DeMasters BK, Tyler KL. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. N Engl J Med 2005; 353: 369–374.
7. Barnett MH, Prineas JW. Relapsing and remitting multiple sclerosis: pathology of the newly forming lesion. Ann Neurol 2004; 55: 458–468.
8. Trapp BD, Peterson J, Ransohoff RM et al. Axonal transection in the lesions of multiple sclerosis. N Engl J Med 1998; 338: 278–285.
9. PRISMS Study Group and the University of British Columbia MS/MRI Analysis Group. PRISMS-4: Long-term efficacy of interferon-beta-1a in relapsing MS. Neurology 2001; 56: 1628–1636.
10. Zhao GJ, R. A. Koopmans RA, Li DKB et al. Effect of interferon β-1b in MS: assessment of annual accumulation of PD/T2 activity on MRI. Neurology 2000; 54: 200–206.
11. Jacobs LD, Beck RW, Simon JH et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. N Engl J Med 2000; 343: 898–904.
12. Paty DW, Li DK. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. UBC MS/MRI Study Group and the IFNB Multiple Sclerosis Study Group. Neurology 1993; 43: 662–667.
13. Rio J, Nos C, Tintore M et al. Assessment of different treatment failure criteria in a cohort of relapsing-remitting multiple sclerosis patients treated with interferon β: Implications for clinical trials. Ann Neurol 2002; 52: 400–406.
14. Rio J, Nos C, Tintore M et al. Defining the response to interferon-β in relapsing-remitting multiple sclerosis patients. Ann Neurol 2006; 59: 344–352.
15. Multiple Sclerosis Therapy Consensus Group. Escalating immunotherapy of multiple sclerosis. J Neurol 2004; 251: 1329–1339.
16. Lublin FD, Baier M, Cutter G. Effect of relapses on development of residual deficit in multiple sclerosis. Neurology 2003; 61: 1528–1532.
17. Weinshenker BG, Bass B, Rice GP et al. The natural history of multiple sclerosis: a geographically based study. 2. Predictive value of the early clinical course. Brain 1989; 112: 1419–1428.
18. Confavreux C, Vukusic S, Moreau T et al. Relapses and progression of disability in multiple sclerosis. N Engl J Med 2000; 343: 1430–1438.
19. Barkhof F, Filippi M, Miller DH et al. Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. Brain 1997; 120: 2059–2069.
20. CHAMPS study group. MRI predictors of early conversion to clinically definite MS in the CHAMPS placebo group. Neurology 2002; 59: 998–1005.
21. Reddy HS, Narayanan SR, Arnoutelis R et al. Evidence for adaptive functional changes in the cerebral cortex with axonal injury from multiple sclerosis. Brain 2000; 123: 2314–2320.
22. Cifelli A, Matthews PM. Cerebral plasticity in multiple sclerosis: insights from fMRI. Mult Scler 2002; 8: 193–199.
23. Filippi M, Rocca MA. Disturbed function and plasticity in multiple sclerosis as gleaned from functional magnetic resonance imaging. Curr Opin Neurol 2003; 16: 275–282.
24. European Study Group on Interferon beta-1b in Secondary Progressive MS. Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. Lancet 1998; 352: 1491–1497.
25. Ciccarelli O, Giugni E, Paolillo A et al. Magnetic resonance outcome of new enhancing lesions in patients with relapsing-remitting multiple sclerosis. Eur J Neurol 1999; 6: 455–459.
26. Weiner H, Guttmann CR, Khoury SJ. Serial magnetic resonance imaging in multiple sclerosis: correlation with attacks, disability, and disease stage. J Neuroimmunol 2000; 104: 164–173.

27. Brex, P. A., Ciccarelli O., O'Riordan JI et al. A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. N Engl J Med 2002; 346: 158–164.
28. Rovaris M, Comi G, Ladkani D et al. Short-term correlations between clinical and MR imaging findings in relapsing-remitting multiple sclerosis. Am J Neuroradiol 2003; 24: 75–81.
29. The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group. Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. Neurology 1995; 45: 1277–1285.
30. PRISMS Study Group and the University of British Columbia MS/MRI Analysis Group. PRISMS-4: Long-term efficacy of interferon-beta-1a in relapsing MS. Neurology 2001; 56: 1628–1636.
31. Cohen J, Garmany G, Goodman A et al. Expert opinion paper. changing therapy in relapsing multiple sclerosis from the Medical Advisory Board of the National Multiple Sclerosis Society 2004; 1–8 Available on line at: http://www.nationalmssociety.org/pdf/forpros/Exp_ChangTherapy.pdf.
32. Cohen BA Khan O, Jeffery DR et al. Identifying and treating patients with suboptimal responses Neurology 2004; 63(suppl 6): S33–S40.
33. Río J, Nos C, Tintoré M et al. Defining the response to interferon-β in relapsing-remitting multiple sclerosis patients. Ann Neurol 2006; 59: 344–352.
34. Kleinschmidt-DeMasters BK, Tyler KL. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. N Engl J Med 2005; 353: 369–374.
35. Langer-Gould A, Atlas SW, Bollen AW, Pelletier D. Progressive multifocal leucoencephalopathy in a patient treated with natalizumab. N Engl J Med 2005; 353: 375–381.
36. Polman CH, O'Connor PW, Havrdova E et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006; 354: 899–910.
37. Polman CH, Uitdehaag BMJ. New and emerging treatment options for multiple sclerosis. Lancet Neurol 2003; 2: 563–566.
38. Durr FE, Wallace RE, Citarella RV. Molecular and biochemical pharmacology of mitoxantrone. Cancer Treat Rev 1983; 10(suppl B): 3–11.
39. Alberts DS, Peng YM, Bowden GT et al. Pharmacology of mitoxantrone: mode of action and pharmacokinetics. Invest New Drugs 1985; 3: 101–107.
40. Ehninger G, Proksch B, Heinzel G et al. Clinical pharmacology of mitoxantrone. Cancer Treat Rep 1986; 70: 1373–1378.
41. Granmer DK, Weil PA. DNA organization, replication, and repair. In: Murray RK, Daryl K, Granner DK et al, eds. Harper's illustrated biochemistry, 26th ed. New York: McGraw-Hill; 2003: 314–341.
42. Harkins TT, Lewis TJ, Lindsley, JE. A chemical kinetic model for the activity of DNA topoisomerase II. Biochemistry 1998; 37: 7299–7312.
43. Savaraj N, Lu K, Manuel V, Loo TL. Clinical kinetics of 1, 4-dihydroxy-5,8-bis [(2-[(2-hydroxyethyl) amino] ethyl] amino]-9, 10-anthracenedione. Cancer Chemother Pharmacol 1982; 8: 113–117.
44. Wiseman LR, Spencer CM. Mitoxantrone. A review of its pharmacology and clinical efficacy in the management of hormone-resistant advanced prostate cancer. Drugs Aging 1997; 10: 473–485.
45. Fidler JM, DeJoy SQ, Gibbons JJ Jr. Selective immunomodulation by the antineoplastic agent mitoxantrone. II. Nonspecific adherent suppressor cells derived from mitoxantrone-treated mice. J Immunol 1986; 136: 2747–2754.
46. Wang BS, Lumanglas AL, Silva J et al. Inhibition of the induction of alloreactivity with mitoxantrone. Int J Immunopharmacol 1986; 8: 967–973.
47. Ghalie RG, Edan G, Laurent M et al. Cardiac adverse effects associated with mitoxantrone (Novantrone) therapy in patients with MS. Neurology 2002; 59: 909–913.
48. Dukart G, Barone JS. An overview of cardiac episodes following mitoxantrone administration. Cancer Treat Symp 1984; 3: 35–41.
49. Cohen BA, Mikol DD. Mitoxantrone treatment of multiple sclerosis: safety considerations. Neurology 2004; 63(suppl 6): S28–S32.
50. Herman EH, Zhang J, Hasinoff BB et al. Comparison of the structural changes induced by doxorubicin and mitoxantrone in the heart, kidney and intestine and characterization of the Fe(III)-mitoxantrone complex. J Mol Cell Cardiol 1997; 29: 2415–2430.
51. Speyer J, Wasserheit C. Strategies for reduction of anthracycline cardiac toxicity. Semin Oncol 1998; 25: 525–537.
52. Linassier C, Barin C, Calais G et al. Early secondary acute myelogenous leukemia in breast cancer patients after treatment with mitoxantrone, cyclophosphamide, fluorouracil and radiation therapy. Ann Oncol 2000; 11: 1289–1294.
53. Hagemeister FB. Are alkylating agents a necessary component in the therapy of Hodgkin's disease? Leuk Lymphoma 1993; 10(suppl): 91–97.
54. Chaplain G, Milan C, Sgro C et al. Increased risk of acute leukemia after adjuvant chemotherapy for breast cancer: a population-based study. J Clin Oncol 2000; 18: 2836–2842.
55. Goodkin DE. Therapy-related leukemia in mitoxantrone treated patients. Mult Scler 2003; 9: 426.
56. Cattaneo C, Almici C, Borlenghi E et al. A case of acute promyelocytic leukaemia following mitoxantrone treatment of multiple sclerosis. Leukemia 2003; 17: 985–986.
57. Mogenet I, Simiand-Erdociain E, Canonge JM et al. Acute myelogenous leukemia following mitoxantrone treatment for multiple sclerosis. Ann Pharmacother 2003; 37: 747–748.
58. Ghalie RG, Mauch E, Edan G et al. A study of therapy-related acute leukaemia after mitoxantrone therapy for multiple sclerosis. Mult Scler 2002; 8: 441–445.
59. Heesen C, Bruegmann M, Gbdamosi J et al. Therapy-related acute myelogenous leukaemia (t-AML) in a patient with multiple sclerosis treated with mitoxantrone. Mult Scler 2003; 9: 213–214.
60. Brassat D, Recher C, Waubant E et al. Therapy-related acute myeloblastic leukemia after mitoxantrone treatment in a patient with MS. Neurology 2002; 59: 954–955.
61. Vicari AM, Ciceri F, Folli F et al. Acute promyelocytic leukemia following mitoxantrone as single agent for the treatment of multiple sclerosis. Leukemia 1998; 12: 441–442.
62. Voltz R, Starck M, Zingler V et al. Mitoxantrone therapy in multiple sclerosis and acute leukaemia: a case report out of 644 treated patients. Mult Scler 2004; 10: 472–474.
63. Stüve O, Kita M, Pelletier D et al. Mitoxantrone as a potential therapy for primary progressive multiple sclerosis. Mult Scler 2004; 10(suppl 1): S58–S61.
64. Gonsette RE. Mitoxantrone immunotherapy in multiple sclerosis. Mult Scler 1996; 1: 329–332.
65. Edan G, Miller D, Clanet M et al. Therapeutic effect of mitoxantrone combined with methylprednisolone in multiple sclerosis: a randomised multicentre study of active disease using MRI and clinical criteria. J Neurol Neurosurg Psychiatr 1997; 62: 112–118.
66. Gonsette RE. Mitoxantrone in progressive multiple sclerosis: when and how to treat? J Neurol Sci 2003; 206: 203–208.
67. Van de Wyngaert FA, Beguin C, D'Hooghe MB et al. A double-blind clinical trial of mitoxantrone versus methylprednisolone in relapsing, secondary progressive multiple sclerosis. Acta Neurol Belg 2001; 101: 210–216.
68. Goodin DS, Arnason BG, Coyle PK et al. The use of mitoxantrone (Novantrone) for the treatment of multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2003; 61: 1332–1338.
69. Krensky AM, Strom TB, Bluestone JA. Immunomodulators. immunosuppressive agents, tolerogens, and immunostimulants: section X – drugs used for immunomodulation. In: Hardman JG, Limbird LE, Goodman Gilman A, eds. Goodman & Gilman's the pharmacological basis of therapeutics 10th ed. New York: McGraw-Hill; 2001: 1461–1485.
70. Bertino JR. Chemical action and pharmacology of methotrexate, azathioprine and cyclophosphamide in man. Arthritis Rheum 1973; 16: 79–83.
71. Chan GL, Canafax DM, Johnson CA. The therapeutic use of azathioprine in renal transplantation. Pharmacotherapy 1987; 7: 165–177.
72. Elion GB. Symposium on immunosuppressive drugs. Biochemistry and pharmacology of purine analogues. Fed Proc 1967; 26: 898–904.
73. Salmaggi A, Corsini E, La Mantia L. Immunological monitoring of azathioprine treatment in multiple sclerosis patients. J Neurol 1997; 244: 167–174.
74. Sinico RA, Sabadini E, Borlandelli S et al. Azathioprine hypersensitivity: report of two cases and review of the literature. J Nephrol 2003; 16: 272–276.
75. Calbo Mayo JM, Blasco Colmenarejo M, Rivera Vaquerizo PJ et al. Hypersensitivity reaction to azathioprine in a patient with

ulcerative colitis. infrequent manifestations. Inflamm Bowel Dis 2004; 10: 700.
76. Singh G, Fries JF, Spitz P et al. Toxic effecrs of azathioprine in rheumatoid arthritis. Arthritis Rheum 1989; 32: 837–843.
77. Hohlfeld R, Michels M, Heininger K et al. Azathioprine toxicity during long-term immunosuppression of gerneralized myasthenia gravis. Neurology 1988; 38: 258–261.
78. Craner MJ, Zajicek JP. Immunosuppressive treatments in MS – side effects from azathioprine. J Neurol 2001; 248: 625–626.
79. British and Dutch Multiple Sclerosis Azathioprine Trial Group. Double-masked trial of azathioprine in multiple sclerosis. Lancet 1988; 2: 179–183.
80. Taylor, L. Hughes RA, McPherson K et al. The risk of cancer from azathioprine as a treatment for multiple sclerosis. Eur J Neurol 2004; 11: 141.
81. Confavreux C, Saddier P, Grimaud J et al. Risk of cancer from azathioprine therapy in multiple sclerosis: a case-control study. Neurology 1996; 46: 1607–1612.
82. Goodkin D, Bailly RC, Teetzen ML. The efficacy of azathioprine in relapsing-remitting multiple sclerosis. Neurology 1991; 41: 20–25.
83. Yudkin, PL Ellison GW, Ghezzi A et al. Overview of azathioprine treatment in multiple sclerosis. Lancet 1991; 338: 1051–1055.
84. Confavreux C, Moreau T. Emerging treatment in multiple sclerosis: azathioprine and mofetil. Mult Scler 1996; 1: 379–384.
85. Markovic-Plese S, Bielekova B, Kadom N et al. Longitudinal MRI study: the effects of azathioprine in MS patients refractory to interferon β-1b. Neurology 2003; 60: 1489–1451.
86. Lus G, Romano F, Scuotto A et al. Azathioprine and interferon $beta_{1a}$ in relapsing–remitting multiple sclerosis patients: increasing efficacy of combined treatment. Eur Neurol 2004; 51: 15–20.
87. Chabner BA, Ryan DP, Paz-Ares L et al. Antineoplastic agents: section x – drugs used for immunomodulation. In: Hardman JG, Limbird LE, Goodman Gilman A, eds. Goodman & Gilman's the pharmacological basis of therapeutics 10th ed. New York: McGraw-Hill; 2001: 1381–1460.
88. Martin RHR, McFarland HF. Neurologic disorders: course and treatment. San Diego, CA: Academic Press; 1996: 497–499.
89. Zimmerman R, Radhakrishnan J, Valeri A et al. Advances in the treatment of lupus nephritis. Annu Rev Med 2001; 52: 63–78.
90. Brock N, Pohl J. Prevention of urotoxic side effects by regional detoxification with increased selectivity of oxazaphosphorine cytostatics., IARC Sci Publ 1986; 78: 269–279.
91. Aimard G, Girard PF, Raveau J. Multiple sclerosis and the autoimmunization process. Treatment by antimitotics. Lyon Med 1966; 215: 345–352.
92. Padmanabhan BKA, Karni A, Hancock WW et al. AAN 53rd Annual Meeting Program, Philadelphia, PA. Neurology 2001; 56(suppl 3): A226.
93. Hommes OR, Aerts F, Bahr U et al. Cyclophosphamide levels in serum and spinal fluid of multiple sclerosis patients treated with immunosuppression. J Neurol Sci 1983; 58: 297–303.
94. Bahr U, Schulten HR, Hommes OR et al. Determination of cyclophosphamide in urine, serum and cerebrospinal fluid of multiple sclerosis patients by field desorption mass spectrometry. Clin Chim Acta 1980; 103: 183–192.
95. Wender M, Tokarz E, Michalowska G et al. Therapeutic trials of multiple sclerosis and intrathecal IgG production. Ital J Neurol Sci 1986; 7: 205–208.
96. Lamers KJ, Uitdehaag BM, Hommes OR et al. The short-term effect of an immunosuppressive treatment on CSF myelin basic protein in chronic progressive multiple sclerosis. J Neurol Neurosurg Psychiatr 1988; 51: 1334–1337.
97. Ten Berge RJ, van Walbeek HK, Schellekens PT. Evaluation of the immunosuppressive effects of cyclophosphamide in patients with multiple sclerosis. Clin Exp Immunol 1982; 50: 495–502.
98. Brinkman CJ, Nillesen WM, Hommes OR. The effect of cyclophosphamide on T lymphocytes and T lymphocyte subsets in patients with chronic progressive multiple sclerosis. Clin Immunol Immunopathol 1983; 29: 341–348.
99. Strauss K, Hulstaert F, Deneys V et al. The immune profile of multiple sclerosis: T-lymphocyte effects predominate over all other factors in cyclophosphamide-treated patients. J Neuroimmunol 1995; 63: 133–142.
100. Smith DR, Balashov KE, Hafler DA et al. Immune deviation following pulse cyclophosphamide/methylprednisolone treatment of multiple sclerosis: increased interleukin-4 production and associated eosinophilia. Ann Neurol 1997; 42: 313–318.
101. Paterson PY, Drobish DG. Cyclophosphamide: effect on experimental allergic encephalomyelitis in Lewis rats. Science 1969; 165: 191–192.
102. Weiner HL, Cohen JA Treatment of multiple sclerosis with cyclphosphamide: critical review of clinical and immunologic effects. Mult Scler 2002; 8: 142–154.
103. Comabella M, Balashov K, Issazadeh S et al. Elevated interleukin-12 in progressive multiple sclerosis correlates with disease activity and is normalized by pulse cyclophosphamide therapy. J Clin Invest 1998; 102: 671–678.
104. Van boxel-Dezaire AH, Hoff SC, van Oosten BW et al. Contrasting responses to interferon beta-1b treatment in relapsing-remitting multiple sclerosis: does baseline interleukin-12p35 messenger RNA predict the efficacy of treatment? Ann Neurol 2000; 48: 313–322.
105. Hommes OR, Prick JJ, Lamers KJ. Treatment of the chronic progressive form of multiple sclerosis with a combination of cyclophosphamide and prednisone. Clin Neurol Neurosurg 1975; 78: 59–72.
106. Theys P, Gosseye-Lissoir F, Ketelaer P et al. Short-term intensive cyclophosphamide treatment in multiple sclerosis. A retrospective controlled study. J Neurol 1981; 225: 119–133.
107. Hommes OR et al. Prognostic factors in intensive immunosuppression on the course of chronic progressive multiple sclerosis. In: Bauer HJ, Poser S, Ritter G, eds. Progress in MU research. Berlin: Springer Verlag; 1980: 396–400.
108. Hommes OR, Prick JJ, Lamers KJ. Treatment of the chronic progressive form of multiple sclerosis with a combination of cyclophosphamide and prednisone. Clin Neurol Neurosurg 1975; 78: 592–597.
109. Hommes OR, Lamers KJB, Reekers P. Effect of intensive immunosuppression on the course of chronic progressive multiple sclerosis. J Neurol 1980; 223: 177–190.
110. Hommes OR, Aerts F, Bahr U et al. Cyclophosphamide levels in serum and spinal fluid of multiple sclerosis patients by field desoprtion mass spectrometry. J Neurol Sci 1983; 85: 297–303.
111. Theys P, Gosseye-Lissoir F, Ketelaer P et al. Short-term intensive cyclophosphamide treatment in multiple sclerosis. A retrospective controlled study. J Neurol 1981; 225: 119–133.
112. Gonsette RE, Demonty L, Delmotte P. Intensive immunosuppression with cyclophosphamide in multiple sclerosis. Follow up of 110 patients for 2–6 years. J Neurol 1977; 214: 173–181.
113. Gobbini MI, Smith ME, Richert ND et al. Effect of open label pulse cyclophosphamide therapy on MRI measures of disease activity in five patients with refractory relapsing-remitting multiple sclerosis. J Neuroimmunology 1999; 99: 142–149.
114. Patti F, Cataldi ML, Nicoletti F et al. Combination of cyclophosphamide and interferon-beta halts progression in patients with rapidly transitional multiple sclerosis. J Neurol Neurosurg Psychiatr 2001; 71: 404–407.
115. Weinstock-Guttmann B, Kinkel RP, Cohen JA et al. Treatment of fulminant multiple sclerosis with intravenous cyclophosphamide. Neurologist 1997; 3: 178–185.
116. Khan OA, Zvartau-Hind M, Caon C et al. Effect of monthly intravenous cyclophosphamide in rapidly deteriorating multiple sclerosis patients resistant to conventional therapy. Mult Scler 2001; 7 185–188.
117. Killian JM, Bressler RB, Armstrong RM et al. Controlled pilot trial of monthly intravenous cyclophosphamide in multiple sclerosis. Arch Neurol 1988; 45: 27–30.
118. Canadian Cooperative Multiple Sclerosis Study Group. The Canadian cooperative trial of cyclophosphamide and plasma exchange in progressive multiple sclerosis. Lancet 1991; 337: 441–446.
119. Likosky WH, Fireman B, Elmore R et al. Intense immunosuppression in chronic progressive multiple sclerosis: the Kaiser study. J Neurol Neurosurg Psychiatr 1991; 54: 1055–1060.
120. Zephir H, de Seze J, Duhamel A et al. Treatment of progressive forms of multiple sclerosis by cyclophosphamide: a cohort study of 490 patients. J Neurol Sci 2004; 218: 73–77.
121. Perini P, Marangoni M, Tzinteva E et al. Two years therapy of secondary progressive multiple sclerosis (SPMS) with pulse intravenous cyclophosphamide/methylprednisolone. Clinical and MRI data. Mult Scler 2001; 7: S62.
122. Portaccio E, Zipoli V, Siracusa G et al. Safety and tolerability of cyclophosphamide 'pulses' in multiple sclerosis: a prospective study in a clinical cohort. Mult Scler 2003; 9: 446–450.

123. Weinstock-Guttman B, Kinkel RP, Cohen JA et al. Treatment of 'transistional MS' with cyclophosphamide and methylprednisolone (CTX/MP) followed by interferon β. Neurology 1997; 48(suppl 2): A341.
124. Patti F, Cataldi ML, Nicoletti F et al. Combination of cyclophosphamide and interferon-beta halts progression in patients with rapidly transitional multiple sclerosis. J Neurol Neurosurg Psychiatr 2001; 7: 404–407.
125. Patti F, Reggio E, Fiorilla T, et al. Rapidly transitional multiple sclerosis patients treated with combination of cyclophosphamide and interferon beta: follow-up 36 months after discontinuation of therapy. Neurology 2003; 60(suppl 1): A148.
126. Patti F, Reggio E, Palermo F et al. Stabilization of rapidly worsening multiple sclerosis for 36 months in patients treated with interferon beta plus cyclophosphamide followed by interferon beta. J Neurol 2004; 251: 1502–1506.
127. Hauser SL, Dawson DM, Lehrich JR et al. Intensive immunosuppression in progressive multiple sclerosis. A randomized, three-arm study of high-dose intravenous cyclophosphamide, plasma exchange, and ACTH. N Engl J Med 1983; 308: 173–180.
128. Carter JL, Hafler DA, Dawson DM et al. Immunosuppression with high-dose i.v. cyclophosphamide and ACTH in progressive multiple sclerosis: cumulative 6-year experience in 164 patients. Neurology 1988; 38(7 Suppl 2): 9–14.
129. Weiner HL, Mackin GA, Orav EJ et al. Intermittent cyclophosphamide pulse therapy in progressive multiple sclerosis: final report of the Northeast Cooperative Multiple Sclerosis Treatment Group. Neurology 1993; 43: 910–918.
130. Natsumeda Y, Carr SF. Human type I and II IMP dehydrogenases as drug targets. Ann NY Acad Sci 1993; 696: 88–93.
131. Fulton B, Markham A. Mycophenolate mofetil. A review of its pharmacodynamic and pharmacokinetic properties and clinical efficacy in renal transplantation. Drugs 1996; 51: 278–298.
132. Bardsley-Elliot A, Noble S, Foster RH. Mycophenolate mofetil: a review of its use in the management of solid organ transplantation. BioDrugs 1999; 12: 363–410.
133. Nagy SE, Andersson JP, Andersson UG. Effect of mycophenolate mofetil (RS-61443) on cytokine production: inhibition of superantigen-induced cytokines. Immunopharmacology 1993; 26: 11–20.
134. Eugui EM, Allison AC. Immunosuppressive activity of mycophenolate mofetil. Ann NY Acad Sci 1993; 685: 309–329.
135. Tran GT, Carter N, Hodgkinson SJ. Mycophenolate mofetil treatment accelerates recovery from experimental allergic encephalomyelitis. Int Immunopharmacol 2001; 1: 1709–1723.
136. Frohman EM, Brannon K, Racke MK et al. Mycophenolate mofetil in multiple sclerosis. Clin Neuropharmacol 2004; 27: 80–83.
137. Reynolds WJ, Perera M, Yoon SJ et al. Evaluation of clinical and prognostic significance of T-cell regulatory subsets in rheumatoid arthritis. J Rheumatol 1985; 12: 49–56.
138. Goto M, Miyamoto T, Nishioka K et al. T cytotoxic and helper cells are markedly increased and T suppressor and inducer cells are markedly decreased in rheumatoid synovial fluids. Arthritis Rheum 1987; 30: 737–743.
139. Lisak RP, Falk GA, Heinze RG et al. Dissociation of antibody production from disease suppression in the inhibition of allergic encephalomyelitis by myelin basic protein. J Immunol 1970; 104: 1435–1446.
140. Currier RD, Haerer AF, Maydrech EF. Low-dose oral methotrexate treatment of multiple sclerosis: a pilot study. J Neurol Neurosurg Psychiatr 1993; 56: 1217–1218.
141. Goodkin DE, Rudick RA, VanderBrug Medendorp S et al. Low-dose (7.5mg) oral methotrexate reduces the rate of progression in chronic progressive multiple sclerosis. Ann Neurol 1995; 37: 30–40.
142. Goodkin D, Rudick RA, VanderBrug Medendorp S et al. Low-dose oral methotrexate in chronic progressive multiple sclerosis: analyses of serial MRIs. Neurology 1996; 47: 1153–1157.
143. Calabresi PA, Wilterdink JL, Rogg JM et al. An open-label trial of combination therapy with interferon β-1a and oral methotrexate in MS. Neurology 2002; 58: 314–357.
144. Rowe VD, Wang D, John HA et al. Rescue therapy with high dose intravenous methotrexate in MS patients worsening despite avonex therapy. 55th Annual Meeting Program. Neurology 2003; 60(suppl 1): A149–A150.
145. Piro LD. 2-Chlorodeoxyadenosine treatment of lymphoid malignancies. Blood 1992; 79: 843–845.
146. Beutler E. Cladribine (2-chlorodeoxyadenosine). Lancet 1992; 340: 952–956.
147. Sipe JC, Romine JS, Koziol JA et al. Development of cladribine treatment in multiple sclerosis. Mult Scler 1996; 1: 343–347.
148. Rice GP, Filippi M, Comi G. Cladribine and progressive MS: Clinical and MRI outcomes of a multicenter controlled trial. Neurology 2000; 54: 1145–1155.
149. Andersson PB, Goodkin DE. Glucocorticosteroid therapy for multiple sclerosis: a critical review. J Neurol Sci 1998; 160: 16–25.
150. Barnes PJ, Adcock I. Anti-inflammatory actions of steroids: molecular mechanisms. Trends Pharmacol Sci 1993; 14: 436–441.
151. Kern JA, Lamb RJ, Reed JC et al. Dexamethasone inhibition of interleukin 1 beta production by human monocytes. Posttranscriptional mechanisms. J Clin Invest 1988; 81: 237–244.
152. Cronstein BN, Kimmel SC, Levin RI et al. A mechanism for the antiinflammatory effects of corticosteroids: the glucocorticoid receptor regulates leukocyte adhesion to endothelial cells and expression of endothelial-leukocyte adhesion molecule 1 and intercellular adhesion molecule 1. Proc Natl Acad Sci USA 1992; 89: 9991–9995.
153. Barkhof F, Hommes OR, Scheltens P et al. Quantitative MRI changes in gadolinium-DTPA enhancement after high-dose intravenous methylprednisolone in multiple sclerosis. Neurology 1991; 41: 1219–1222.
154. Troiano RA, Hafstein MP, Zito G et al. The effect of oral corticosteroid dosage on CT enhancing multiple sclerosis plaques. J Neurol Sci 1985; 70: 67–72.
155. Troiano RA, Hafstein M, Ruderman M et al. Effect of high-dose intravenous steroid administration on contrast-enhancing computed tomographic scan lesions in multiple sclerosis. Ann Neurol 1984; 15: 257–263.
156. Rosenberg GA, Dencoff JE, Correa, Jr N et al. Effect of steroids on CSF matrix metalloproteinases in multiplesclerosis: relation to blood–brain barrier injury. Neurology 1996; 46: 1626–1632.
157. Fauci AS, Dale DC. The effect of in vivo hydrocortisone on subpopulations of human lymphocytes. J Clin Invest 1974; 53: 240–246.
158. Panitch HS, Bever CT. Clinical trials of interferons in multiple sclerosis. What have we learned? J Neuroimmunol 1993; 46: 155–164.
159. Ossege LM, Sindern E, Voss B et al. Corticosteroids induce expression of transforming-growth-factor-beta1 mRNA in peripheral blood mononuclear cells of patients with multiple sclerosis. J Neuroimmunol 1998; 84: 1–16.
160. Gelati M, Lamperti E, Dufour A et al. IL-10 production in multiple sclerosis patients, SLE patients and healthy controls: preliminary findings. Ital J Neurol Sci 1997; 18: 191–194.
161. Melcangi RC, Cavarretta I, Magnaghi V et al. Corticosteroids protect oligodendrocytes from cytokine-induced cell death. NeuroReport 2000; 11: 3969–3972.
162. Beck RW, Cleary PA, Anderson MM et al. A randomized, controlled trial of corticosteroids in the treatment of acute optic neuritis. The Optic Neuritis Study Group. N Engl J Med 1992; 326: 581–588.
163. Beck RW, Cleary PA, Trobe JD et al. The effect of corticosteroids for acute optic neuritis on the subsequent development of multiple sclerosis. N Engl J Med 1993; 329: 1764–1766.
164. Myers LW, Rudick R, Goodkin DE, eds. Multiple sclerosis. New York: Springer Verlag; 1992: 135–156.
165. Goodkin DE, Kinkel RP, Weinstock-Guttman B et al. A Phase II study of IV methylprednisolone in secondary progressive multiple sclerosis. Neurology 1998; 51: 239–245.
166. Weiss W, Stadlan EM, Goodkin DE, Rudick RA, eds. Treatment of multiple sclerosis. Trial design, results and future perspectives. New York: Springer Verlag; 1992: 91–122.
167. Zivadinov R, Rudick RA, De Masi et al. Effects of IV methylprednisolone on brain atrophy in relapsing–remitting multiple sclerosis. Neurology 2001; 5: 1239–1247.
168. Dalakas MC. Mechanism of action of intravenous immunoglobulin and therapeutic considerations in the treatment of autoimmune neurologic diseases. Neurology 1998; 51: 2–8.
169. Jorgensen SH, Sorensen PS. Intravenous immunoglobulin treatment of multiple sclerosis and its animal model, experimental autoimmune encephalomyelitis. J Neurol Sci 2005; 233: 61–65.

170. Fazekas F, Deisenhammer F, Strasser-Fuchs Siegrid et al. Randomized placebo controlled trial of monthly intravenous immunoglobulin therapy in relapsing–remitting multiple sclerosis. Lancet 1997; 349: 589–593.
171. Achiron A, Barak Y, Goren M et al. Intravenous immune globulin in multiple sclerosis: clinical and neuroradiological results and implications for possible mechanisms of action. Clin Exp Immunol 1996; 104(suppl 1): 67–70.
172. Achiron A, Rotstein Z, Barak Y et al. Intravenous immunoglobulin in multiple sclerosis and experimental autoimmune encephalomyelitis – the Israeli experience. Mult Scler 1997; 3: 142–144.
173. Sørensen PS, Wanscher B, Schreiber K et al. A double-blind, cross-over trial of intravenous immunoglobulin G in multiple sclerosis: preliminary results. Mult Scler 1997; 3: 145–148.
174. Hommes OR, Sørensen PS, Fazekas F et al. Intravenous immunoglobulin in secondary progressive multiple sclerosis: randomized placebo-controlled trial. Lancet 2004; 364: 1149–1156.
175. Fazekas F, Sørensen PS, Filippi M et al. MRI results from the European Study on Intravenous Immunoglobulin in Secondary Progressive Multiple Sclerosis. Mult Scler 2005; 11: 433–440.
176. Hughes RAC, Wijdicks EFM, Barohn R et al. Practice parameter: immunotherapy for Guillain–Barré syndrome: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2003; 61: 736–740.
177. Blom RJ, Kuks JB, Westerterp-Maas A et al. Favorable results of plasmapheresis in severe myasthenia gravis. Ned Tijdschr Geneeskd 1997; 141: 381–384.
178. Weinshenker BG, O'Brien PC, Petterson TM et al. A Randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease. Ann Neurol 1999; 46: 878–886.
179. Keegan M, Pineda AA, McClelland RL et al. Plasma exchange for severe attacks of CNS demyelination: predictors of response. Neurology 2002; 58: 143–146.
180. Keegan M, Konig F, McClelland R et al. Relation between humoral pathological changes in multiple sclerosis and response to therapeutic plasma exchange. Lancet 2005; 366: 579–833.
181. Goto T, Kino T, Hatanaka H et al. Discovery of FK-506, a novel immunosuppressant isolated from *Streptomyces tsukubaensis*. Transplant Proc 1987; 19(suppl 6): 4–8.
182. Schreiber SL, Crabtree GR. The mechanism of action of cyclosporin A and FK506. Immunol Today 1992; 13: 136–142.
183. Gold BG, Voda J, Yu X et al. FK506 and a nonimmunosuppressant derivative reduce axonal and myelin damage in experimental autoimmune encephalomyelitis: neuroimmunophilin ligand-mediated neuroprotection in a model of multiple sclerosis. J Neurosci Res 2004; 77: 367–377.
184. Gonsette RE. New immunosuppressants with potential implication in multiple sclerosis. J Neurol Sci 2004; 223: 87–93.
185. Kahan BD. Cyclosporine. N Engl J Med 1989; 32: 1725–1738.
186. Khanna A, Li B, Stenzel KH et al. Regulation of new DNA synthesis in mammalian cells by cyclosporine. Demonstration of a transforming growth factor beta-dependent mechanism of inhibition of cell growth. Transplantation 1994; 57: 577–582.
187. Steck AJ, Regli F, Ochsner F et al. Cyclosporine versus azathioprine in the treatment of multiple sclerosis: 12-month clinical and immunological evaluation. Eur Neurol 1990; 30: 224–228.
188. Multiple Sclerosis Study Group. Efficacy and toxicity of cyclosporine in chronic progressive multiple sclerosis: a randomized, double-blinded, placebo-controlled clinical trial. Ann Neurol 1990; 27: 591–605.
189. Jafri S, Pasricha PJ. Agents used in inflammatory bowel disease: section vi – agents used for diarrhea, constipation, and inflammatory bowel disease; agents used for biliary and pancreatic disease. In: Hardman JG, Limbird LE, Goodman Gilman A, eds. Goodman & Gilman's the pharmacological basis of therapeutics 10th ed. New York: McGraw-Hill; 2001: 1037–1059.
190. Noseworthy JH, O'Brien P, Erickson BJ et al. The Mayo Clinic–Canadian Cooperative trial of sulfasalazine in active multiple sclerosis. Neurology 1998; 51: 1342–1352.
191. Moreau T, Coles A, Wing M et al. CAMPATH-IH in multiple sclerosis. Mult Scler 1996; 1: 357–365.
192. Coles AJ, Deans J, Compston A. Campath-1H treatment of multiple sclerosis: lessons from the bedside for the bench. Clin Neurol Neurosurg 2004; 106: 270–274.
193. Coles A, Wing MG, Molyneux P et al. Monoclonal antibody treatment exposes three mechanisms underlying the clinical course of multiple sclerosis. Ann Neurol 1999; 46: 296–304.
194. Coles A, Wing M, Smith S et al. Pulsed monoclonal antibody treatment and autoimmune thyroid disease in multiple sclerosis. Lancet 1999; 354: 1691–1695.
195. Genzyme Press Release. Genzyme and Schering AG announce interim results from trial of Campath for multiple sclerosis. 16 September 2005. Available on line at: http://www.genzyme.co.uk/corp/news/all_news/GENZ%20PR-091605.asp.
196. Rastetter W, Molina A, White CA. Rituximab: expanding role in therapy for lymphomas and autoimmune diseases. Annu Rev Med 2004; 55: 477–503.
197. Reff ME, Carner K, Chambers KS et al. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. Blood 1994; 83: 435–445.
198. Valentine MA, Clark EA, Shu GL et al. Phosphorylation of the CD20 phosphoprotein in resting B lymphocytes. Regulation by protein kinase C. J Biol Chem 1989; 264: 1182–1187.
199. Einfeld DA Brown JP, Valentine MA et al. Molecular cloning of the human B cell CD20 receptor predicts a hydrophobic protein with multiple transmembrane domains. EMBO J 1988; 7: 711–717.
200. Anderson KC, Bates MP, Slaughenhoupt BL et al. Expression of human B cell-associated antigens on leukemias and lymphomas: a model of human B cell differentiation. Blood 1984; 63: 1424–1433.
201. Maloney DG, Grillo-Lopez AJ, White CA et al. IDEC-C2B8 (Rituximab) anti-CD20 monoclonal antibody therapy in patients with relapsed low-grade non-Hodgkin's lymphoma. Blood 1997; 90: 2188–2195.
202. Taji H, Kagami Y, Okada Y et al. Growth inhibition of CD20-positive B lymphoma cell lines by IDEC-C2B8 anti-CD20 monoclonal antibody. Jpn J Cancer Res 1998; 89: 748–756.
203. Clynes RA, Towers TL, Presta LG et al. Inhibitory Fc receptors modulate in vivo cytoxicity against tumor targets. Nat Med 2000; 6: 443–446.
204. Cree B, Lamb S, Chin A et al. Tolerability and effects of rituximab (anti-CD20 antibody) in neuromyelitis optica (NMO) and rapidly worsening multiple sclerosis (MS). AAN 56th Annual Meeting Program. Neurology 2004; 7(suppl 5): A492.
205. Pender MP. The pathogenesis of primary progressive multiple sclerosis: antibody-mediated attack and no repair? J Clin Neurosci 2004; 11: 689–692.
206. Mohrbacher A. B cell non-Hodgkin's lymphoma: rituximab safety experience. Arthritis Res Ther 2005; 7(suppl 3): S19–S25.
207. Coiffier B, Haioun C, Ketterer N et al. Rituximab (anti-CD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma: a multicenter phase II study. Blood 1998; 92: 1927–1932.
208. Rose JW, Lorberboum-Galski H, Fitzgerald D et al. Chimeric cytotoxin IL2-PE40 inhibits relapsing experimental allergic encephalomyelitis. J Neuroimmunol 1991; 32: 209–217.
209. Hayosh NS, Silberg DG, Swanborg RH. Autoimmune effector cells. Part 10: Effector cells of autoimmune encephalomyelitis in healthy nonimmune rats. J Immunol 1987; 138: 3771–3775.
210. Englehardt B, Diamantstein T, Wekerle H. Immunotherapy of experimental autoimmune encephalomyelitis (EAE): differential effect of anti-IL-2 receptor antibody therapy on actively induced and T-line mediated EAE of the Lewis rat. J Autoimmun 1989; 2: 61–73.
211. Bielekova B, Richert N, Howard T et al. Humanized anti-CD25 (daclizumab) inhibits disease activity in multiple sclerosis patients failing to respond to interferon beta. Proc Natl Acad Sci USA 2004; 101: 8705–8708.
212. Stone LA, Frank JA, Albert PS et al. Characterization of MRI response to treatment with interferon beta-1b: contrast-enhancing MRI lesion frequency as a primary outcome measure. Neurology 1997; 49: 862–869.
213. Miller DH, Khan OA, Sheremata WA et al. A controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2003; 348: 15–23.
214. Rose J, Watt HE, White AT et al. Treatment of multiple sclerosis with an anti-interleukin-2 receptor monoclonal antibody. Ann Neurol 2004; 56: 864–867.
215. National Institute of Neurological Disorders and Stroke (NINDS). Zenapax (daclizumab) to treat relapsing remitting multiple sclerosis. Available online at: http://clinicaltrials.

gov/ct/show/NCT00071838?order=3.
216. Fassas A, Anagnostopoulos A, Kazis A et al. Peripheral blood stem cell transplantation in the treatment of progressive multiple sclerosis: first results of a pilot study. Bone Marrow Transplant 1997; 20: 631–638.
217. Karussis D, Vourka-Karussis U, Mizrachi-Koll R et al. Acute/relapsing experimental autoimmune encephalomyelitis: induction of long lasting, antigen-specific tolerance by syngeneic bone marrow transplantation. Mult Scler 1999; 5: 17–21.
218. Fassas A, Passweg JR, Anagnostopoulos A et al. Hematopoietic stem cell transplantation for multiple sclerosis. A retrospective multicenter study. J Neurol 2002; 249: 1088–1097.
219. Burt RK, Fassas A, Snowden J et al. Collection of hematopoietic stem cells from patients with autoimmune diseases. Blood 2001; 28: 1–12.
220. McAllister LD, Beatty PG, Rose J. Allogeneic bone marrow transplant for chronic myelogenous leukemia in a patient with multiple sclerosis. Bone Marrow Transplant 1997; 19: 395–397.
221. Meloni G, Capria S, Salvetti M et al. Autologous peripheral blood stem cell transplantation in a patient with multiple sclerosis and concomitant Ph^+ acute leukemia. Haematologica 1999; 84: 665–667.
222. Mandalfino P, Rice G, Smith A et al. Bone marrow transplantation in multiple sclerosis. J Neurol 2000; 247: 691–695.
223. Fassas A, Kazis A. High dose immunosuppression and autologous hematopoietic stem cell rescue for severe multiple sclerosis. J Hematother Stem Cell Res 2003; 12: 707–711.
224. Fassas A, Anagnostopoulos A, Kazis A et al. Autologous stem cell transplantation in progressive multiple sclerosis – an interim analysis of efficacy. J Clin Immunol 2000; 20: 24–30.
225. Openshaw H, Stuve O, Antel JP et al. Multiple sclerosis flares associated with recombinant granulocyte colony-stimulating factor. Neurology 2000; 54: 2147–2150.
226. Kimiskidis VK, Tsimourtou V, Papagiannopoulos S et al. Autologous stem cell transplantation in multiple sclerosis: the MRI study. J Neurol 2002; 249(suppl 1): I/61.
227. Bredesen C, Forman SJ, Horowitz M et al. Conference synopsis: Hematopoietic stem cell therapy in autoimmune diseases, October 2001. Biol Blood Marrow Transplant 2002; 8: 407–411.
228. Hintzen RQ. Stem cell transplantation in multiple sclerosis: multiple choices and multiple challenges. Mult Scler 2002; 8: 155–160.