

Current treatments for multiple sclerosis

CA Young

Consultant Neurologist and Honorary Professor in Neurology, Walton Centre for Neurology and Neurosurgery, Liverpool, England

ABSTRACT Multiple sclerosis is a complex lifelong condition, with the severity of symptoms varying greatly between patients. In this article, requested by visitors to the www.behindthemedicalheadlines.com site, Professor Carolyn Young provides an overview of the different sub-types of MS and the diverse treatments which are currently available for this disease.

KEYWORDS Disease-modifying treatment, multiple sclerosis, progressive, relapses, stem cells

LIST OF ABBREVIATIONS central nervous system (CNS), multiple sclerosis (MS), National Institute of Health and Clinical Excellence (NICE), randomised controlled trial (RCT)

DECLARATION OF INTERESTS Professor Young has held research funding for trials of many new treatments and has been a member of advisory panels for the Association of British Neurologists and commercial organisations.

Published online April 2007

Correspondence to CA Young, Consultant Neurologist and Honorary Professor in Neurology, Walton Centre for Neurology and Neurosurgery, Lower Lane, Liverpool, L9 7LT

tel. +44 (0)151 529 5528

fax. +44 (0)151 529 5512

e-mail carolyn.young@thewaltoncentre.nhs.uk

INTRODUCTION

Multiple sclerosis is a complex and variable lifelong condition. There are several disease patterns, and these clinical sub-types may alter in an individual over time. The severity of the condition, in terms of relapse frequency, degree of disability, and level of symptoms, varies within and between individual patients. It follows that the treatment options for MS are diverse, and in order to appropriately utilise them, one needs to understand the clinical sub-types of MS.¹

MULTIPLE SCLEROSIS SUB-TYPES

Multiple sclerosis typically begins in young adults as a relapsing–remitting neurological condition with a strong immuno-inflammatory pathogenesis. Only about 15% of patients fall into a primary progressive category, with progression from onset, typically a spastic paraparesis without super-imposed relapses, and such primary progressive patients are usually older and, more often, male.

Over time, many initially relapsing–remitting patients convert to a secondary progressive course. They accrue disability slowly over months due to gradual increase in neurological symptoms and signs, rather than the abrupt deterioration of a relapse, and typically they do not show remissions from such gradual deterioration.

Some people who continue to follow a relapsing–remitting course will also become disabled, because they achieve only incomplete recovery from relapses. Visually, the decline into disability might be considered as a gradual downhill slope in secondary progressive MS (or primary progressive MS) or a more step-wise one in

relapsing–remitting MS with incomplete recovery. A minority remain relapsing–remitting, and do not develop disability even after decades. These constitute the benign MS group (about 20% of people with MS).

IMMUNOLOGICAL BACKGROUND TO MULTIPLE SCLEROSIS

There are many immunological, inflammatory and degenerative processes underlying MS which are interrelated and dynamic, changing over time and varying between patients. A simplified summary would be to consider the earlier stages of the disease as being due to destruction of myelin from activity of the individual's own immune system, i.e. an autoimmune process. This stage may be treatable with drugs which alter immune or inflammatory responses. Later there may be more insidious loss of myelin, axons and death of the neurones themselves, partly as a result of Wallerian degeneration.

MULTIPLE SCLEROSIS TREATMENTS

Consideration of these clinical scenarios suggests that MS treatments should be categorised into three broad areas:

- 1 Treatments that alter disease course, such as frequency of relapses, onset of secondary progressive MS or rate of deterioration in secondary progressive or primary progressive MS.
- 2 Treatments that can be used to treat relapses when they have occurred.
- 3 Treatments for symptoms, which may be primary and secondary level symptoms. Primary symptoms arise directly from MS, like neuropathic pain from demyelinated neurones, and secondary symptoms

come indirectly from the consequences of MS, like musculoskeletal pain due to paralysis, spasticity, contractures etc.

DRUGS TO ALTER DISEASE COURSE

The development of licensed treatments to alter the disease course of relapsing–remitting MS has been an exciting development of recent decades. There have been four agents available for several years; three are forms of Beta Interferon (Beta Interferon IA, Avonex, Rebif, Beta Interferon IB, Betaferon) and Glatiramer Acetate (Copaxone),² which is an amino acid polymer. The Association of British Neurologists and Department of Health have agreed guidelines for prescription, recently reviewed.³

These four drugs are all parenteral, involving subcutaneous injections from daily to three times per week, with the exception of Avonex which is a once-weekly intramuscular injection.⁴ The pivotal papers report up to one third reduction in relapse rate. Apart from injection site reactions and various systemic side effects, there has been concern about the induction of antibodies. For the Beta Interferons, it appears these can be neutralising and reduce the efficacy of the drugs.⁵

Natalizumab has recently been licensed for the treatment of relapsing MS, though in the UK it has not yet undergone review by NICE. Natalizumab is a monthly infusion and reduces relapse rate by about 70%.⁶ Its mechanism of action as an adhesion molecule inhibitor reduces lymphocyte trafficking across the blood–brain barrier. Recently, Natalizumab was shown to carry a risk of progressive multi-focal leukoencephalopathy, with three cases in trial patients. In the USA, this agent is being made available with surveillance under a special restricted distribution programme, to patients who have not responded or proved intolerant to existing therapies. Guidelines for its use in Europe are not fully established.

Mitoxantrone is an intravenously administered chemotherapeutic agent which has been shown to reduce relapse rate in MS. It has powerful immunomodulatory effects, such as inhibiting T-cell proliferation and decreasing antibody production. It carries rare, but significant, risks, such as induction of leukaemia, and it is cumulatively cardiotoxic, so it is restricted for administration to patients with aggressive relapsing–remitting MS.⁷ Trials are in progress to consider whether it can be used as an induction agent before switching to drugs like Glatiramer Acetate.

DRUGS TO TREAT RELAPSES

Steroids are the only drugs with RCT evidence of benefit once a relapse has occurred. Most MS specialists believe

that steroids do not necessarily alter the long-term outlook, i.e. the use of steroids would not have converted someone with residual disability from a relapse to someone enjoying complete recovery. However, steroids may hasten recovery and are often, therefore, offered as a three- or five-day course of infusions of Methyl Prednisolone 0.5–1g daily. The majority of evidence shows that long-term steroids are detrimental.

DRUGS AND NON-PHARMACOLOGICAL TREATMENTS FOR SYMPTOMS

Symptomatic treatments are very plentiful and often inexpertly prescribed. Space precludes an exhaustive list of treatments for primary symptoms, but there are RCTs for drugs and sometimes non-pharmacological treatments, for neuropathic pain, bladder problems, fatigue, tremor,⁹ spasticity,⁸ depression and cognitive impairment. The methodological quality of these trials is mixed and more research is needed to develop more robust outcome measures and further trials.

FUTURE TREATMENTS

These are exciting times in MS treatment research, with several promising disease modifying agents in development. Reconsidering the various clinical subtypes, it is evident that the needs of people with secondary progressive MS and primary progressive MS for drugs which will reduce or reverse disease progression have not yet been met, as, regrettably, published trials are generally negative. There are currently RCTs in secondary progressive MS in progress, utilising agents such as MBP8298, or Lamotrigine.

Stem cells have had enormous publicity, with little dissemination of the complicated underlying issues. The knowledge that endogenous neural stem cells do exist is exciting. An attractive research area is the use of growth factors or other agents to enhance endogenous neurogenesis. Neural stem cell lines from aborted fetal tissue have been generated, raising the possibility of trials in neurodegenerative disease. Embryonic stem cells derived from blastocytes (cells of the pre-implantation embryo) are capable of generating any cell type, but raise significant ethical issues, and scientific issues such as how to grow them, control their differentiation, and switch them off as they could be tumorigenic. Non-CNS stem cells have been tested from olfactory sheathing cells, haematological stem cells (bone marrow or umbilical cord blood derived) or mesodermal. Their potential utility has risen with the knowledge that tissue-specific stem cells can differentiate into a different lineage, the so-called ‘blood into brain’ experiment.¹⁰ There have been trials of stem cells in MS and other conditions, although not all work meets accepted standards for methodology and patient follow-up. Even this brief description should illustrate that none of these therapies are ready for commercial sale to patients.

KEYPOINTS

- Multiple sclerosis is a variable lifelong condition. There are several disease patterns, and these clinical subtypes may alter in an individual over time.
- The severity of the condition, in terms of relapse frequency, degree of disability and level of symptoms varies within and between individuals.
- The treatment of MS is aimed at symptoms, relapse and clinical course.
- Steroids are the only drugs shown to be of benefit in acute relapse.
- Beta Interferons, glatiramer acetate, some monoclonal antibodies against adhesion molecules and some chemotherapeutic agents have been shown to alter disease course.
- Future treatments which have not yet been evaluated may include neural growth factors and stem cell therapy.

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A BOOK YOU SHOULD READ

The Eye

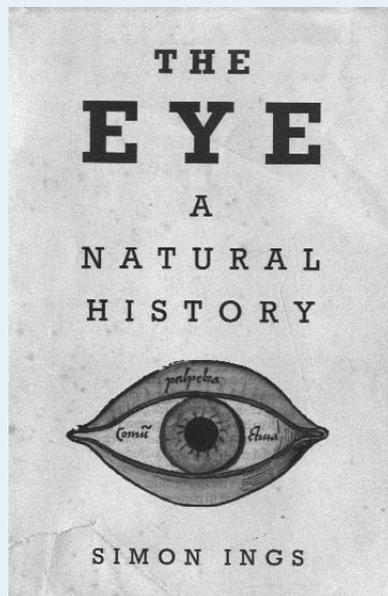
Simon Ings

ISBN 9780747578055

Bloomsbury Publishing; 2007 £17.99

Readers, wearied by medical reading, could be forgiven for wondering why they should be encouraged to read yet more medicine in their limited leisure time. Be reassured, this book is unlike any medical text you have ever read. Not that it is always an easy read (there are parts your reviewer still does not understand) as the author buries you under a welter of information. However, do not be put off. This is a fascinating and hugely informative look at vision which, among other things, has undermined my confidence in believing what I see!

Ings' panoramic overview of vision covers archaeology, evolution, genetics, biology, physics, chemistry, philosophy and neuroscience, all considered in the historical context of the gradual advance of human



knowledge and ideas over the centuries. Consideration includes the relation of vision to the other senses, the development in nature of different types of eye, structure and function, colours seen and unseen, and seeing as a cerebral function related to thinking rather than a matter of optics.

A feel for the book comes from

sampling some of its information nuggets. Rhodopsin, the chemical most doctors associate specifically with vision, has been around for some 600 million years (much longer than *Homo sapiens*), and has remained virtually unchanged in that time. Humans have a 180° horizontal field of view, but visual acuity falls quickly to a half more than 1° outside central (foveolar) vision and then to below legal blindness standards beyond 20° from central vision. We may not rate our night vision highly but, in favourable circumstances, we have the capacity to see a single candle flame 17 miles away. Eyes and vision are central to human behaviour; 'We do not merely look at faces. We read them.'

Read this book slowly and refresh your pleasure in learning things you don't need to know. There are innumerable references to the giants of the past, but a good quote to conclude is 'We see nothing, save through reason' (Schopenhauer).

Nial Finlayson
Director of Communications, RCPE