

Multiple sclerosis and its treatment

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Summary

Multiple sclerosis (MS) is a common neurological disorder responsible for substantial neurological morbidity. Although it is considered to be an autoimmune demyelinating disease of the central nervous system (CNS), mediated by antigen-specific CD4+ T helper (Th1) T-cells, therapeutic strategies aimed at generalised immunosuppression have been disappointing. Recently, immunomodulatory therapies like interferon (IFN)- β and glatiramer acetate have proved more effective. They reduce the rate and severity of clinical relapses and, in the case of IFN- β , delay the rate of disease progression. Symptomatic therapies and rehabilitation, however, remain the mainstay of treatment for the majority of patients with MS. The immunopathogenesis of MS and its treatments, both disease modifying and symptomatic, are reviewed below.

Background

MS is the most common debilitating neurological illness to afflict young adults. The average prevalence across the UK is approximately 130 per 100,000, with an annual incidence of 0.2%. MS is more common in women and Caucasians on a genetic background associated with specific major histocompatibility complex (MHC) haplotypes (DR15/DQ6) and possibly other genetic loci. Epidemiological studies support an environmental aetiological factor. The disease usually manifests clinically in the third and

fourth decades, typically presenting with a relapsing-remitting course which, after a period of time (average 5–15 years), enters the secondary progressive phase. Secondary progression can occur in the presence or absence of superimposed relapses. Approximately 10% of patients have a primary progressive course from the outset, without clinical relapses. About 25% have a benign course, with little or no disability after 15 or more years. Rarely, patients have malignant MS with a rapidly progressive course. Favourable prognostic features include young age of onset, a long duration between the first and second clinical events, initial symptoms limited to visual and sensory pathways, and a low lesion load on magnetic resonance imaging (MRI) during the first clinical episode. However, an accurate prognosis is not possible for individual cases.

The belief, although unproven, that MS is an organ-specific autoimmune disorder has dominated most therapeutic strategies, which are aimed at either generalised immunosuppression or more targeted immunomodulation to reduce or switch off the specific autoimmune reaction. Following a brief summary of the immunopathogenesis of MS, this review will concentrate on recent developments in therapies aimed at modifying the underlying disease process, as well as symptomatic therapies which are still the mainstay of treatment for most patients with MS.

Immunopathogenesis of multiple sclerosis

MS is considered to be an organ-specific autoimmune disease orchestrated by autoreactive CD4+ T-cells (Fig 1 and 2)¹. Genetic factors interact with an environmental factor to establish or maintain pathological autoreactive T-cells which, after a long and variable latency period (10–20 years), are activated, possibly by a systemic trigger

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such as a viral infection or superantigen. The activated T-cells selectively cross the blood-brain barrier, and on re-exposure to a putative autoantigen initiate a cell-mediated (Th1) inflammatory reaction. The resulting complex immunological cascade with T-cell, B-cell, macrophage and endothelial activation, and the induction of cytokines and inflammatory mediators results in demyelination and axonal loss. This in turn releases sequestered CNS antigens that are hypothesised to initiate further episodes of autoimmune-induced inflammation, via intra- and/or intermolecular antigenic spread. The potential for triggering inflammation locally by neurotropic viruses (eg human herpesvirus 6)², with a secondary autoimmune response, remains an attractive alternative hypothesis.

The mechanisms underlying autoimmunity in MS are unknown. However, the activation of T-cells requires an antigen-specific signal transduced via the T-cell receptor (TCR)/CD3-CD4 complex interacting with MHC class II molecules. T-cell activation is thought to occur in the perivascular space, with the macrophage as the most likely antigen presenting cell. Other cells that express MHC class II molecules (eg pericytes and astrocytes) may also play a role in antigen presentation. Stimulation of a threshold number of TCRs and additional costimulatory signals via the interaction of accessory molecule ligand pairs like B7/CD28 are also required to

ensure T-cell activation. Current evidence supports MS as a disease mediated by Th1-CD4+ $\alpha\beta$ T-cells, but CD8+ T-cells, $\gamma\delta$ T-cells, natural killer cells, and B-cells have all been implicated in the disease process. Putative autoantigens implicated in MS include the myelin proteins:

- 1 myelin basic protein (MBP),
- 2 proteolipid protein,
- 3 myelin-associated glycoprotein,
- 4 myelin oligodendrocyte glycoprotein (MOG).

Other potential autoantigens include transaldolase, 2',3'-cyclic nucleotide 3'-phosphodiesterases, and α B-crystallin.

Pro-inflammatory cytokines produced by the activated T-cells result in activation of macrophages and microglia which play a central role in the disease process. They produce an array of pro-inflammatory monokines and chemokines which activate astrocytes and endothelial cells, upregulate adhesion molecule expression, and disrupt the blood-brain barrier. In addition, they are responsible for antigen presentation, production of myelinotoxic and neurotoxic factors, myelin phagocytosis, and possibly also for assisting in the process of remyelination via the local production of growth factors.

Th1-like pro-inflammatory cytokines IFN- γ , interleukin (IL)2 and tumour necrosis factor (TNF) α and β appear to be pivotal in the inflammatory reaction of MS. Prior to clinical relapse, stimulated peripheral blood cells of MS

patients produce increased quantities of IFN- γ and TNF α . Pro-inflammatory cytokines, as well as their mRNAs, have been demonstrated in MS plaques, and increased levels of IL2, IL1 and TNF α/β have been found in the cerebrospinal fluid (CSF) of MS patients. These pro-inflammatory cytokines are potent activators of macrophages, microglia and astrocytes, greatly inducing and augmenting their production of cytokines, stimulating oxygen and nitrogen free radical release, and increasing MHC, Fc receptors and adhesion molecule expression. The anti-inflammatory cytokines, IL4, IL10, IL13 and transforming growth factor (TGF) β , which counteract the effects of the pro-inflammatory cytokines, may play a role in the induction and maintenance of remission. Increased levels of IL10 and TGF β mRNA expression in mononuclear cells from the peripheral blood and CSF are associated with the recovery phase of a relapse, periods of remission and possibly a less aggressive disease course. The humoral, or B-cell, response is very important in demyelinating diseases. The production of complement-fixing anti-myelin antibodies, especially to MOG, is required to induce demyelination. These antibodies are also responsible for oligodendrocyte toxicity, Fc-receptor stimulation, chemotaxis and myelin opsonisation.

Upregulated expression of adhesion molecules in MS allows recruitment of circulating leukocytes, and they function as accessory molecules in antigen presentation. Chemokines like macrophage inflammatory protein (MIP)-1 α are chemoattractant cytokines responsible for the selective recruitment of specific subsets of inflammatory cells. Elevated levels of MIP-1 α have been found in the CSF of patients with MS. Once cells have adhered to the endothelium they penetrate the basal lamina and extracellular matrix. Matrix metalloproteinases (MMP) are a large group of enzymes responsible for the lysis of the extracellular matrix. Increased levels of MMP-9 have been found in the CSF of patients with MS and correlate with blood-brain barrier disturbance on MRI. The non-specific

Key Points

- ▶ MS is the commonest disabling neurological disease of young adults
- ▶ The aetiology of MS is unknown
- ▶ Although unproven, MS is considered an organ-specific autoimmune disease
- ▶ Interferon-beta is the first disease modifying therapy to be licensed for use in patients with MS
- ▶ Symptomatic therapies remain the cornerstone of MS treatment
- ▶ Patients with MS are best managed by multidisciplinary teams

mediators of inflammation, such as reactive oxygen and nitrogen free radicals, proteases, pro-inflammatory cytokines and eicosanoids, are all capable of damaging myelin and oligodendrocytes. The death of oligodendrocytes in MS appears to occur via apoptosis. Similar mechanisms may also be responsible for axonal and neuronal loss, accounting for irreversible clinical disability.

Disease modifying agents

Targeted immunotherapies

Interferon beta. IFN- β is currently the treatment of choice for patients with

relapsing-remitting MS³⁻⁵. Three preparations of two recombinant forms of IFN- β are currently approved for use in relapsing-remitting patients, one of which has recently been licensed for use in ambulatory patients with secondary progressive disease⁶. IFN- β decreases the relapse rate by a third, the rate of severe relapses probably by a half, and the acquisition of new lesions on MRI by up to 80%. In a single study, IFN- β lowered the probability of progression of disability, albeit modestly, independent of its effect on relapse rate in patients with secondary progressive disease⁶.

The most common side effects are flu-like symptoms after each injection

which usually subside within 2–3 months of initiating therapy. Subcutaneous injection of IFN- β can cause redness, tenderness, swelling, and occasionally skin necrosis at the injection site. Neutralising anti-IFN- β antibodies develop in 20–30% of patients within two years of starting treatment. Evidence is conflicting, but suggests the development of a neutralising humoral response is associated with loss of efficacy on relapse rate. Further studies are needed to determine the clinical significance of neutralising antibodies. There is some evidence of dose effect with regard to the clinical and MRI efficacy of IFN- β ^{5,7}.

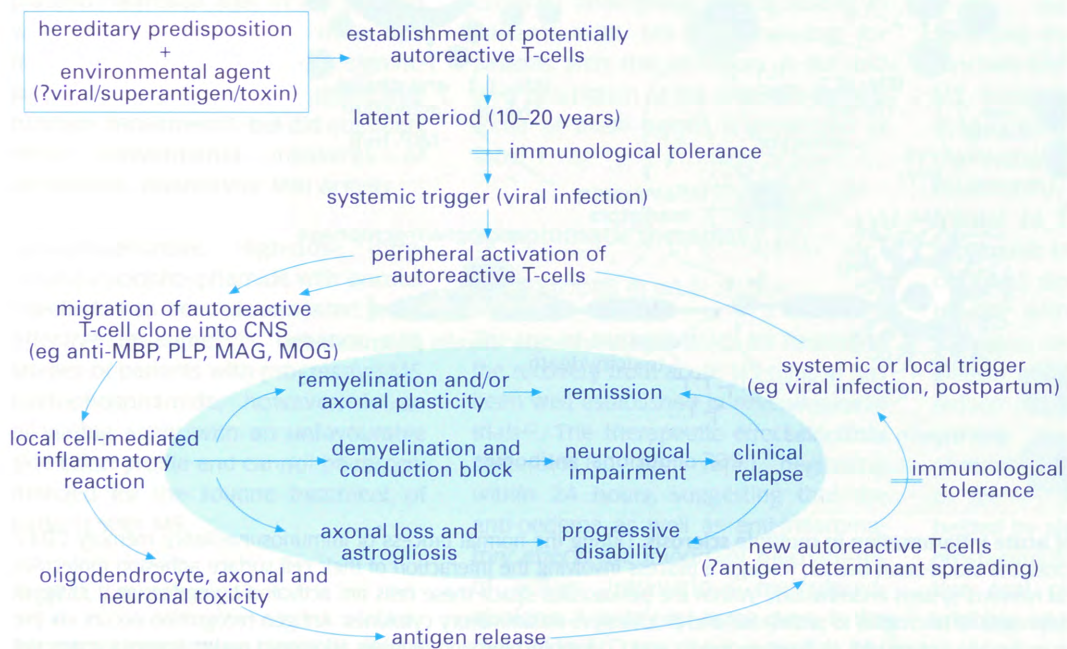


Fig 1. The immunopathogenesis of multiple sclerosis. An environmental agent and/or agents combined with a hereditary predisposition establishes or maintains pathological autoreactive T-cells. After a latency period of 10–20 years a breakdown in immunological tolerance, possibly by a systemic trigger (eg viral infection or exposure to a superantigen), activates these autoreactive T-cells which then selectively cross the blood-brain barrier and, on re-exposure to their autoantigen, initiate a cell-mediated (T helper 1) inflammatory reaction. Potential autoantigens include myelin basic protein (MBP), proteolipid protein (PLP), myelin-associated glycoprotein (MAG) and myelin oligodendrocyte glycoprotein (MOG). This cell-mediated inflammatory cascade causes oligodendrocyte, axonal and neuronal toxicity, which in turn releases sequestered central nervous system (CNS) antigens which are hypothesised to initiate further cycles of autoimmune induced inflammation via an intra- or intermolecular antigen determinant spreading. Demyelination leads to reduction in the safety factor of conduction, with complete or intermittent conduction block, producing clinical relapse or intermittent negative neurological symptoms. Remyelination and/or axonal plasticity (synthesis of new sodium channels) restores axonal conduction, albeit with a reduced safety factor of conduction. This results in remission, or sometimes transient neurological symptoms secondary to reversible conduction block (eg in relation to fatigue, temperature changes, and in response to systemic inflammation). There is evidence that growth factors produced as part of the inflammatory response stimulate the process of remyelination. Axonal loss and gliosis, an inevitable consequence of recurrent or persistent inflammation, cause permanent neurological impairment and disability. The events highlighted in the inner shaded oval, refer to the clinical consequences of focal inflammation.

Glatiramer acetate. Glatiramer acetate (previously known as copolymer-1) is a mixture of synthetic polypeptides. The peptide mix (glutamic acid, lysine, alanine and tyrosine) is believed to mimic peptide fragments of MBP, a putative autoantigen in MS, blocking T-cell activation. In a trial of 251 patients with early relapsing-remitting MS, daily subcutaneous administration of glatiramer acetate reduced the relapse rate over a two-year period by 29%⁸. It also appeared to have a favourable

effect on the development of disability⁹, but this requires confirmation in further clinical studies. It is licensed for use in the USA, but has yet to be approved for use in Europe. When available, glatiramer acetate may prove to be a reasonable alternative to IFN- β in patients with relapsing disease. A trial of its use in primary progressive MS is shortly to begin.

Azathioprine. Recent meta-analyses of randomised, double-blind, placebo-

controlled trials support the conclusion that oral azathioprine, 2–3 mg/kg/day, reduces the relapse rate by about a third¹⁰ and has a moderate effect on the progression of disability¹¹. There are intrinsic biases associated with meta-analyses¹², so these data support the need for a large definitive trial on the effects of azathioprine in MS. A large multicentre trial of azathioprine in combination with IFN- β is being planned in Europe.

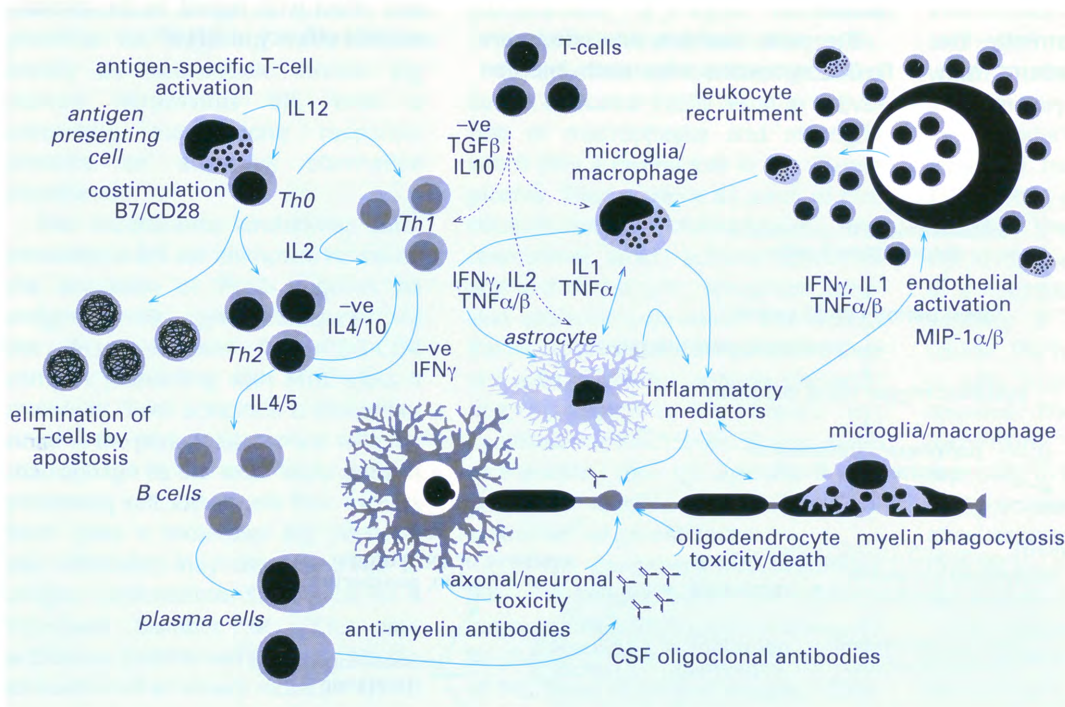


Fig 2. Cellular mechanisms of acute inflammation in multiple sclerosis. During the normal process of immunosurveillance memory CD4+ T helper (Th) cells selectively cross the blood-brain barrier, through a process involving the interaction of their cell surface adhesion molecules with those expressed on central nervous system endothelium. Within the perivascular space these cells are activated by professional antigen-presenting cells (probably macrophages or microglia) to proliferate and produce pro-inflammatory cytokines. Antigen recognition occurs via the trimolecular complex of human leukocyte antigen (HLA), T-cell receptors and CD3 molecules, and requires additional costimulatory signals; the important ones include interactions between HLA-major histocompatibility complex I and II molecules and their respective CD8 and CD4 molecules, and CD28/B7-2/1 pairs. The presence of specific cytokines like interleukin (IL)12 govern the type of Th response. Th1-like cytokines (IL2, interferon (IFN)- γ and tumour necrosis factor (TNF) α/β) initiate a classical cell-mediated inflammatory cascade which activates macrophages, microglia, astrocytes and endothelial cells. This results in further cytokine production and recruitment of inflammatory cells by upregulation of adhesion molecule expression on endothelial cells and by the production of chemoattractants (eg chemokines macrophage inflammatory protein (MIP)-1 α/β). Astrocytes and macrophages produce mutually stimulating cytokines (IL1 and TNF α). These and other pro-inflammatory T-cell cytokines upregulate the production of numerous noxious substances (eg TNF α/β , free oxygen and nitrogen radicals, complement, proteases and eicosanoids) which are toxic to oligodendrocytes, axons and neurones. Autoantibodies, particularly to surface myelin antigens (eg myelin oligodendrocyte glycoprotein), appear crucial to the development of demyelination. Autoantibodies to axonal elements (eg gangliosides) may have functional consequences and contribute to conduction abnormalities. In addition to myelin damage, apoptosis of the oligodendrocyte may occur as a result of oxidative stress and death signalling induced by TNF α . Antibodies and complement assist Fc-receptor-mediated phagocytosis by opsonisation. Phagocytosis also occurs via the macrophage scavenger and low-density lipoprotein receptors. Immunomodulatory cytokines (IL4, IL10 and transforming growth factor (TGF) β) produced by suppressor and Th2 T-cells are important in downregulating and controlling the above inflammation. Elimination of autoreactive T-cells by apoptosis may be important in controlling inflammation (CSF = cerebrospinal fluid).

Cyclosporin A. Cyclosporin has been shown in a multicentre, placebo-controlled trial to have modest clinical effects on disease progression¹³, unfortunately outweighed by toxicity, especially nephrotoxicity which developed in 84% of treated patients.

Immunoglobulin. Favourable effects were noted on relapse rate in a preliminary, two-year trial of intravenous immunoglobulin (Ig) (150–200 mg/kg/month) compared to placebo in 150 patients with relapsing-remitting MS¹⁴. This has prompted a large, multicentre, placebo-controlled, phase III clinical trial which is currently in progress.

Non-targeted immunotherapies

Methotrexate. In a small double-blind, placebo-controlled trial in 60 patients with progressive MS, low dose oral methotrexate (7.5 mg/week) significantly reduced progression of upper limb function impairment¹⁵, but did not affect more conventional measures of ambulation, disability or MRI activity.

Cyclophosphamide. High-dose intravenous cyclophosphamide with booster injections has been documented to be effective in some^{16–18}, but not all¹⁹, studies of patients with progressive MS. Cyclophosphamide, however, is an alkylating agent with an unfavourable side effect profile and cannot be recommended for the routine treatment of patients with MS.

Recently failed therapies

Recently, several large phase III clinical trials of putative disease modifying agents have proved ineffective or have been aborted in patients with MS. After a promising 18-month interim analysis, sulphasalazine, an effective oral anti-inflammatory agent in inflammatory bowel disease, proved no better than placebo in delaying sustained disease progression in patients with progressive MS over three years²⁰.

A widely publicised phase III oral tolerance trial using bovine myelin as the oral antigen was also negative. A

MRI-based phase II trial comparing a depleting chimeric anti-CD4 antibody with placebo was negative²¹, although this antibody therapy appeared to have some effect on relapse rate. Three phase III trials of linomide (Roquinimex), a novel immunomodulatory compound, were terminated after an excessive number of acute myocardial infarctions were noted in the treated groups of MS patients. A trial assessing the efficacy of a recombinant soluble fusion protein consisting of a soluble TNF α -receptor and an Ig Fc receptor was prematurely terminated when the relapse rate in the treated arm of the trial was found to be unexpectedly increased.

Potential future therapies in trial

The increasing number of agents currently undergoing clinical testing in patients with MS is reassuring for patients with the condition. A list and brief description of the rationale behind some of these agents is presented in Table 1.

Symptomatic therapies

Corticosteroids in acute relapse

The use of corticosteroids for hastening the recovery from acute MS relapse has been well established in several clinical trials²². The therapeutic effect of corticosteroids is often rapid, beginning within 24 hours, suggesting that the anti-oedema as well as anti-inflammatory effects are important mechanisms of action. Intravenous methylprednisolone, 1 g/day for three days, is the most widely prescribed regimen, but high-dose oral corticosteroids are probably as effective^{23–25}. There is no evidence to support the practice of tapering the dose or prescribing prolonged courses.

Spasticity

Spasticity is a common problem in MS. Established oral anti-spasticity agents include baclofen, diazepam and dantrolene. An established oral, centrally-acting α 2 agonist, tizanidine hydro-

chloride, with similar efficacy to baclofen, has become available for use in patients with MS. Surprisingly, tizanidine has been reported to reduce spasticity without increasing weakness^{26,27}. The development of baclofen for continuous intrathecal delivery via an implanted depo-pump has been revolutionary²⁸. It is remarkably effective in severe cases of spasticity with moderate disability. For severely disabled patients, intrathecal phenol²⁹, the effects of which are usually irreversible, is beneficial. Local botulinum toxin injections or surgical tenotomy (eg of the adductor muscles) assists in the management of sphincter function in severe cases.

Sphincter disturbances and sexual dysfunction

Sphincter disturbances and sexual dysfunction are common in patients with MS, usually as a result of spinal cord dysfunction. The principles for managing these problems are well established. New developments for control of urinary symptoms include suprapubic bladder neck vibration³⁰ and chemical denervation of the detrusor muscle with intravesical capsaicin³¹. Judicious use of intermittent vasopressin, in tablet or nasal spray form, to reduce temporarily urine volume and urinary frequency can make an enormous difference to patients' quality of life^{32,33}. Male impotence may be helped by alprostadil³⁴, an intraurethral prostaglandin analogue, and the selective oral phosphodiesterase type 5 inhibitor, sildenafil³⁵.

Fatigue

Fatigue is a common complaint in patients with MS. It is not necessarily related to disability or depression and is rarely the primary presenting feature of the disease. Approximately 40% of patients respond to amantadine 100 mg twice daily³⁶. Stimulants such as pemoline (discontinued in the UK), methylphenidate and amphetamines are generally not recommended. 4-Aminopyridine, a voltage-dependent

Table 1. Potential therapeutic agents currently undergoing clinical evaluation in multiple sclerosis (MS).

Agent	Rationale
IFN-β1a	Two large clinical trials are currently testing whether IFN-β administration to patients with clinically isolated syndromes compatible with demyelination delays the onset of clinically definite MS. IFN-β has several immunomodulatory actions
Mitoxantrone	Less cardiotoxic anthracycline chemotherapeutic agent related to adriamycin. Generalised immunosuppressive agent
Antigen/MHC complex binder (Anergix)	Downregulates putative autoimmune T-cell responses
Peptide therapies	Induce immune tolerance to putative autoantigens
T-cell vaccination	Induces cytotoxic response against putative autoreactive T-cells
Tacrolimus (or FK-506)	Immunophylin with T-cell specificity. Effective in organ transplantation
Thalidomide	Functional TNFα antagonist
Pentoxifylline	Phosphodiesterase inhibitor, downregulates effects of TNFα
Anti-CD52 (Campath 1H)	Potent generalised immunosuppressive agent with long-term immunological effects resulting in immune deviation with a Th2 bias
IL10	Anti-inflammatory cytokine therapy
2-Chlorodeoxyadenosine (cladaribine)	Selective lymphocytotoxic agent
Matrix metalloproteinase inhibitors	Multiple immunological effects
Anti-adhesion molecule (VLA-4) monoclonal antibody (Antegren)	Decreases migration of lymphocytes into the CNS and interferes with T-cell activation
Plasmapheresis	Removal of putative autoantibodies
Intravenous gammaglobulin	Complex immunomodulatory effects and reduces circulating half-life of endogenous autoantibodies
Vitamin D	Immune modulation
Retinoic acid	Immune modulator, given in combination with IFN-β
Ganciclovir	Anti-viral agent
Valaciclovir	Anti-viral agent
Insulin-like growth factor (myotrophin)	Immunomodulatory activity and promotes remyelination
Hydrolytic enzymes (Phylogenzym)	Modulate adhesion molecule function and suppress activation of autoimmune T lymphocytes
Bone marrow transplantation	Generalised immune reconstitution

CNS = central nervous system; IFN = interferon; IL = interleukin; MHC = major histocompatibility complex; Th = T helper; TNF = tumour necrosis factor.

potassium channel blocker, is effective in improving fatigue, but its use is limited by undesirable side effects³⁷. Patients with fatigue benefit from behavioural therapy and lifestyle adaptations. Limited physical activities, with planned periods of rest, are helpful. If temperature-sensitive, patients should be advised to avoid hot baths and warm environments. Swimming is a useful form of exercise in these patients. As a last resort, some patients may benefit from the use of a cooling suit.

Pain

Paroxysmal pain disorders, like trigeminal neuralgia, due to plaques in the posterior root entry zone, usually respond to carbamazepine or phenytoin. Chronic myelopathic pain, which usually occurs in patients with extensive spinal cord disease, is difficult to treat and often resistant to standard therapies. Gabapentin, a new generation anticonvulsant, has been added to the therapeutic armoury for the treatment of chronic pain.

Seizures

The prevalence of epilepsy in MS is approximately twice that of the general population. It typically develops later in the course of the disease and requires standard anticonvulsant therapy.

Tonic spasms

Tonic spasms are an uncommon motor manifestation of MS. They tend to be unilateral, painful and self-limiting, usually settling down within 4–6 weeks. Like other paroxysmal disorders in MS, they respond to carbamazepine or phenytoin.

Tremor

The disabling coarse intention or rubral tremor which occurs in patients with cerebellar or cerebellar pathway lesions has been reported to respond to high doses of isoniazid, 600–1,200 mg/day, given in association with pyridoxine, 100 mg/day, to prevent the develop-

ment of peripheral neuropathy. In clinical practice, isoniazid rarely results in functional improvement. Clonazepam sometimes has a moderate beneficial effect. Stereotaxic thalamotomy or stimulation has proved remarkably effective in controlling this form of tremor. Patients should ideally be considered for neurosurgery before they become significantly disabled – at a stage when they stand to derive the most functional benefit from these procedures.

Mood disorders

Depression is the most common mood disorder in patients with MS and usually responds to standard antidepressant therapies. Sedating tricyclic antidepressants (eg amitriptyline) are particularly useful for patients who have chronic pain or suffer from insomnia, despite their unfavourable side effect profile. Hypomania and psychosis are rare manifestations of MS and should be managed according to standard psychiatric principles.

Pathological crying and laughing

Pathological crying and laughing distress both patients and their carers and can be difficult to treat as they commonly occur in the context of significant cognitive impairment. A sedating tricyclic antidepressant (eg amitriptyline) or citalopram, one of the newer selective serotonin reuptake inhibitors, may be effective^{38,39}.

Bulbar symptoms

Acute bulbar dysfunction as a result of a brainstem relapse should be treated expectantly. Decisions to perform tracheostomy and percutaneous gastrostomy for chronic bulbar dysfunction in MS should be made on the merits of the individual case.

Cognitive impairment

Cognitive impairments are increasingly recognised as significant features of MS and can have a major impact on dis-

ability and handicap. They usually occur in association with progressive disease, but on rare occasions can be the presenting feature. Currently, there is no evidence to support any specific therapies for their treatment. It has yet to be determined whether or not disease modifying therapies like IFN- β prevent the development of cognitive impairments.

Diet

There is no evidence to support or refute any dietary claims made concerning MS. Linoleic acid may moderately reduce relapse rate⁴⁰.

Rehabilitation

The effective management of a chronic disease like MS requires a multidisciplinary approach. In appropriate circumstances, intensive inpatient neuro-rehabilitation improves disability, handicap, emotional well-being and health-related quality of life, but has no effect on neurological impairment⁴¹.

Multiple sclerosis societies

The importance cannot be overemphasised of national and international MS societies representing the needs and aspirations of MS patients. They provide an invaluable information service to MS patients, their carers and health service professionals involved with MS. They are large sponsors of clinical and basic research into various aspects of MS. As a lobby group for MS sufferers, they are able to influence health policy, set research priorities, recruit patients for clinical trials, and raise the profile of MS.

A useful resource is the International Federation of Multiple Sclerosis Societies' website, 'The World of Multiple Sclerosis' (www.ifmss.org.uk), with links to national MS societies and other MS-related websites.

Conclusion

Symptomatic treatments remain the cornerstone of MS management. Neurorehabilitation has now become a

science with a new and growing evidence base. The emphasis in managing MS patients has shifted to multidisciplinary teams working in specialist groups. The last five years have seen the introduction of some useful new symptomatic therapies, the successful clinical introduction of IFN- β – the first disease modifying therapy – and the promise of other therapies in the future.

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